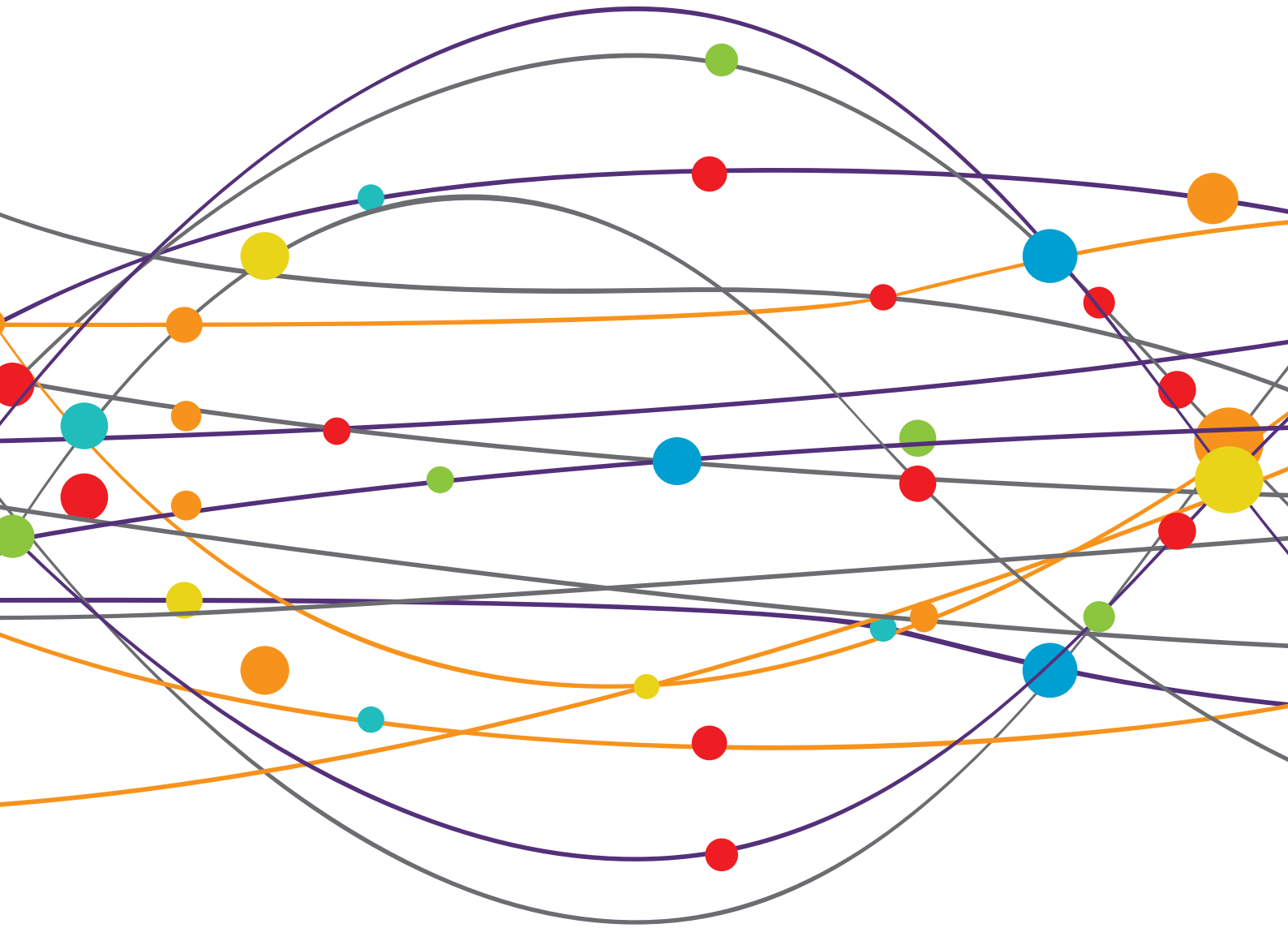
TRANSITIONAL AND LONG-TERM CONTINUOUS CARE & REHABILITATION AFTER STROKE

EDITED BY: Won-Seok Kim, Masahiro Abo, Surjo R. Soekadar and Caterina Pistarini

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88976-976-6
DOI 10.3389/978-2-88976-976-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

TRANSITIONAL AND LONG-TERM CONTINUOUS CARE & REHABILITATION AFTER STROKE

Topic Editors:
Won-Seok Kim, Seoul National University Bundang Hospital, South Korea
Masahiro Abo, Jikei University School of Medicine, Japan
Surjo R. Soekadar, Charité Universitätsmedizin Berlin, Germany
Caterina Pistarini, Scientific Clinical Institute Maugeri (ICS Maugeri), Italy

Citation: Kim, W.-S., Abo, M., Soekadar, S. R., Pistarini, C., eds. (2022). Transitional and Long-term Continuous Care & Rehabilitation After Stroke. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-976-6

Table of Contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 05 August 2022
DOI 10.3389/fneur.2022.965762

OPEN ACCESS

EDITED BY
Thomas Platz,
University of Greifswald, Germany

*CORRESPONDENCE
Won-Seok Kim
wondol77@gmail.com

SPECIALTY SECTION
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

RECEIVED 10 June 2022
ACCEPTED 18 July 2022
PUBLISHED 05 August 2022

CITATION
Kim W-S, Abo M, Soekadar SR and Pistarini C (2022) Editorial: Transitional and long-term continuous care & rehabilitation after stroke. *Front. Neurol.* 13:965762. doi: 10.3389/fneur.2022.965762

Editorial: Transitional and long-term continuous care & rehabilitation after stroke

Won-Seok Kim[1]*, Masahiro Abo[2], Surjo R. Soekadar[3] and Caterina Pistarini[4]

[1]Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [2]Department of Rehabilitation Medicine, Jikei University School of Medicine, Tokyo, Japan, [3]Clinical Neurotechnology Lab, Department of Psychiatry and Neurosciences, Charité–Universitätsmedizin Berlin, Berlin, Germany, [4]Department of Neurorehabilitation Istituti Clinici Scientifici Maugeri, Istituto di Ricovero e Cura a Carattete Scientifico (IRCCS), Pavia, Italy

KEYWORDS

stroke, rehabilitation, transitional care, long-term care, clinical trial, protocol, observational study

Editorial on the Research Topic
Transitional and long-term continuous care & rehabilitation after stroke

Stroke incidence and prevalence are increasing, causing substantial socioeconomic burdens and loss of healthy life-years worldwide (1). Timely acute treatment, such as thrombolysis, is crucial to reduce mortality and disability; however, many stroke survivors have to live with disabilities after acute care (1–4). Therefore, continuous rehabilitation and long-term care to meet the needs of individual stroke survivors is mandatory.

Establishing novel therapeutics to promote the recovery and management to avoid complications along with adequate rehabilitation in acute and subacute phases is important because the time window for recovery after stroke is limited (5). After adequate intensive rehabilitation, many stroke survivors and their caregivers lack a personalized long-term continuous care plan. Moreover, important information has often not been provided at the time of discharge from acute treatment. Because such need for long-term care is unmet in many cases, subjective and objective outcomes remain unfavorable (6). Therefore, adequate transitional and long-term care strategies and therapeutics to compensate or reduce the effect of impairments after stroke are required.

The Research Topic "Transitional and Long-term Continuous Care & Rehabilitation After Stroke" included 14 manuscripts, ranging from a study protocol, case report and observational study to randomized controlled trials, a mini-review, systematic review, and meta-analysis. These timely contributions offer an interesting insight from acute rehabilitation to transitional and long-term care in patients with stroke.

Effective rehabilitation and medical management to promote functional recovery and reduce complications are important, and three related papers in this area were presented. A large randomized controlled trial (AVERT) showed that early mobilization within 24 h of stroke onset was feasible but not effective in terms of favorable outcomes defined as a modified Rankin Scale (mRS) score of 0–2 at 3 months post-stroke (7). However, the prespecified dose–response analysis from the AVERT revealed that shorter and more frequent mobilization early after acute stroke can be beneficial (8). One randomized controlled trial on intracerebral hemorrhage demonstrated that early rehabilitation within 48 h can improve functional outcomes and reduce mortality (9). A recent randomized controlled trial in patients with mild and moderate intracerebral hemorrhage also revealed that early mobilization within 24 to 72 h of stroke onset can improve the early functional independence (10). Therefore, the study aimed to investigate the effect of early mobilization after stroke in various stroke patients' group in terms of stroke type or severity and using different mobilization protocol in terms of timing, frequency, session duration is needed. Wang et al. conducted a randomized controlled trial investigating the effect of early out-of-bed mobilization within 48 h of stroke symptom onset compared to the conventional rehabilitation group in the unique patient group who underwent mechanical thrombectomy. In this study, early mobilization reduced non-fatal complications 3 months post-stroke and improved the activities of daily living at 3 months and 1-year post-stroke, although the effects on mortality and mRS were comparable with that of conventional rehabilitation.

Dysphagia is a common impairment after stroke that is considered important due to its association with the incidence of pneumonia as confirmed by Chang M. et al. (OR 9.60; 95% CI 5.75–16.05) in their systematic review and meta-analysis of five studies.

Statins have a potential to promote recovery after stroke by their possible pleiotropic effects; however, their results in human studies are controversial (11–13). Mele et al. retrospectively analyzed the data of 413 patients with stroke from a single neurorehabilitation center and reported that statin therapy was not associated with recovery and functional outcomes but associated with a lower incidence of bone fractures.

Earlier subacute stroke rehabilitation trials are necessary, considering the preclinical studies reporting that earlier rehabilitation after stroke is better for neuromotor recovery (14, 15). However, previous stroke rehabilitation trials have conventionally focused on patients at >3–6 months post-stroke. Geed et al. reported screening and enrollment data from the Critical Periods After Stroke Study (CPASS), which recruited patients within 30 days of stroke (16). In an acute care setting, a short length of stay and prior stroke were the major reasons for exclusion in CPASS. In an inpatient rehabilitation setting, "too late" to participate in an early stroke trial, prior stroke and too mild impairment were the major reasons for exclusion. The Mean Action Research Arm Test score for the affected upper extremity in a patient with mild impairment (NIH stroke scale for motor arm item = 0 or 1) was 39 (max score = 57), which indicates significant impairment having a potential benefit from participation in upper limb rehabilitation trials. Therefore, patients with stroke should be screened when they are in the acute care phase, and screening of patients with mild impairment should be conducted using a motor function specific scale for successful recruitment for early stroke rehabilitation trials.

Our topic includes four manuscripts regarding the issues in transitional care strategies or systems after stroke. One of the transitional care strategies after stroke is "early supported discharge (ESD)" aiming to expedite home discharge after stroke by providing adequate management and rehabilitation services after discharge in the patient's home. ESD has been known to reduce long-term dependency and length of the hospital stay; however, most studies on ESD have been conducted in western countries (17). Moreover, the recent meta-analysis (18 studies from western countries and two studies from eastern countries) by Jee et al. reported that ESD and transitional care in patients with stroke did not have significant beneficial effects on functional outcomes, mortality, caregiver strain, and length of hospital stay. ESD or transitional care services should be implemented in accordance with each specific national medical rehabilitation pathways. Chang W. et al. proposed the study protocol for a multicenter randomized controlled trial to investigate the effect of ESD compared with the conventional rehabilitation on activities of daily living, patient- or caregiver-reported outcomes, and socioeconomic outcomes in 90 Korean patients with post-acute stroke with mild-to-moderate disability. Kinoshita et al. and Leigh et al. elaborated on the transitional and long-term care system in Japan and South Korea, respectively, which will be helpful for making comparisons to improve long-term stroke care.

Stroke survivors can have long-term stroke-related impairments or complications associated with poor quality of life. Kim et al. conducted a face-to-face cross-sectional survey to investigate the unmet needs for rehabilitative management in common health-related problems after stroke. Approximately half of the respondents reported at least one unmet need, and the total number of unmet needs was significantly associated with a poor health-related quality of life after adjusting for age, sex, and mRS.

Post-stroke spasticity is associated with complications such as contractures pressure ulcers or pain and poor quality of life (18, 19). Adequate treatments for spasticity can improve patient function and quality of life (20, 21). Zhang et al. conducted

Abbreviations: mRS, modified Rankin scale; CPASS, critical periods after stroke study; ESD, early supported discharge; BCI, brain–computer interface.

a multicenter randomized controlled trial to investigate the effect of dry needling at the myofascial trigger point (30 min in each session for a total of five sessions for 4 weeks) on hand spasticity in 210 patients with chronic stroke. The dry needling demonstrated significantly better immediate spasticity relief than sham needling and control groups, and the spasticity relief persisted at 4 weeks after baseline. Fan et al. presented a randomized, double-blind, sham-controlled trial protocol to investigate the short-term effects of radial extracorporeal shock wave therapy on flexor spasticity of the upper limb in 100 patients with >1 month first-ever stroke and elbow joint spasticity grade >1, determined using the modified Ashworth scale.

The incidence of sarcopenia in patients with stroke ranges from 14 to 54% and is associated with poor outcomes (22). Park et al. prospectively enrolled patients with <3 months after stroke, who ingested dietary supplement power containing 6 g of branched-chain amino acids twice a day for 1 month. They selected the control group by a retrospective medical chart review to balance the age and stroke lesions with the intervention group. The branched-chain amino acid supplementation group demonstrated better improvement in skeletal muscle index measured by dual-energy X-ray absorptiometry and in functional scales such as the modified Barthel index.

Novel therapeutics for stroke motor recovery or compensating the impaired function are needed especially for patients with more severe impairments considering their poor recovery potentials (23). Singh et al. reported a case of a 52-year-old woman with a 9-year chronic stroke, who received 20 therapy sessions (45 min/session) with robotic exoskeleton assistance to extend the wrist and flex the fingers in the affected upper limb triggered by electromyography activity of the extensor digitorum communis. She demonstrated improvements in the Fugl–Meyer Assessment score, Barthel index, and modified Ashworth scale with relevant changes in neurophysiologic parameters. Finally, Angerhöfer et al. reviewed the need for brain–computer interface (BCI)-enabled neurorehabilitation in severe upper limb paresis. Specifically, the authors discussed how BCI-based long-term treatment strategies could be established in Germany and outlined the challenges in this process. This review will be an excellent reference for researchers who are interested in effective BCI applications and their clinical implementation.

Author contributions

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

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 handling editor TP declared a past collaboration with the author(s) W-SK and CP.

Publisher's note

References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/s1474-4422(21)00252-0

2. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive Summary of Stroke Statistics in Korea 2018: A Report from the Epidemiology Research Council of the Korean Stroke Society. *J Stroke.* (2019) 21:42–59. doi: 10.5853/jos.2018.03125

3. Kim SE, Lee H, Kim JY, Lee KJ, Kang J, Kim BJ, et al. Three-month modified Rankin Scale as a determinant of 5-year cumulative costs after ischemic stroke: An analysis of 11,136 patients in Korea. *Neurology.* (2020) 94:e978–e91. doi: 10.1212/WNL.0000000000011295

4. Kwon S, Park JH, Kim WS, Han K, Lee Y, Paik NJ. Health-related quality of life and related factors in stroke survivors: Data from Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2014. *PLoS ONE.* (2018) 13:e0195713. doi: 10.1371/journal.pone.0195713

5. Winters C, Kwakkel G, van Wegen EEH, Nijland RHM, Veerbeek JM, Meskers CGM. Moving stroke rehabilitation forward: The need to change research. *NeuroRehabilitation.* (2018) 43:19–30. doi: 10.3233/NRE-172393

6. Im HW, Kim WS, Kim S, Paik NJ. Prevalence of worsening problems using post-stroke checklist and associations with quality of life in patients with stroke. *J Stroke Cerebrovasc Dis.* (2020) 29:105406. doi: 10.1016/j.jstrokecerebrovasdis.2020.105406

7. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet.* (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0

8. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology.* (2016) 86:2138–45. doi: 10.1212/WNL.0000000000002459

9. Liu N, Cadilhac DA, Andrew NE, Zeng L, Li Z, Li J, et al. Randomized controlled trial of early rehabilitation after intracerebral hemorrhage stroke: difference in outcomes within 6 months of stroke. *Stroke.* (2014) 45:3502–7. doi: 10.1161/STROKEAHA.114.005661

10. Yen HC, Jeng JS, Chen WS, Pan GS, Chuang Pt Bs WY, Lee YY, et al. Early mobilization of mild-moderate intracerebral hemorrhage patients in a stroke center: a randomized controlled trial. *Neurorehabil Neural Repair.* (2020) 34:72–81. doi: 10.1177/1545968319893294

11. Biffi A, Devan WJ, Anderson CD, Cortellini L, Furie KL, Rosand J, et al. Statin treatment and functional outcome after ischemic stroke: case-control and meta-analysis. *Stroke.* (2011) 42:1314–9. doi: 10.1161/STROKEAHA.110.605923

12. Silva Marques J, Ennis G, Venade G, João Soares R, Monteiro N, Gomes A. Association of Statins With Functional Outcome and 30-Day Mortality in Patients With Intracerebral Hemorrhage. *Cureus.* (2021) 13:e14421. doi: 10.7759/cureus.14421

13. Callaly NC. Duggan J, Merwick Á, Hannon N, Sheehan Ó, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. *Stroke.* (2011) 42:1021–9. doi: 10.1161/STROKEAHA.110.596734

14. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair.* (2012) 26:923–31. doi: 10.1177/1545968312440745

15. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci.* (2004) 24:1245–54. doi: 10.1523/JNEUROSCI.3834-03.2004

16. Dromerick AW, Geed S, Barth J, Brady K, Giannetti ML, Mitchell A, et al. Critical Period After Stroke Study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. *Proc Natl Acad Sci U S A.* (2021) 118:e2026676118. doi: 10.1073/pnas.2026676118

17. Langhorne P, Baylan S. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev.* (2017) 7:Cd000443. doi: 10.1002/14651858.CD000443.pub4

18. Ayoub S, Smith JG, Cary I, Dalton C, Pinto A, Ward C, et al. The positive and the negative impacts of spasticity in patients with long-term neurological conditions: an observational study. *Disabil Rehabil.* (2021) 43:3357–64. doi: 10.1080/09638288.2020.1742803

19. Schinwelski MJ, Sitek EJ, Waz P, Sławek JW. Prevalence and predictors of post-stroke spasticity and its impact on daily living and quality of life. *Neurol Neurochir Pol.* (2019) 53:449–57. doi: 10.5603/PJNNS.a2019.0067

20. Bavikatte G, Subramanian G, Ashford S, Allison R, Hicklin D. Early Identification, Intervention and Management of Post-stroke Spasticity: Expert Consensus Recommendations. *J Cent Nerv Syst Dis.* (2021) 13:11795735211036576. doi: 10.1177/11795735211036576

21. Hamaguchi T, Abo M, Murata K, Kenmoku M, Yoshizawa I, Ishikawa A, et al. Association of Long-Term Treatment by Botulinum Neurotoxins and Occupational Therapy with Subjective Physical Status in Patients with Post-Stroke Hemiplegia. *Toxins (Basel).* (2019) 11:453. doi: 10.3390/toxins11080453

22. Mas MF, González J, Frontera WR. Stroke and sarcopenia. *Curr Phys Med Rehabil Rep.* (2020) 8:452–60. doi: 10.1007/s40141-020-00284-2

23. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain.* (2012) 135:2527–35. doi: 10.1093/brain/aws146

frontiers in Neurology

ORIGINAL RESEARCH
published: 08 June 2021
doi: 10.3389/fneur.2021.674237

Why Are Stroke Rehabilitation Trial Recruitment Rates in Single Digits?

Shashwati Geed[1,2]*, *Preethy Feit*[2], *Dorothy F. Edwards*[3] and *Alexander W. Dromerick*[1,2,4]

[1] Center for Brain Plasticity and Recovery, Department of Rehabilitation Medicine, Georgetown University Medical Center, Washington, DC, United States, [2] MedStar National Rehabilitation Hospital, Washington, DC, United States, [3] Department of Kinesiology and Occupational Therapy, University of Wisconsin, Madison, WI, United States, [4] Department of Neurology, Georgetown University Medical Center, Washington, DC, United States

Background: Recruitment of patients in early subacute rehabilitation trials (<30 days post-stroke) presents unique challenges compared to conventional stroke trials recruiting individuals >6 months post-stroke. Preclinical studies suggest treatments be initiated sooner after stroke, thus requiring stroke rehabilitation trials be conducted within days post-stroke. How do specific inclusion and exclusion criteria affect trial recruitment rates for early stroke rehabilitation trials?

Objectives: Provide estimates of trial recruitment based on screening and enrollment data from a phase II early stroke rehabilitation trial.

Methods: CPASS, a phase II intervention trial screened ischemic stroke patients in acute care (18-months, $N = 395$) and inpatient rehabilitation (22-months, $N = 673$). Patients were stratified by upper extremity (UE) impairment into *mild* (NIHSS motor arm = 0, 1); *moderate* (NIHSS = 2, 3); *severe* (NIHSS = 4) and numbers of patients disqualified due to CPASS exclusion criteria determined. We also examined if a motor-specific evaluation (Action Research Arm Test, ARAT) increases the pool of eligible patients disqualified by the NIHSS motor arm item.

Results: CPASS recruitment in acute care (5.3%) and inpatient rehabilitation (5%) was comparable to prior trials. In acute care, a short stay (7–17-days), prior stroke (13.5% in *moderately*; 13.2% in *severely* impaired) disqualified the majority. In inpatient rehabilitation, the majority (40.8%) were excluded for "too mild" impairment. The next majority were disqualified for reaching inpatient rehabilitation "too late" to participate in an early stroke trial (15% in *moderately*; 24% in *severely* impaired). Mean ARAT in the "too mild" showed significant impairment and potential to benefit from participation in select UE rehabilitation trials.

Conclusions: Screening of ischemic stroke patients while they are still in acute care is crucial to successful recruitment for early stroke rehabilitation trials. A significant proportion of eligible patients are lost to "short length of stay" in acute care, and arrive to inpatient rehabilitation "too late" for an early rehabilitation trial. Additional screening of mildly impaired patients using a motor function specific scale will benefit the trial recruitment and generalizability.

Trial Registration Number: http://www.clinicaltrials.gov Identifier: NCT02235974.

Keywords: prospective study, rehabilitation, clinical trial, stroke, trial design

Edited by:
Won-Seok Kim,
Seoul National University Bundang Hospital, South Korea

Reviewed by:
Kathryn S. Hayward,
The University of Melbourne, Australia
SuYeon Kwon,
Ewha Womans University Seoul Hospital, South Korea

***Correspondence:**
Shashwati Geed
shashwati.geed@medstar.net

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *01 March 2021*
Accepted: *06 May 2021*
Published: *08 June 2021*

Citation:
Geed S, Feit P, Edwards DF and Dromerick AW (2021) Why Are Stroke Rehabilitation Trial Recruitment Rates in Single Digits? Front. Neurol. 12:674237. doi: 10.3389/fneur.2021.674237

INTRODUCTION

Stroke rehabilitation trials have conventionally focused on individuals whose motor recovery has plateaued at more than 3–6 months post-stroke (1–5) so that spontaneous post-stroke recovery does not confound intervention-related recovery (6). However, preclinical studies increasingly suggest that post-stroke rehabilitation intervention trials need to be conducted within days of stroke onset for better neuromotor outcomes (2, 7–9). In traditional stroke rehabilitation trials, investigators have a long window of recruitment often lasting up to several years post stroke because patients who are more than 6-months post stroke are included. Additionally, rehabilitation trialists have conventionally recruited from outpatient stroke clinics and community centers that offer multiple opportunities with repeated contact to enroll the same individuals.

To enable acute (<7 days) and early-subacute (8–90 days post stroke) trials (10, 11), rehabilitation trial recruitment methods need to adapt by shifting into the acute care and inpatient rehabilitation settings where patient stays are limited for 2 weeks post stroke on average (12). Thus, early stroke rehabilitation trialists have a brief window of identifying and enrolling eligible patients in trials. This brief period coincides with a particularly confusing time in patients' lives given their recent stroke diagnosis and the long commitment required of them to participate in a stroke rehabilitation trial with a typical follow up at 12-months post randomization (5, 7, 13–15). Even small efficiencies in patient screening and enrollment in this scenario can make large differences in the eventual trial recruitment rates and costs. However, there are no data at present that give reliable estimates of how trial inclusion and exclusion criteria affect the pool of eligible patients in a US healthcare setting for an early stroke rehabilitation trial.

Lasagna's law (16) notes that "the incidence of any disease decreases sharply as soon as a clinical trial begins and returns to its original level as soon as the trial is completed." No matter how conservative one is about their recruitment goals, it is difficult to recruit study participants according to expectations. Incorrect estimates of trial recruitment lead to delays in study completion, abandoned studies, and mismanagement of research funds (17). Underpowered studies increase the probability of type II errors affecting study integrity and validity. Inadequate trial inclusion/exclusion criteria negatively affect generalizability and internal validity of the study. Thus, reliable estimates of trial recruitment rates are central to any trial's planning and logistics.

Here, we report screening and enrollment data from the phase II Critical Periods After Stroke Study (CPASS), an early stroke rehabilitation trial designed to identify optimal timing of upper extremity (UE) motor rehabilitation after stroke (7, 18). CPASS recruited individuals within 30 days of stroke and followed participants up to 12 months post randomization. CPASS screening data are from an urban safety-net acute-care hospital and an inpatient rehabilitation setting that used StrokeNet (19) resources. We also report the trial inclusion/exclusion criteria that most affected trial recruitment rates to help future investigators re-evaluate their own trial inclusion and exclusion to aid trial recruitment. Finally, UE stroke rehabilitation trial screening often relies on a *prescreen* (an easily available measure of motor function from medical history or charts to filter the patients for evaluation with the full trial inclusion/exclusion criteria), e.g., scores on the National Institutes of Health (NIHSS) Stroke Scale items (2, 20). Using CPASS data, we asked if stroke rehabilitation trial recruitment rates would benefit from using a motor function-specific screening tool over the commonly used NIHSS. This is a first report to our knowledge that highlights the typical characteristics of patients recruited or excluded for an early-subacute stroke neurorehabilitation trial in the US healthcare setting.

METHODS

Study procedures were approved by the Institutional Review Board at the MedStar Health Research Institute. The trial was registered at http://www.clinicaltrials.gov (Identifier: NCT02235974). Registry data from inpatients at MedStar Washington Hospital Center and MedStar National Rehabilitation Hospital (NRH) were used. The registry identifies potential participants for post-acute stroke studies at 24–48 h after admission. Data from neuroimaging-confirmed ischemic stroke survivors were extracted; additionally, data on the earliest available National Institutes of Health Stroke Scale (NIHSS) score, demographics, thrombectomy status, tissue plasminogen activator (tPA) administration, duration of stay, and discharge location were extracted. Patients entering inpatient rehabilitation at NRH are evaluated using the Action Research Arm Test (ARAT), a UE motor function specific assessment (21–24) as part of their intake evaluation; these ARAT scores were also extracted. We report CPASS screening data for an 18-month (02/2016 – 07/2017) duration from acute care, and 22-month duration (06/2015 — 04/2017) from the inpatient rehabilitation setting.

UE rehabilitation trials typically stratify enrolled participants using severity of UE motor impairment (2, 5, 7, 14, 25). Therefore, to examine the effect of motor severity on trial eligibility rates, we used NIHSS arm motor score to categorize UE impairment into *mild* (NIHSS = 0, 1), *moderate* (NIHSS = 2, 3), or *severe* (NIHSS = 4) impairment (12).

To examine the impact of other trial inclusion/exclusion criteria on trial qualification rate, we used the medical, disability, and social support criteria from CPASS (**Table 1**). CPASS criteria are similar to multiple major stroke rehabilitation trial inclusion/exclusion criteria, including, VECTORS (2), ICARE (5), EXCITE (14), and LEAPS (4), and TRANSPORT-2.

Even a single exclusion criterion will put the patient out of the "qualified" pool of participants during screening. We followed a similar strategy to quantify patients excluded from the pool of eligible patients, but it is likely a patient in a given category has multiple exclusionary characteristics. Further, not all patients qualifying for the trial will eventually be enrolled. We therefore report the actual enrollment numbers in CPASS from acute care and inpatient rehabilitation to give trialists an estimate of the total numbers of patients screened for the number enrolled in the trial. Specifically, the results report the numbers of patients excluded due to each trial exclusion criteria from the acute care and inpatient rehabilitation screening. To determine

TABLE 1 | CPASS trial inclusion and exclusion criteria.

Inclusion criteria

1. Ischemic or hemorrhagic stroke (with confirmatory neuroimaging) within 28 days of admission to inpatient rehabilitation
2. Age ≥21 years
3. Able to participate in first study-related treatment session within 30 days of stroke onset
4. Able to participate in all study-related activities, including 1 year follow up and blood draws
5. Persistent hemiparesis leading to impaired UE function as indicated by a score ≥1 on the NIHSS motor arm score, and motor impairment judged clinically appropriate as defined by one or more of the following:
   a. Proximal UE voluntary activity indicated by a score of ≥3 on the upper arm item of the motor assessment scale; wrist and finger movements are not required
   b. Manual muscle test (MMT) score ≥2 on shoulder flexion and either elbow flexion or extension or
   c. Active range of motion (AROM) to at least 50% of range in gravity eliminated position for shoulder flexion or abduction, and for any of the following motions: elbow flexion, elbow extension, wrist flexion, wrist extension, finger flexion or finger extension
6. Score of ≤8 on the Short Blessed Memory Orientation and Concentration scale
7. Follows 2-step commands
8. No upper extremity injury or conditions that limited use prior to the stroke
9. Pre-stroke independence: Modified Rankin Scale score of 0 or 1

Exclusion criteria

1. Inability to give informed consent.
2. Prior stroke with persistent motor impairment or other disabling neurologic conditions such as multiple sclerosis, Parkinsonism, ALS, dementia requiring medication.
3. Rapidly evolving motor function.
4. Clinically significant fluctuations in mental status in the 72 hours prior to randomization.
5. Hemispatial neglect as determined by an asymmetry >3 errors on the Mesulam symbol cancellation test.
6. Not independent prior to stroke (determined by scores of <95 on Barthel Index or >1 on modified Rankin scale.
7. Dense sensory loss indicated by a score of 2 on NIHSS sensory item.
8. Ataxia out of proportion to weakness in the affected arm as defined by a score ≥1 on the NIHSS limb ataxia item.
9. Active or prior (within 2 years) psychosis.
10. Active or prior (within 2 years) substance abuse.
11. Not expected to survive 1 year due to other illnesses (cardiac disease, malignancy, etc.).
21. Received UE botulinum toxin within 6 months (other meds do not exclude).

the added benefit of using a UE motor-function specific scale on trial qualification rate, we examined the ARAT, in patients that were disqualified from CPASS due to their UE being "too mild" (NIHSS motor arm score<1). Descriptive statistics on the ARAT scores in patients with NIHSS motor arm score < 1 were computed.

RESULTS

In Acute Care, Short Length of Stay and Prior Stroke Lead to the Most Exclusions

We identified 395 ischemic stroke survivors with an available NIHSS motor arm score from the acute care registry over the 18-month screening duration. Mean NIHSS total score was 9.1 ± 9.3. Of these, 46.6% were male, and 77.2% identified as African American (12.3% as White, and 1.4% as Asian with the rest Unknown or Refused to identify). Of the 395 patients, 21.2% received tPA, and 8.2% received a thrombectomy. Examining the degree of motor impairment, 64.8% had mildly impaired UE (NIHSS motor arm = 0 or 1), 18.3% had moderately impaired UE (NIHSS motor arm = 2 or 3), and 15.6% had severe UE impairment (NIHSS motor arm = 4). Overall, 5.3% of the 395 individuals identified in screening eventually enrolled in CPASS from acute care.

TABLE 2 | Length of Stay and Discharge locations in Acute Care and Inpatient Rehabilitation.

	Mild		Moderate		Severe	
	Acute	**Inpatient**	**Acute**	**Inpatient**	**Acute**	**Inpatient**
Length of stay (days)	6.9	13.7	13.6	20.5	17.2	32.1
Discharge home, no service (%)	36.7	45.9	10.7	32.5	6.2	16.3
Discharge home, home health (%)	11.3	5.8	4.0	2.5	6.2	4.9
Discharge home, outpatient OT/PT (%)	5.1	30.2	1.3	37.5	0.0	28.5
Acute inpatient rehabilitation (%)	34.0	0.7	49.3	0.8	30.8	2.4
Subacute rehabilitation/SNF (%)	9.4	13.3	17.3	19.2	32.3	35.0
Another acute care hospital (%)	0.0	3.6	2.7	6.7	4.6	12.2
Hospice (%)	0.8	0.2	4.0	0.8	0.0	0.0
Death (%)	1.6	0.2	9.3	0.0	20.0	0.8
Other (%)	0.0	0.0	1.3	0.0	0.0	0.0

To determine the average window of time to enroll patients, we examined patients' average length of stay. The length of stay in acute care and discharge locations for the three groups (mild, moderate, and severely impaired) is shown in **Table 2**. Length of stay correlated with degree of UE impairment, mild impairment = 6.9 ± 6.9 days, moderate = 13.6 ± 15.4 days, and severe = 17.2 ± 13.1 days. Only 34% of the mildly impaired, 49% of the moderately impaired, and 31% of the severely impaired patients were discharged to an inpatient rehabilitation facility, which opens a second window to recruit these patients if the trialist implements screening resources at acute care and inpatient rehabilitation. 83/395 ischemic stroke patients screened in this acute care report were admitted to inpatient rehabilitation at NRH and are included in the data on inpatient rehabilitation screening data as well to maintain integrity of the independent screening numbers at acute care and inpatient rehabilitation. A majority (54%) were discharged home or to a skilled nursing facility. Unless a trial budgets for outreach to enroll patients discharged home, this large majority of potentially eligible patients may be entirely lost to trial enrollment if not recruited during their short hospital stay (6–17 days).

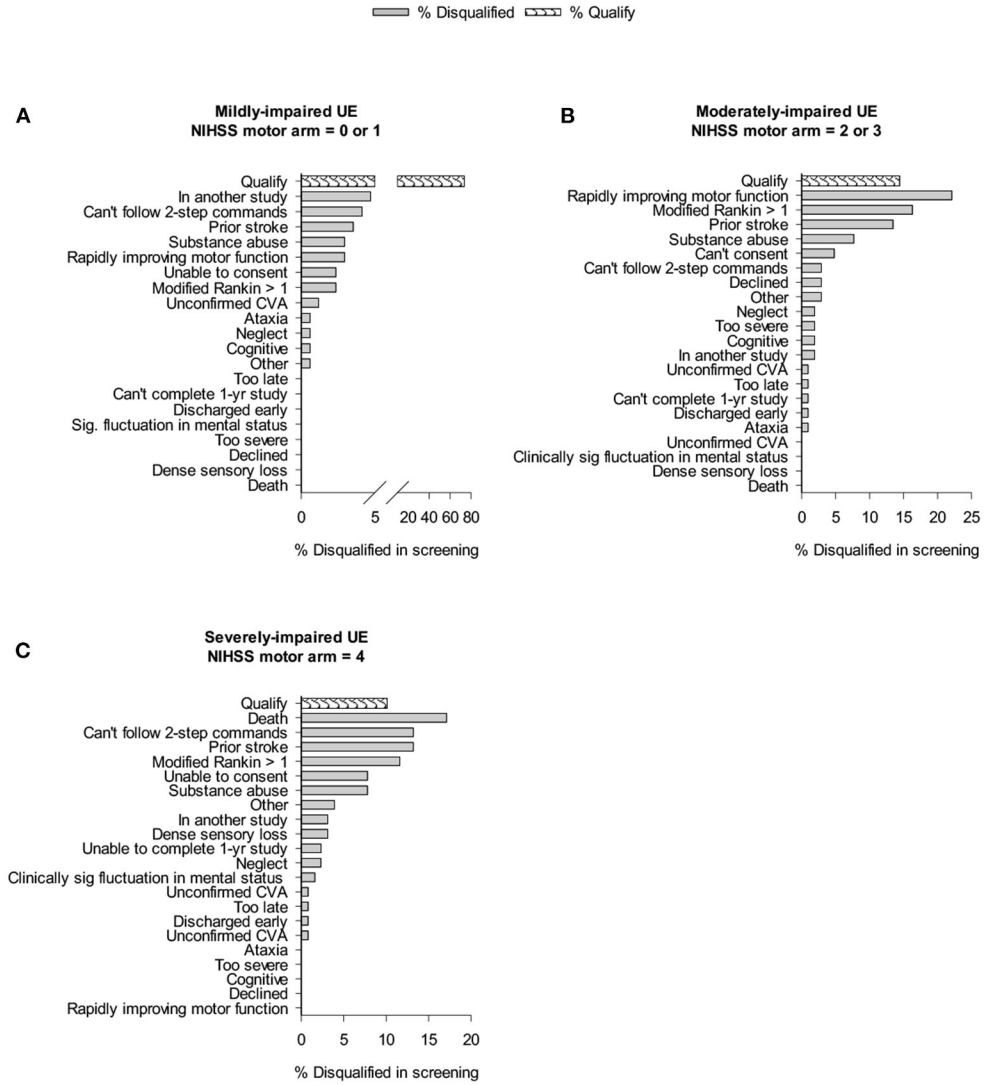


FIGURE 1 | Cumulative impact of study criteria on trial recruitment rates in acute care. Bar graphs show % of individuals screened that were disqualified because of given trial exclusion criteria. "Qualify" shows % of those screened who qualified for CPASS-like trial. Cumulative effects of the exclusion criteria result in a progressively smaller pool of patients that will qualify for a trial.

Figure 1 shows the impact of trial exclusion criteria on the pool of eligible patients from the mild, moderate, and severe UE impairment groups. In patients with mild impairment (**Figure 1A**), 73.5% would potentially qualify for motor studies recruiting subjects with NIHSS motor arm score = 0 or 1. Examination of general medical, disability, and social criteria showed that main reasons for ineligibility include "in another study" (4.7%), and "inability to follow 2-step commands" (4.1%). In patients with a moderately-impaired arm (**Figure 1B**), a mere 14.4% (3.7% of *all* ischemic stroke patients) would qualify for a CPASS-like UE trial. In this moderately-impaired cohort, "rapidly improving motor function" (22%), "disabled prior to stroke" (16.3%), and "prior stroke with persistent impairments" (13.5%) were the most frequent exclusions. In the severely impaired group (**Figure 1C**), 89.9% of patients were eliminated by medical, disability, and social criteria. Patients with severe UE impairment were most frequently excluded by prior stroke (13.2%), or pre-stroke disability (11.6%). Overall, 64% of patients with moderately-impaired (and 70% of those with severely impaired) UE's were excluded not by stroke, but rather inability to consent, substance abuse, prior stroke, pre-stroke disability, or rapid clinical improvement.

At Inpatient Rehabilitation, Arriving Too Late, Mild Impairment, and Prior Stroke Lead to the Most Exclusions

We identified 673 ischemic stroke survivors with an available NIHSS motor arm score during the 22-month screening for CPASS. Mean NIHSS total score was 6.6 ± 5. Of these 53.9% were male, 65.1% identified as African American, 16.8% as White, 0.9 and remaining as Asian, Other, or Refused to

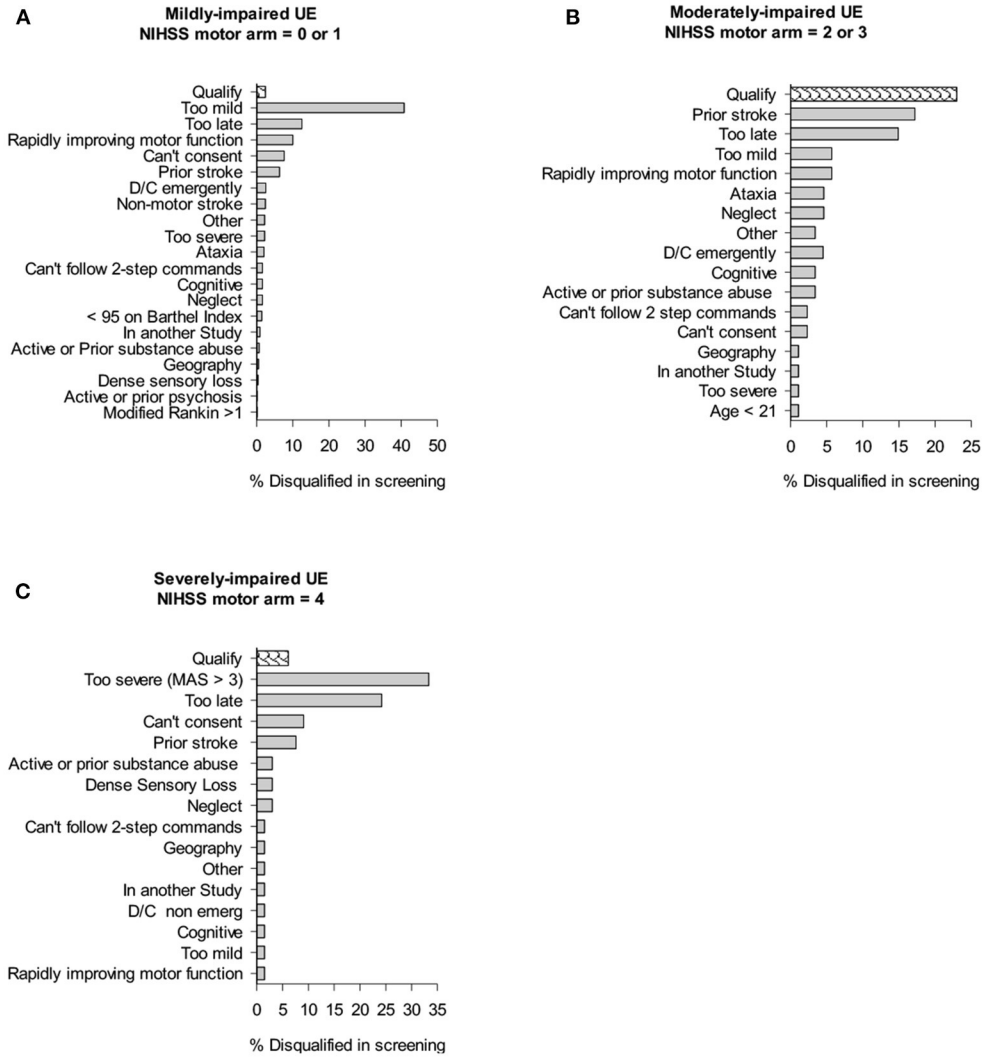


FIGURE 2 | Cumulative impact of study criteria on trial recruitment rates in inpatient rehabilitation. Bar graphs show % of individuals screened that were disqualified because of given trial exclusion criteria. "Qualify" shows % of those screened who qualified for CPASS trial.

identify. Overall, 5% of the 673 individuals screened enrolled in CPASS.

Examining the degree of motor impairment, 62.1% showed Mild, 19.7% Moderate, and 18.2% showed severe UE impairment. Average length of stay correlated with the degree of motor impairment; patients with mild impairment were inpatients for 13.7 ± 13.4 days, moderate impairment for 20.5 ± 15.6 days, and patients with severe impairment were inpatients for 32.1 ± 20.4 days. Discharge locations by degree of motor impairment are shown in **Table 2**.

Figure 2 shows the impact of trial exclusion criteria on the available pool of qualified patients for the UE trial. Of all the mildly impaired participants, 40.8% of patients in inpatient rehabilitation were excluded because their impairment was too mild for the subacute intervention study (NIHSS motor arm score = 0 or 1). The next largest group (12.5%) was disqualified for being "too late," i.e., they arrived at inpatient rehabilitation too late and would not receive the first study-related treatment session within 30-days of stroke onset. Ten percentage of mild inpatients were disqualified because their arm was recovering too rapidly for the context of this trial, e.g., the chart sheet recorded NIHSS motor arm item score = 2 but in-person screening showed little to no deficit in the UE. The next largest group, 7.6% were disqualified for being unable to consent because of language issues, inability to understand the consent process, or aphasia. Lastly, "prior stroke" disqualified 6.3% of the patients. Of all the moderately impaired patients (NIHSS = 2 or 3), the largest percentage (17.2%) were disqualified because of a prior stroke. The next largest group (14.9%) were disqualified because they arrived at inpatient rehabilitation "too late." Of all the severely impaired patients, the largest disqualification rate (33.3%) came from patients being too severe for the CPASS trial (enrolling mild-moderately impaired), and 24.2% of patients were disqualified for being "too late" to inpatient rehabilitation.

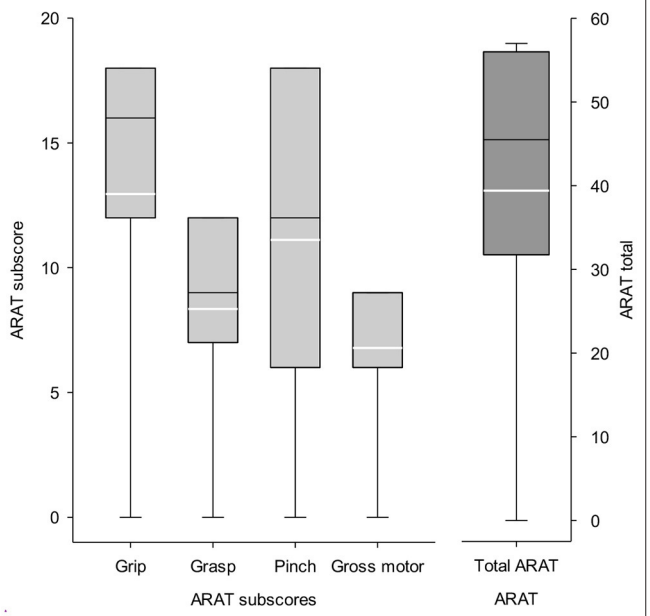


FIGURE 3 | ARAT scores in mildly impaired patients (NIHSS = 0 or 1). Left y-axis represents the ARAT sub scores for *grasp, grip, pinch, and gross*. Right y-axis shows the scale for ARAT total score (max = 57). Participants typically disqualified from a study seeking moderately impaired UE (NIHSS motor arm < 1) show potential for clinically meaningful recovery given their mean ARAT score = 39/57. White lines in boxplots show the mean score. There is some benefit in completing a motor specific screening like the ARAT for UE stroke rehabilitation trials to engage a subset of patients typically disqualified with the NIHSS screening criteria.

Screening With ARAT Instead of NIHSS Motor Arm Item Benefits Trial Recruitment

A large percentage of all patients admitted to acute care (64.8%) and inpatient rehabilitation (62.1%) that were screened for CPASS were disqualified for what would be classified as a "mildly impaired arm (NIHSS = 0 or 1)." These patients would be automatically disqualified from UE stroke rehabilitation trials if screening were completed using only the NIHSS motor arm item and CPASS-like rehabilitation trial Inclusion/Exclusion criteria. Given the large percentages disqualified due to a "too mild" score on NIHSS motor arm item, we evaluated if there is any added benefit in numbers of patients qualifying for a UE stroke study if screening were done using a dedicated motor function specific scale like the ARAT. The distribution of ARAT scores in a random selection of 389/438 patients screened at inpatient rehabilitation is shown in **Figure 3**. Mean ARAT score for the affected UE was 39.41±18.6, and 52.7±9.9 for the unaffected UE (max score = 57).

DISCUSSION

Of the 395 ischemic stroke patients screened in acute care over 18 months, 5.3% were enrolled in CPASS. On the inpatient rehabilitation side, of the 673 ischemic stroke patients screened over 22 months, 5% were enrolled in CPASS. These single-digit recruitment rates are comparable with major stroke rehabilitation trials. ICARE (5) recruiting patients in the subacute stage screened 11,051 patients to randomize 361 patients (recruitment rate of 3.2%), EXCITE recruiting patients in the subacute phase (14, 26) screened 3,626 patients to randomize 222 patients (6.1%), AVERT (17) screened 25,237 patients in the hyperacute stage, to randomize 2,104 (8.3%). Thus, trial recruitment rates have remained in the single-digits for a majority of large multisite stroke rehabilitation trials.

Randomized controlled trials are the gold standard for evaluating treatment effectiveness. Major stroke rehabilitation trials so far have shown only marginal effectiveness in improvement of motor function compared to the standard of care (2, 5, 27–36). In the US, a stroke occurs every 40 sec (37); most individuals survive but with long-term motor impairments that seriously limit independent living. Nearly two thirds of stroke survivors are unable to use their affected arm even at 6 months post stroke (38–40). Thus, there is an urgent need for effective UE neurorehabilitation. Single-digit recruitment rates significantly slow down translation of preclinical to phase II/III studies while increasing the costs of stroke rehabilitation trials. Stroke trial recruitment rates have remained unchanged, in single digits between 1990 and 2014 (41) necessitating a systematic examination of how specific trial inclusion/exclusion criteria affect recruitment.

Recruitment logistics for acute-and early subacute stroke rehabilitation trials (<30-days post) contrast sharply with conventional stroke rehabilitation trials typically conducted in the chronic phase (>6-months post-stroke). This early trial recruitment is challenging because patients are admitted for short duration (6–17 days). Patients' medical status changes rapidly during this time including their degree of motor arm impairment as shown by the large fractions of patients excluded because of a rapidly recovering UE. Correctly estimating if future motor impairment will be suitable for the trial, given patients' current motor function status is difficult (42, 43). This is especially relevant in the neurorehabilitation where interventions involve daily sessions for weeks and follow-ups at 12-months post-stroke (5, 7, 13–15, 26, 44).

Given the unique challenges in recruiting for neurorehab studies early after stroke, we presented prospectively collected estimates of how specific trial inclusion and exclusion criteria affect trial recruitment rates. Based on our data, we also provide recommendations for best practices in optimizing trial inclusion/exclusion criteria to strike a balance between trial generalizability and maintaining a homogenous enough sample in the trial (**Box 1**). Importantly, multisite trials need to conduct thorough screening of potential recruitment sites prior to commencing trials such as CPASS to ensure that the site has adequate patient throughput and to identify potential site-specific barriers to recruitment (2). Patients' length of stay, transfer from acute care to inpatient rehabilitation or community rehabilitation services affects access to patients for recruitment.

BOX 1 | Recommendations for best practices in screening for acute and early subacute trials.

1. Prescreening with a motor function specific tool like SAFE or ARAT may be better than NIHSS motor arm item alone, especially for the mildly impaired patients as it leads to a large percentage of exclusions.
2. Patients excluded for being too mild based on NIHSS criteria alone should be considered for inclusion in trials as their mean ARAT score (39.4±18.6) is substantially lower than the ARAT ceiling of 57. The difference between mean ARAT in mildly-impaired and ARAT's ceiling is greater than the ARAT MCID, suggesting these patients are likely to benefit from participating in the trial, and show clinically meaningful improvement.
3. Screening and recruitment efforts must begin in acute care as a large percentage arrive to inpatient rehabilitation too late to be enrolled in early stroke trials.
4. Prior strokes lead to a large percentage of exclusions. Trialists need a pragmatic definition for which patients should be excluded given the large percentages of second strokes. For phase II/III motor function intervention trials, "prior stroke without residual motor impairment" may be acceptable; translational neurophysiological studies may need prior strokes to be fully excluded.
5. Multisite trials selecting sites for trials need to evaluate screening data from local studies to determine site-specific barriers to recruitment, transfer from acute care to inpatient rehabilitation or community services which may enhance recruitment potential of a site.

In Acute Care: Short Length of Stay, mRS>1, and Prior Stroke Limit Recruitment

CPASS screening data from the acute care setting showed patients' length of stay varied from 6 days for the mildly impaired to 17 days for the severely impaired patients. On average, the moderately impaired were admitted for 13.6 days. A majority of these moderately-impaired (49%) were discharged to Inpatient rehabilitation, which opened another window to recruit them for stroke trials, but the remaining 32% discharged to home (15%) or to a skilled nursing facility (17%) would be lost to recruitment forever unless a trial developed extensive outreach resources to recruit them from the community. These lengths of stay and discharge data are specific to an urban safety net hospital in the US where CPASS screening was conducted. Similar exhaustive data on recruitment for rehabilitation trials from across the US are missing at this time. Recently [29)], screening for acute stroke patients at the University Hospital Zurich in Switzerland reported on the eligibility criteria for a comparable UE trial. The typical length of stay (mean = 8; range 4–12 days; not stratified by severity as in the present report) was consistent with the brief length of stay we found with CPASS screening. It is critical for early stroke rehabilitation trials to develop efficient screening methods to rapidly identify eligible patients at the earliest time point after stroke. Other exclusion criteria that led to most exclusions in acute care included "rapidly improving motor function," "unable to follow two-step commands," "prior stroke," and "modified Rankin score (mRS)>1;" many of these are unmodifiable. Prior stroke led to exclusion of a large proportion of potentially eligible patients in our cohort. Similar findings have been reported in the European setting, 17% excluded due to "recurrent stroke" (45). Given the incidence of recurrent and silent strokes, a judicious definition of "prior stroke" is necessary to not miss out on an otherwise large majority of eligible participants. For motor function studies, "prior strokes without residual impairment" may be an acceptable definition, although these depend on the specific research questions and trial phase. Similarly, a blanket exclusion based on mRS may be impractical for stroke rehabilitation trials since nearly 20% of all moderately impaired individuals were disqualified due to this single exclusion criteria.

In Inpatient Rehabilitation: Too Mild, Prior Stroke, Arriving to Rehabilitation Too Late for The Study

A large fraction of patients screened at inpatient rehabilitation were excluded because they were already out of the enrollment window when they arrived at the inpatient facility. CPASS enrolled patients <30-days post stroke, nearly 12% were disqualified because they could not be identified as eligible within this timeframe. Thus, it is recommended to screen eligible patients while they are still admitted to acute care; it is crucial to develop streamlined screening, chart review, and identification of potentially eligible patients at the earliest. Inability to consent due to language or aphasia led to another potentially modifiable exclusion criteria (7% in mildly impaired; 9% in severely impaired).

Nearly 62% of individuals with ischemic stroke arriving to inpatient rehabilitation were "too mild" (NIHSS motor arm item<1) for an early neurorehabilitation trial and thus disqualified from CPASS. Given the large percentage disqualified due to this single exclusion criteria, we examined patients' arm impairment using a dedicated motor function impairment test, the ARAT. ARAT evaluates fine motor function and reaching to grasp and ARAT sub-scores are highly relevant to UE stroke trials. The mean ARAT score in this cohort was 39.41±18.6 (max = 57). The minimal clinically important difference (MCID), the minimal change in score for patients to perceive an improvement in their UE motor function with the ARAT is 5.7 points (46). Thus, although classified ineligible, individuals with an NIHSS motor arm score <1 show potential for UE motor recovery and are not at the ceiling of their UE motor function. Trials may benefit from performing additional screening using a motor function-specific measure like the ARAT or SAFE for a subset of individuals. This is particularly important because prior studies have also highlighted that disqualifying "too mild" impairment in stroke trials excludes large proportions of stroke patients (41, 45). Alternately, motor-specific (pre-screening) measures such as the SAFE score have shown good predictive validity at 1 year and may be more sensitive than the NIHSS motor item score or mRS in the context of UE neurorehabilitation trials (47, 48). Similar screening data (as presented in the present report) from trials implementing the SAFE score as a prescreening measure for trial recruitment will fill an important gap for trialists. Our data on NIHSS and ARAT highlight the need for a simple, quick, motor-function specific prescreening tool that is sensitive throughout the range of UE motor impairment and shows

good predictive validity for motor outcomes at 12-months or more post stroke (the typical primary outcome in post-stroke UE trials).

LIMITATIONS

Although we present a first set of exhaustive data on trial recruitment statistics in an early subacute stroke rehabilitation trials in the US, it must be noted that these recruitment data come from a single-site phase II stroke trial. Patients were screened at a single site, an urban safety net hospital and inpatient rehabilitation facility and as such is limited to trial recruitment and patient behaviors within the US. Generalizability to other recruitment settings needs more data. Patients were screened using the motor arm item of the NIHSS, which was adequate for CPASS inclusion/exclusion criteria as shown by CPASS recruitment rates that remained comparable to similar trials, but trialists should consider adding a more sensitive motor-specific screening tool such as the SAFE score or ARAT given the relatively large numbers of patients' with demonstrated impairment on the ARAT excluded from the trial for being "too mild."

CONCLUSIONS

A large percentage of trial eligible patients are excluded because trialists do not get to patients in time, before discharge from acute care, and patients arrive to inpatients rehabilitation too late for trial recruitment. Trialists performing early stroke rehabilitation trials therefore need to develop streamlined screening and recruitment pipeline to engage patients while they are still in acute care. For a subset of mildly impaired patients, trialists will benefit from performing a motor function specific test like the ARAT in addition to using the NIHSS motor arm item during in-person screening for a subset of patients.

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 human participants were reviewed and approved by the Institutional Review Board at the MedStar Health Research Institute. The trial was registered at http://www.clinicaltrials.gov (Identifier: NCT02235974). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG, PF, DE, and AD conceived the research. SG conducted the research. SG, AD, and DE interpreted the findings. SG, PF, DE, and AD wrote and approved the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by NINDS StrokeNet SCANR grant 1U10NS086513-01, American Heart Association 17POST33410485, NICHD/NCMRR K12HD093427, and the Greenberg Family Foundation.

REFERENCES

1. Cramer SC. The EXCITE trial: a major step forward for restorative therapies in stroke. *Stroke.* (2007) 38:2204–5. doi: 10.1161/STROKEAHA.107.486555
2. Dromerick AW, Lang CE, Birkenmeier RL, Wagner JM, Miller JP, Videen TO, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology.* (2009) 73:195–201. doi: 10.1212/WNL.0b013e3181ab2b27
3. Alcobendas-Maestro M, Esclarin-Ruz A, Casado-Lopez RM, Munoz-Gonzalez A, Perez-Mateos G, Gonzalez-Valdizan E, et al. Lokomat robotic-assisted versus overground training within 3 to 6 months of incomplete spinal cord lesion: randomized controlled trial. *Neurorehabil Neural Rep.* (2012) 26:1058–63. doi: 10.1177/1545968312448232
4. Nadeau SE, Wu SS, Dobkin BH, Azen SP, Rose DK, Tilson JK, et al. Effects of task-specific and impairment-based training compared with usual care on functional walking ability after inpatient stroke rehabilitation: LEAPS trial. *Neurorehabil Neural Repair.* (2013) 27:370–80. doi: 10.1177/1545968313481284
5. Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, et al. Effect of a task-oriented rehabilitation program on upper extremity recovery following motor stroke: the ICARE randomized clinical trial. *JAMA.* (2016) 315:571–81. doi: 10.1001/jama.2016.0276
6. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke Part I: outcome the copenhagen stroke study. *Arch Phys Med Rehabil.* (1995) 76:399–405. doi: 10.1016/S0003-9993(95)80567-2
7. Dromerick AW, Edwardson MA, Edwards DF, Giannetti ML, Barth J, Brady KP, et al. *Critical Periods After Stroke Study: A phase II trial.* Netherlands: Congress on Neurorehabilitation and Neural Repair, Maastrecht (2015).
8. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair.* (2012) 26:923–31. doi: 10.1177/1545968312440745
9. Biernaskie J, Chernenko G, Corbett D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J Neurosci.* (2004) 24:1245–54. doi: 10.1523/JNEUROSCI.3834-03.2004
10. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *Neurorehabil Neural Repair.* (2017) 31:793–9. doi: 10.1177/1545968317732668
11. Bernhardt J, Borschmann K, Boyd L, Carmichael ST, Corbett D, Cramer SC, et al. Moving rehabilitation research forward: developing consensus statements for rehabilitation and recovery research. *Neurorehabil Neural Repair.* (2017) 31:694–8. doi: 10.1177/1545968317724290
12. Briggs DE, Felberg RA, Malkoff MD, Bratina P, Grotta JC. Should mild or moderate stroke patients be admitted to an intensive care unit? *Stroke.* (2001) 32:871–6. doi: 10.1161/01.STR.32.4.871
13. Wolf SL, Winstein CJ, Miller JP, Thompson PA, Taub E, Uswatte G, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. *Lancet Neurol.* (2008) 7:33–40. doi: 10.1016/S1474-4422(07)70294-6

14. Wolf SL, Thompson PA, Winstein CJ, Miller JP, Blanton SR, Nichols-Larsen DS, et al. The EXCITE stroke trial: comparing early and delayed constraint-induced movement therapy. *Stroke.* (2010) 41:2309–15. doi: 10.1161/STROKEAHA.110.588723
15. Lang KC, Thompson PA, Wolf SL. The EXCITE trial: reacquiring upper-extremity task performance with early versus late delivery of constraint therapy. *Neurorehabil Neural Repair.* (2013) 27:654–63. doi: 10.1177/1545968313481281
16. Lasagna L. Problems in publication of clinical trial methodology. *Clin Pharmacol Ther.* (1979) 25 (5 Pt 2):751–3. doi: 10.1002/cpt1979255part2751
17. Kasenda B, Von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA.* (2014) 311:1045–52. doi: 10.1001/jama.2014.1361
18. Edwardson MA, Zhong X, Fiandaca MS, Federoff HJ, Cheema AK, Dromerick AW. Plasma microRNA markers of upper limb recovery following human stroke. *Sci Rep.* (2018) 8:12558. doi: 10.1038/s41598-018-31020-5
19. Cramer SC, Wolf SL, Adams Jr HP, Chen D, Dromerick AW, Dunning K, et al. Stroke recovery and rehabilitation research: issues, opportunities, and the national institutes of health stroke net. *Stroke.* (2017) 48:813–9. doi: 10.1161/STROKEAHA.116.015501
20. Brott T, Adams Jr HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
21. Lang CE, Wagner JM, Dromerick AW, Edwards DF. Measurement of upper-extremity function early after stroke: properties of the action research arm test. *Arch Phys Med Rehabil.* (2006) 87:1605–10. doi: 10.1016/j.apmr.2006.09.003
22. McDonnell M. Action research arm test. *Aust J Physiother.* (2008) 54:220. doi: 10.1016/S0004-9514(08)70034-5
23. Nordin A, Alt Murphy M, Danielsson A. Intra-rater and inter-rater reliability at the item level of the action research arm test for patients with stroke. *J Rehabil Med.* (2014) 46:738–45. doi: 10.2340/16501977-1831
24. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair.* (2008) 22:78–90. doi: 10.1177/1545968307305353
25. Dromerick AW, Edwards DF, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? *Stroke.* (2000) 31:2984–8. doi: 10.1161/01.STR.31.12.2984
26. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA.* (2006) 296:2095–104. doi: 10.1001/jama.296.17.2095
27. Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet.* (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0
28. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Eng J Med.* (2010) 362:1772–83. doi: 10.1056/NEJMoa0911341
29. Yelnik AP, Quintaine V, Andriantsifanetra C, Wannepain M, Reiner P, Marnef H, et al. AMOBES (active mobility very early after stroke): a randomized controlled trial. *Stroke.* (2017) 48:400–5. doi: 10.1161/STROKEAHA.116.014803
30. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of unilateral upper limb training in two distinct prognostic groups early after stroke: the EXPLICIT-stroke randomized clinical trial. *Neurorehabil Neural Repair.* (2016) 30:804–16. doi: 10.1177/1545968315624784
31. Cramer SC, Dodakian L, Le V, See J, Augsburger R, McKenzie A, et al. Efficacy of home-based telerehabilitation vs in-clinic therapy for adults after stroke: a randomized clinical trial. *JAMA Neurol.* (2019) 76:1079–87. doi: 10.1001/jamaneurol.2019.1604
32. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. *Lancet.* (2019) 394:51–62. doi: 10.1016/S0140-6736(19)31055-4
33. Saposnik G, Cohen LG, Mamdani M, Pooyania S, Ploughman M, Cheung D, et al. Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. *Lancet Neurol.* (2016) 15:1019–27. doi: 10.1016/S1474-4422(16)30121-1
34. Pomeroy VM, Hunter SM, Johansen-Berg H, Ward NS, Kennedy N, Chandler E, et al. Functional strength training versus movement performance therapy for upper limb motor recovery early after stroke: a RCT. *Effic Mechan Eval.* (2018) 5:1–112. doi: 10.3310/eme05030
35. Brunner I, Skouen JS, Hofstad H, Aßmus J, Becker F, Sanders AM, et al. Virtual reality training for upper extremity in subacute stroke (VIRTUES): a multicenter RCT. *Neurology.* (2017) 89:2413–21. doi: 10.1212/WNL.0000000000004744
36. Adie K, Schofield C, Berrow M, Wingham J, Humfryes J, Pritchard C, et al. Does the use of Nintendo Wii Sports(TM) improve arm function? Trial of Wii(TM) in stroke: a randomized controlled trial and economics analysis. *Clin Rehabil.* (2017) 31:173–85. doi: 10.1177/0269215516637893
37. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation.* (2020) 141:e139–596. doi: 10.1161/CIR.0000000000000757
38. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke.* (2003) 34:2181–6. doi: 10.1161/01.STR.0000087172.16305.CD
39. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke Part II: time course of recovery the copenhagen stroke study. *Arch Phys Med Rehabil.* (1995) 76:406–12. doi: 10.1016/S0003-9993(95)80568-0
40. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Stroke: neurologic and functional recovery the copenhagen stroke study. *Physical Med Rehab Clin.* (1999) 10:887–906. doi: 10.1016/S1047-9651(18)30169-4
41. Feldman WB, Kim AS, Chiong W. Trends in recruitment rates for acute stroke trials 1990–2014. *Stroke.* (2017) 48:799–801. doi: 10.1161/STROKEAHA.116.014458
42. Kwah LK, Herbert RD. Prediction of walking and arm recovery after stroke: a critical review. *Brain Sci.* (2016) 6:53. doi: 10.3390/brainsci6040053
43. Hawe RL, Scott SH, Dukelow SP. Taking proportional out of stroke recovery. *Stroke.* (2018) 50:204–11. doi: 10.1161/STROKEAHA.118.023006
44. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, et al. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. *Stroke.* (2011) 42:153–8. doi: 10.1161/STROKEAHA.110.594598
45. Held JP, van Duinen J, Luft AR, Veerbeek JM. Eligibility screening for an early upper limb stroke rehabilitation study. *Front Neurol.* (2019) 10:683. doi: 10.3389/fneur.2019.00683
46. Lang CE, Edwards DF, Birkenmeier RL, Dromerick AW. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehabil.* (2008) 89:1693–700. doi: 10.1016/j.apmr.2008.02.022
47. Stinear CM, Byblow WD, Ackerley SJ, Barber PA, Smith MC. Predicting recovery potential for individual stroke patients increases rehabilitation efficiency. *Stroke.* (2017) 48:1011–9. doi: 10.1161/STROKEAHA.116.015790
48. Lang CE, DeJong SL, Beebe JA. Recovery of thumb and finger extension and its relation to grasp performance after stroke. *J Neurophysiol.* (2009) 102:451–9. doi: 10.1152/jn.91310.2008

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.

frontiers in Neurology

CASE REPORT
published: 12 July 2021
doi: 10.3389/fneur.2021.680733

A Case Report: Effect of Robotic Exoskeleton Based Therapy on Neurological and Functional Recovery of a Patient With Chronic Stroke

Neha Singh[1], *Megha Saini*[1], *Nand Kumar*[2], *M. V. Padma Srivastava*[3], *S. Senthil Kumaran*[4] *and Amit Mehndiratta*[1,5]*

[1] Centre for Biomedical Engineering, Indian Institute of Technology Delhi (IITD), New Delhi, India, [2] Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi, India, [3] Department of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, India, [4] Department of Nuclear Medicine and Resonance, All India Institute of Medical Sciences (AIIMS), New Delhi, India, [5] Department of Biomedical Engineering, All India Institute of Medical Sciences (AIIMS), New Delhi, India

OPEN ACCESS

Edited by:
Caterina Pistarini,
Istituti Clinici Scientifici Maugeri (ICS Maugeri), Italy

Reviewed by:
Niamh C. Kennedy,
Ulster University, United Kingdom
Der-Sheng Han,
National Taiwan University Hospital, Taiwan

***Correspondence:**
Amit Mehndiratta
amit.mehndiratta@keble.oxon.org

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 15 March 2021
Accepted: 17 May 2021
Published: 12 July 2021

Citation:
Singh N, Saini M, Kumar N, Srivastava MVP, Kumaran SS and Mehndiratta A (2021) A Case Report: Effect of Robotic Exoskeleton Based Therapy on Neurological and Functional Recovery of a Patient With Chronic Stroke. Front. Neurol. 12:680733. doi: 10.3389/fneur.2021.680733

Background: In this study, a novel electromechanical robotic exoskeleton was developed for the rehabilitation of distal joints. The objective was to explore the functional MRI and the neurophysiological changes in cortical-excitability in response to exoskeleton training for a 9-year chronic stroke patient.

Case-Report: The study involved a 52-year old female patient with a 9-year chronic stroke of the right hemisphere, who underwent 20 therapy sessions of 45 min each. Cortical-excitability and clinical-scales: Fugl-Mayer (FM), Modified Ashworth Scale (MAS), Brunnstrom-Stage (BS), Barthel-Index (BI), Range of Motion (ROM), were assessed pre-and post-therapy to quantitatively assess the motor recovery.

Clinical Rehabilitation Impact: Increase in FM wrist/hand by 6, BI by 10, and decrease in MAS by 1 were reported. Ipsilesional Motor Evoked Potential (MEP) (obtained using Transcranial Magnetic Stimulation) was increased by 98 μV with a decrease in RMT by 6% and contralesional MEP was increased by 43 μV with a decrease in RMT by 4%. Laterality Index of Sensorimotor Cortex (SMC) reduced in precentral- gyrus (from 0.152 to −0.707) and in postcentral-gyrus (from 0.203 to −0.632).

Conclusion: The novel exoskeleton-based training showed improved motor outcomes, cortical excitability, and neuronal activation. The research encourages the further investigation of the potential of exoskeleton training.

Keywords: case report, robotic exoskeleton, stroke, rehabilitation, electromyogram, cortical excitability, fMRI

INTRODUCTION

Post-stroke motor recovery follows a non-linear trajectory (1). Although, there is a period of enhanced plasticity or spontaneous recovery of motor function following a stroke, it is insufficient and often negligible in patients with chronic-stroke. Intensive therapeutic and rehabilitative interventions primarily lead to functional restoration in chronic-stroke survivors (2). While research studies have explored neuronal and motor recovery, patients with chronic-stroke often manifest long-term disability and limitations in the activities of daily living (3). The exact behavior of neurophysiological aspects at a neuronal level showing enhanced responsiveness to treatment in chronic-stroke is not clear yet (1).

Robotic-training for physical therapy is now becoming a new normal for the rehabilitation community (4). It might share a good amount of the clinical load of the therapist and can substantially facilitate the phenomenon of functional neuro-rehabilitation and recovery. An electro-mechanical robotic-exoskeleton was developed for distal joints that synchronize wrist-extension with Metacarpophalangeal (MCP) flexion and wrist-flexion with MCP-extension (4). The exoskeleton targets spasticity through a synergy-based rehabilitation approach while also maintaining patient-initiated therapy through residual muscle activity using Electromyogram (EMG) for maximizing voluntary effort. Here, we present the case of a 52-year old female with late chronic-stroke of 9 years, who had a partial recovery, and its convergent association of potential brain reorganization in response to the novel exoskeleton. The objective of this case study was to explore the neurophysiological repertoire of behavior behind motor recovery in response to the goal-directed treatment using exoskeleton for a patient with chronic-stroke.

CASE DESCRIPTION

The Institutional Review Board (IRB) at the All India Institute of Medical Sciences, New Delhi, India approved the study (protocol number: IEC/NP-99/13.03.2015). The patient provided written informed consent before enrolling in the study.

Patient

The 52-year old female patient (right-handed) is henceforth referred to as Mrs. X. She was well-educated and an airline pilot by profession. She has a family history of stroke; her mother suffered from a stroke. There was no other relevant genetic or psychosocial history. She survived acute right Anterior Cerebral Artery (ACA) and Middle Cerebral Artery (MCA) ischemic infarct and a small left ACA infarct in April 2009. She was conscious at the time of stroke onset. She was immediately admitted to ICU in a local hospital in Delhi. She was conscious, oriented, and cooperative. Her MRA, MRV, and neck angio, ECG, ECHO, and Holter monitoring were normal. She had gaze preference to right. After 2.5 h of admission, she developed jerky movements in the left upper-limb and was loaded with injection epsolin 1,000 mg. The infarct resulted in left hemiparesis, less control, and functional outcomes in the left-limb with power-0/5. The power in the right-limb was 5/5. She also presented left facial palsy, weak left eye closure, and slurring of speech. She did not have health issues like hypertension, diabetes, tobacco smoking, or alcohol but had a history of diabetes in the family (mother).

She was moved to the ward after 4 days and discharged to home in stable condition after 15 days. She was on antiplatelet therapy for 5 years and later she continued prophylactic antiplatelet therapy (details in **Supplementary Material**). She underwent physiotherapy immediately following her discharge and had acupressure-therapy, acupuncture-therapy, home-based exercises for an initial few (∼5) years before enrolling in this study, (Timeline **Figure 1**, full details in **Supplementary Material**).

At the enrolment in 2018, the volume of the lesion was 11.72 cm^3, Edinburg laterality-index was 90 (non-dominant hand affected) and Mini-Mental Score Examination (MMSE) was 30. She was given physiotherapy exercises for home (details in **Supplementary Material**). The patient scored Modified Ashworth-Scale (MAS) 2 at wrist-joint, Brunnstrom Stages (BS) 4, Modified Rankin Scale (MRS) 2, Barthel Index (BI) 85, upper-limb Fugl Meyer (FM) scale 43/66, lower-limb FM scale 29/34, at wrist joint Passive ROM (PROM) 45°, and Active ROM (AROM) 25°.

Therapy Protocol

Robotic-Therapy-Sessions

The device (**Supplementary Figure 1**) is actively initiated by EMG activity of Extensor Digitorum Communis (EDC) muscle with robot motion triggered only if the EMG thresholds are crossed and it provides an interactive adaptive performance visual biofeedback in real-time. At baseline position, the patient tries to extend the wrist voluntarily for the first 3 s after the green LED cue. If the EMG crosses the predefined threshold, the exoskeleton will be triggered for an assisted wrist extension and finger flexion movement. Once it reaches the final position, the exoskeleton then assists the patient's hand back to the baseline position, wrist flexion with finger extension. Simultaneous with this motion assistance, the performance feedback is given to the patient in real-time. The device was patient-specific as has flexibility in accommodating patients as per the varying clinical presentation, with customizable motion-parameters: (i) initial-position for a range of motion (ROM), (ii) final-position for ROM, (iii) speed, (iv) residual muscle-activity, and (v) height of finger-support (4). It is a simple and easy-to-operate exoskeleton with a user friendly interface of LCD and knobs for inputs, as presented in the device paper by Singh et al. (4). The configurability of the threshold was adjusted during the study manually and individually using the BIOPAC MP150 EMG acquisition software according to the residual EMG activity of an individual patient with the advantage of making the system patient-specific by including patients with minimal residual muscle-activity in the protocol. Pre to post-therapy, the amplitude of the EMG threshold changed from 0.4 to 0.6 V (amplified with gain = 2,000, Band Pass Filter = 10–500 Hz, Notch Filter = 50 Hz, Sampling Frequency = 1,000 Hz) (4).

Robotic training was given for 45-min a day for 20 sessions, with ∼250 trials of 10 s each undertaken (4). The therapy sessions were given by the trained physiotherapists with more than 5

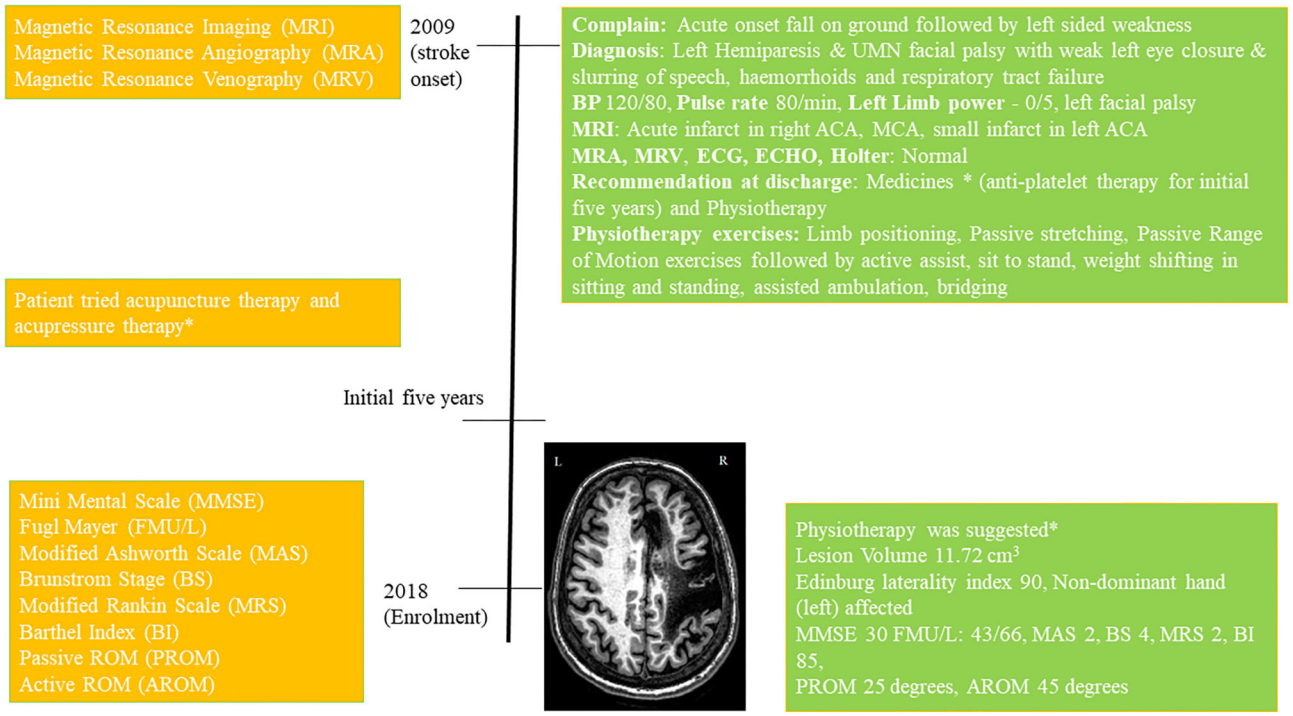


FIGURE 1 | Timeline with relevant data from the episode of care, *details in **Supplementary Material**.

years of experience in stroke rehabilitation. Mrs. X completed this therapy in clinical settings in 31-days with pre-to-post-therapy clinical data acquired on day-1 and day-32, respectively. She adhered well to the therapy and tolerated therapy with no adverse effects. There was no change in the therapy session for the whole 20 sessions. As the device is easy to operate, she took interest in operating it on her own. The patient's peripheral vision was very strong, probably because of her occupation (airline pilot by profession) and she was able to see visual feedback even when she was not actively watching it. Though, she had no contractures, she chose 45° as range-of-motion (ROM) on day-1 with speed being constant (30°/s), as she felt comfortable. Due to flexor-hypertonia, active-ROM (AROM) of the wrist was 30°, started from −5° flexion to 25° extension. While wearing the robotic exoskeleton in baseline position with wrist and fingers tied up with Velcro-straps, her wrist was maintained at −5° flexion. The time required by the patient to put the exoskeleton on was 105-s and taking off the exoskeleton took 22-s on day 1.

Pre and Post-therapy Clinical-Data Acquisition

Clinical scales including MAS, BS, MRS, BI, FM scale, Passive ROM, and Active ROM, were acquired at day 1 and day 32. On day-32, a self-designed subjective feedback-form, and System Usability Scale (SUS), and question-answer session were also undertaken to gain the patient's perspective of the device (**Supplementary Tables 1, 2** and Subjective Questions). SUS form, a standard reliable method for measuring product usability of a novel developed product across a wide range of industries (5), was also obtained from the patient. The SUS scores ranged from 80 to 100, a score of 87.5 from the patient, reflecting the promising scope of "acceptance" and usability from the patient score, which ranged from 80 to 100 (**Supplementary Table 2**).

Mrs. X was compliable with Transcranial Magnetic Stimulation (TMS). Single-pulse TMS stimuli were applied at 100% Motor Threshold with the procedure widely used (6), using a flat 70 mm figure-of-eight coil [type-D70 (AC), Magstim Rapid^2, UK] from EDC muscle (Details in **Supplementary Material**). Five MEP signals out of 10 consecutive trials were averaged. Cortical-excitability measures, Resting Motor-Threshold (RMT), and Motor Evoked Potential (MEP) on cortical representation area of EDC muscle on the ipsilesional and contralesional-hemisphere, were obtained as per the procedure described in the literature including our previous study (6).

Structural T1 image (**Supplementary Figure 2**) and fMRI BOLD images were acquired for affected and unaffected hand movement, using 3T MR-scanner (Achieva 3T TX, M/s. Philips Healthcare). Patient repeated self-paced sequential-maximum extension and flexion of the wrist in block-design paradigm using the affected and unaffected hand (separately). Data-analysis (in SPM12) included realignment by aligning images to mean-image, co-registration using T1-image, normalized and smoothing with 8 × 8 × 8 Full Width at Half-Maximum (FWHM) filter on pre- and post-BOLD acquisitions. The Talairach client was used to correlate the MNI coordinates for further analysis.

Clinical Rehabilitation Impact

The protocol was smooth and Mrs. X tolerated the therapy sessions well and had no complaints. An SUS score value of 87.5,

TABLE 1 | Details of clinical scales, cortical excitability measures.

Clinical scales	Pre	Post	Difference	Cortical excitability	Pre	Post	Difference
FM	43	52	9 (↑)	Ipsilateral MEP (μV)	108	206	98 (↑)
FM (W/H)	9	15	6 (↑)				
F M (S/E)	34	37	3 (↑)	Ipsilateral RMT (%)	85	79	6 (↓)
MAS	2	1	1 (↓)				
BS	4	4	0	Contralateral MEP (μV)	84	127	43 (↑)
BI	85	95	10 (↑)				
MRS	2	2	0	Contralateral RMT (%)	80	76	4 (↓)
AROM	*25°	**30°	5° (↑)				
PROM	45°	60°	15° (↑)	Normalization (RMT ratio)	1.062	1.039	0.023 (↓)

FMA (max 66): Fugl-Meyer Assessment, FM W/H (max 24): Wrist / Hand component of FMA, S/E (max 42): Shoulder/Elbow component of FMA, MAS (0–4): Modified Ashworth Score, BS (max 7): Brunnstrom Stages, BI (max 100): Barthel Index, MRS (max 5): Modified Rankin Scale, Passive ROM (max 70): Active ROM (max 70), MEP: Motor Evoked Potential (in μV), RMT: Resting Motor threshold (in %, max 100), Normalization (RMT ratio) = Ipsilateral RMT/Contralateral RMT.

**Starts from −5° wrist flexion.*

***Starts from 0°, (↑) indicates increase, (↓) indicates decrease.*

subjective feedback, and questions-answers were obtained after 20 sessions (**Supplementary Tables 1, 2**).

Clinical Scores

Clinical scales and cortical-excitability measures for the patient pre-and post-therapy are outlined in **Table 1**. The reduction in impairment was quantitatively observed to be increased in upper-limb FM scale value by 9 units, an increase in the distal-component of FMW/H was 6 units. Spasticity decreased from the MAS value from 3 to 2 (**Table 1**). BI increased from a value of 85 to 95 with no change in BS and Mrs. X PROM was observed to improve by 15° at wrist joint. AROM was observed to increase by 5° at wrist joint. Pre-therapy, she used to start wrist-flexion from −5°, however, in post-therapy-sessions she was able to start the wrist-extension from 0° only, because of release in flexor hypertonia. After the 20th therapy session, she had set the ROM of the robotic-exoskeleton at 60° (day-1 ROM 45°) at the same speed.

Cortical-Excitability Measures

Pre- to post-therapy, the ipsilesional RMT was decreased by 6%, and MEP amplitude was increased by 98 μV with muscle contraction response being observed in the dorsal wrist and third digit in more than 5 out of 10 consecutive attempts. Pre to post-therapy, the contralesional RMT decreased by 4%, and MEP amplitude increased by 43 μV with muscle contraction response observed in the dorsal wrist (**Table 1**). The relative % change, expressed in terms of percentages as the ratio of the difference between post-therapy and pre-therapy scales normalized to their pre-therapy scales, pre to post-therapy, for MEP amplitude showed a 90.7% increase for ipsilateral-hemisphere and 51.1% increase for the contralateral-hemisphere, and for RMT was 7% decrease for ipsilateral-hemisphere and 5% decrease for the contralateral-hemisphere. RMT-asymmetry, a ratio of ipsilateral RMT and contralateral RMT, indicated a trend towards normality (close to 1) decreasing from 1.062 to 1.039 post-therapy (**Table 1**).

fMRI Measures

Post-therapy, during the affected-hand trial, the number of activated voxels were observed to substantially decrease in ipsilesional sensorimotor-cortex (SMC) - precentral (from 1346 to 114) and postcentral-gyrus (from 914 to 100) (**Figure 2**, **Table 2**). Reduction in contralesional precentral (from 991 to 665) and postcentral-gyrus (from 605 to 444) were also observed. Though, there was a decrease in ipsilateral activated voxels, a considerable reduction in Laterality-index (LI), ranged from 1.0 (all contralateral activation) to −1.0 (all ipsilateral activation), of sensorimotor-cortex (SMC) was also observed in precentral (from 0.152 to −0.707) and postcentral-gyrus (from 0.203 to −0.632). This decrease in laterality index demonstrates a substantial decrease in the number of contralateral activated voxels. A large activation increase in ipsilateral-cerebellum (CBM) exterior (from 1908 to 3395) and a decrease in contralateral-CBM exterior (from 4502 to 2261) was observed post-therapy. An activation decrease in contralateral CBM white-matter (from 999 to 462) was also observed. Ipsilateral cerebellum-ratio was observed to substantially increase in CBM exterior (from 0.298 to 0.6) and CBM white-matter (0.528 to 0.69), indicating an increased ipsilateral CBM activation.

Post-therapy, during the unaffected hand trial, the number of activated voxels were decreased in contralateral/contralesional SMC - precentral (from 930 to 168) and postcentral-gyrus (from 655 to 58) (**Figure 2**, **Table 2**). Reduction in ipsilateral/ipsilesional precentral (from 247 to 0) and postcentral-gyrus (from 13 to 0) were also observed. With ipsilateral voxels reduced to zero, the LI of the SMC was observed to increase in precentral (from 0.58 to 1) and postcentral-gyrus (from 0.961 to 1). Ipsilateral cerebellum-ratio was observed to decrease in the CBM exterior (from 0.98 to 0.94) and CBM white-matter (from 1 to 0.91).

DISCUSSION

Changes in Clinical Scores

Mrs. X demonstrated a substantial reduction in impairment as seen with the improvement in clinical scales: increase in FMU/L by 9, BI by 10, and decrease in MAS by 1. Out of a total 9 units increase in FMU/L, the Wrist/Hand component of FM increased by 6 units indicating an enhanced distal functionality

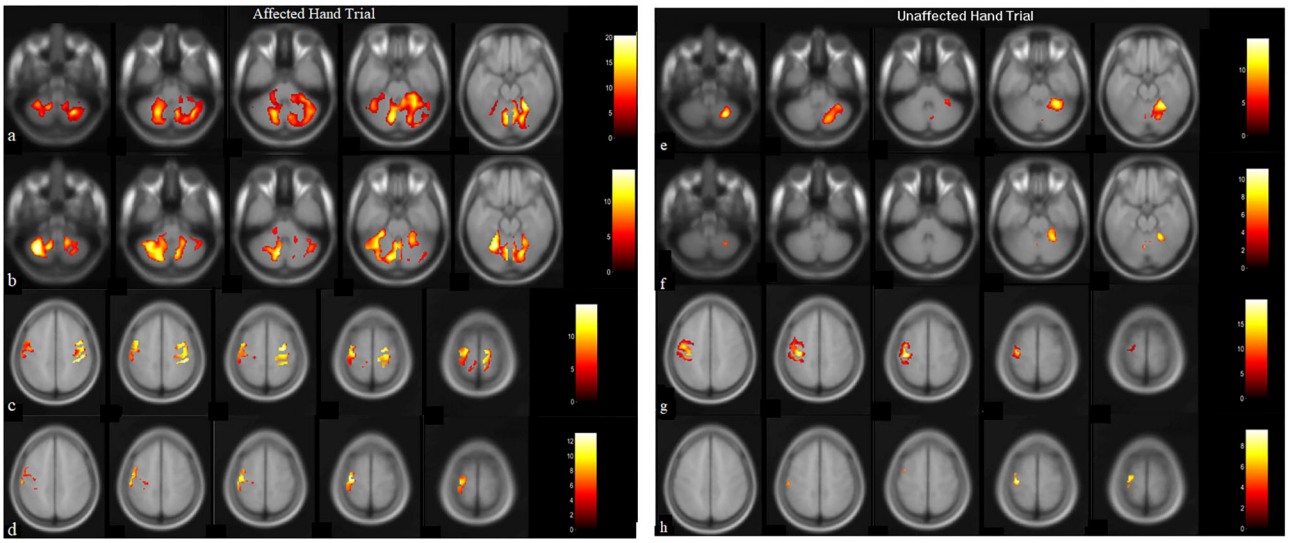


FIGURE 2 | BOLD images for wrist extension task with voxel level threshold $p < 0.05$ (FWE-corrected) and cluster size threshold of 10 voxels. Thirty-one ascending transversal slices, repetition time (TR): 2,000 ms, field of view (FOV): 230 × 230 × 155 mm, Flip-angle: 90 degrees, voxel size: 1.8 × 1.8 × 5 mm and echo time (TE) = 30 ms. Presentation on MR compatible 20" LCD monitor (Esys *in vivo* eprime 1.1) with projection on mirror attached to head coil where image-of-hand notifies the active-block and cross on image-of-hand represents the rest-block. Data-analysis (in SPM12) included realignment by aligning images to mean-image, co-registration using T1-image, normalized, and smoothing with 8 × 8 × 8 Full Width at Half-Maximum (FWHM) filter on pre and post-BOLD images. Talairach-client was used to correlate MNI-coordinates with gray and white matter. **(a,c)** are pre-robotic training images, **(b,d)** are post-robotic training images during affected-hand trial, **(e,g)** are pre-robotic training images and, **(f,h)** are post-robotic training images of masked regions cerebellum (−52:8: −20 slices) and sensorimotorcortex (48:6:72 slices) during the unaffected-hand trial ($p < 0.05$).

TABLE 2 | Pre and post-robotic sessions Blood Oxygen Level Dependent (BOLD) activation pattern in affected and unaffected hand trials in mask regions.

Mask regions	Pre-therapy					Post-therapy				
	No. of voxels	Threshold	No. of voxels	Threshold	LI/Ips CB ratio	No. of voxels	Threshold	No. of voxels	Threshold	LI/Ips CB ratio
Task by the affected hand										
Hemisphere	Right		Left			Right		Left		
Precentral gyrus	1,346	14	991	14.8	0.152	114	9.4	665	13.1	−0.707
Postcentral gyrus	914	14.2	605	9.5	0.203	100	9.7	444	10.9	−0.632
CBM exterior	4,502	20.3	1,908	17.5	0.298	2,261	12.3	3,395	14.5	0.6
CBM white matter	999	15.2	1,116	17.1	0.528	462	10.2	1,030	13.6	0.69
Task by the unaffected hand										
Precentral gyrus	247	8.6	930	19.9	0.580	0	0	168	9.5	1
Postcentral gyrus	13	5.5	655	17.4	0.961	0	0	58	6.2	1
CBM exterior	1,760	14.7	27	7.6	0.98	341	11.1	19	6.7	0.94
CBM white matter	320	9.7	0	0	1	83	7.7	8	5.2	0.91

CBM, Cerebellum; Laterality Index (LI) = (contralateral voxels – Ipsilateral voxels)/(contralateral voxels + Ipsilateral voxels); Ipsilateral cerebellum (Ips CBM) ratio = Ipsilateral cerebellum voxels/(Ipsilateral cerebellum voxels + Contralateral cerebellum voxels).

post-therapy. As shown in the studies by Gladstone et al. (7) and Shin et al. (8), a value of 6.6 on a scale of 66 (FMU/L) reflects the potential Minimally Clinically Important Difference (MCID) and in this study, FMU/L and FMW/H reached the MCID. An increase in passive and active ROM gave increased the degree of movement in the wrist to confidently participate in ADL, as evidenced by an increase in BI by 10 units. She was able to do activities such as opening and closing clips (for drying clothes), held the plates straight while carrying them, etc., which she was not able to do pre-therapy.

Changes in Cortical-Excitability

An increase in cortical-excitability in both hemispheres might suggest an increase in neuroplasticity and motor-cortex excitability in terms of a decrease in RMT and an increase in MEP amplitude for EDC muscle cortical-representation

(hotspot), a muscle involved in exoskeleton-training (9). The changes in the threshold were most likely due to the intervention received rather than inter-session variability as MEPs, which were acquired at two time points with an interval of 31 days: day 1 (pre-therapy) and day 32 (post-therapy) (10–13). Moreover, critical studies like that by Hendrics et al., and Jong et al., have established MEP as a sensitive and valid prognostic marker of motor recovery after stroke (14–16). For cortical-excitability to be increased in the ipsilesional-hemisphere for patients with stroke (after recovery), the ipsilesional-RMT should be decreased from pre-to-post-therapy and hence, normalization or RMT ratio (RMT Ipsilesional/RMT contralesional) should decrease to approach normalization (17–20). A reduction in interhemispheric-asymmetry was observed in the normalization ratio, from pre-to-post-therapy (**Table 1**), from 1.062 to 1.039 with a mean decrease of 0.023, indicated toward a trend of normalization. A potential increase in cortical-excitability in the ipsilesional-hemisphere might suggest restoration and improvement in the functional integrity of corticospinal tract as functional recovery potential in chronic-stroke depends largely on the integrity of these tract (21). The recruitment of perilesional areas or exploitation of preserved functional recovery reservoir in the ipsilesional-hemisphere may be attributed to the normalization of the RMT ratio (17, 22).

Changes in fMRI Activations

Increased cortical excitability was paralleled by the observed reduced BOLD signal intensity in both hemispheres. With intact MEP at the ipsilesional-hemisphere pre-therapy, ipsilesional-SMC displaying substantially reduced activation after the intervention; putatively reflects improved synaptic efficiency (23). Reduction in motor-cortex activations post-therapy might correspond to strengthened synaptic efficiency modulated by repetitive task-oriented exoskeleton training. The laterality-index of SMC was also observed to decrease in precentral (from 0.152 to −0.707) and postcentral gyrus (from 0.203 to −0.632) which might be demonstrating a substantial decrease in the number of contralateral activated voxels and shifting of cortical-reorganization from contra to ipsilateral-hemisphere. A considerable reduction in LI of SMC (change in LI: ΔLI postcentral = 0.835 and ΔLI precentral = 0.859), especially with decreased contralateral-hemisphere activations indicates that the patient achieved skilled motor performance (24). To the best of our knowledge, a change of ∼0.85 in LI has never been reported in the literature with any intervention or conventional therapy, however, any direct comparison would be inappropriate, considering different factors like chronicity, site of lesion, age, etc. It is plausible that exoskeleton training might have promoted use-dependent reorganization during motor training, resulting in shifting of activation from contra to ipsilateral corresponding to good recovery (vicariation) (18). It might indicate that with focused exoskeleton training the potential recovery might be accelerated. Few studies in the wider literature have explored LI through fMRI activation for affected-hand pre and post rehabilitation intervention, except Brain Computer Interface (reported ΔLI∼0.23), Constrain Induced movement therapy (ΔLI∼0.25), and low-frequency repetitive TMS over the contralateral hemisphere of the primary motor area (ΔLI∼0.14) (25–27).

Prominently increased cerebellar-motor activation in the Left-CBM exterior ipsilateral to the affected hand could be associated with the recovery process reinforcing CBM's postulated role in motor learning (28). The increased ipsilateral cerebellum-ratio during the affected-hand trial could potentially be a possible consequence of increased cerebellar-cerebral functional connectivity (28). SUS score (of ∼87.5), falling in the "excellent-acceptability" category, along with subjective feedback and question answers exhibited acceptance of the robotic-exoskeleton in clinical settings (**Supplementary Tables 1, 2**, Subjective Questions asked).

Compared with other available wrist rehabilitation devices, the HWARD robot saw an improvement in FMW/H (∼4) post-therapy. The SMC laterality index represents a shift in interhemispheric balance over time from the contralateral to the ipsilateral side (29). The Hand Mentor Pro robot observed improvement with FMW/H being 5.6, FMU/L 10.33 in combination with a home exercise program (which alone reported FMW/H 4.9 and FMU/L 9.3) in 99 patients with stroke (30). The reported gain post Constraint-Induced Movement therapy (CIMT), was FMU/L ∼13 and BI ∼13.5 (31). Furthermore, a meta-analysis and systematic review of CIMT evidenced an enhancement in FMU/L and Action Research Arm Test (ARAT) scores with improved hand control, arm placement, and increased strength as compared to standard therapy in patients with subacute and chronic-stroke (32). With sparse literature exploring cortical-excitability changes in the lower-limb (33) and upper-limb (34), virtual mirror task with biofeedback observed an increased MEP by up to 46.3% (95% CI: 30.4∼80.0) compared with the real mirror task (34). The observed increase in FMW/H of patients with chronic-stroke in robotic-assisted wrist-training and dose-matched conventional intervention was ≤4 (8, 35–38), however, any direct comparison would be inappropriate considering different factors like chronicity, site of lesion, and age, etc.

Although there are research studies targeting improvement in motor functions in chronic stroke survivors, most of the patients are left with long-term disabilities (3). Our data imply that 4 weeks of focused motor-learning training (with only 20 sessions of 45 min each) using novel voluntary muscle-activity triggered goal-directed exoskeleton is capable of producing clinically relevant neuroplasticity in terms of cortical-excitability and LI change (of ∼0.85 in SMC) in functional MRI activation even in chronic-stroke as long as 9 years when any improvement in motor performance is likely to be attributed to being exercise-induced rather than spontaneous recovery. Various strategies could have enhanced the clinically relevant neuroplasticity e.g., target movement of robotic-exoskeleton was specific, measurable, achievable, repetitive, and timed (39), reinforced with maximizing voluntary residual muscle-activity combined with real-time visual performance-biofeedback and proprioceptive-feedback for sensorimotor-integration in every cycle of the movement as was also reported by (40, 41). However, the exoskeleton is in the prototype stage, and the Biopac EMG system was used in the data acquisition for

research and validation. In the future, the EMG system should be replaced by a lightweight EMG amplifier to make the whole system compact. The device needs to be further optimized in terms of weight and aesthetics in order to be used for home-based rehabilitation in the future. This case study provided distinct dynamics of post-stroke recovery that deserve further investigation using a larger sample and examining the potential of the exoskeleton.

Limitations

The study lacks mid-term clinical assessment, and long-term follow-up of the patient, and activity level measurements like Wolf-Motor Function test and Action-Research Arm Test, Functional Independence Measure, Motor Activity Log, and Stroke Impact Scale, etc.,

CONCLUSION

The potential of the robotic exoskeleton must be considered further for accelerating post-stroke motor recovery.

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 human participants were reviewed and approved by Institute Review Board, All India Institute of Medical Sciences, New Delhi, India. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NS and AM conceptualized and designed the study. AM led the study, provided the scientific inputs, and reviewed the multiple iterations of the manuscript with NS. NS performed a literature survey, developed the device, data analysis, data interpretation, and wrote the manuscript. MS performed patient recruitment, robotic therapy, and data collection. NK, SK, and MVPS provided the scientific inputs, clinical support, and clinical resources for experiments. All authors read and approved the final version of the manuscript.

FUNDING

The authors would like to thank SERB, the Department of Science and Technology of the Government of India (YSS/2015/000697), and the Defence Research and Development Organization (DRDO) of the Government of India (DGTM/DFTM/GIA/18-19/0441) for funding.

ACKNOWLEDGMENTS

The authors would like to express sincere gratitude to the patient who agreed to participate in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.680733/full#supplementary-material

REFERENCES

1. Ballester BR, Maier M, Duff A, Cameirão M, Bermúdez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. *J Neurophysiol.* (2019) 122:350–7. doi: 10.1152/jn.00762.2018
2. Hara Y. Brain plasticity and rehabilitation in stroke patients. *J Nippon Med Sch.* (2015) 82:4–13. doi: 10.1272/jnms.82.4
3. Rind B, Dalton S. Chronic stroke rehabilitation: restoring CNS function with a nutriceutical-oxygen intervention. *J Stroke Cerebrovasc Dis.* (2003) 12:251. doi: 10.1016/j.jstrokecerebrovasdis.2003.11.017
4. Singh N, Saini M, Anand S, Kumar N, Srivastava MVP, Mehndiratta A. Robotic exoskeleton for wrist and fingers joint in post-stroke neuro-rehabilitation for low-resource settings. *IEEE Trans Neural Syst Rehabil Eng.* (2019) 27:2369–77. doi: 10.1109/TNSRE.2019.2943005
5. Brooke J, Brooke J. *SUS: A Quick and Dirty Usability Scale*. (1996). Available online at: http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.232.5526 (accessed April 01, 2018).
6. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application: an updated report from an I.F.C.N. Committee. *Clin Neurophysiol.* (2015) 126:1071–107. doi: 10.1016/j.clinph.2015.02.001
7. Gladstone DJ, Danells CJ, Black SE, Article R. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. (2002) 16:232–40. doi: 10.1177/154596802401105171
8. Shin J-H, Kim M-Y, Lee J-Y, Jeon Y-J, Kim S, Lee S, et al. Effects of virtual reality-based rehabilitation on distal upper extremity function and health-related quality of life: a single-blinded, randomized controlled trial. *J Neuroeng Rehabil.* (2016) 13:17. doi: 10.1186/s12984-016-0125-x
9. Talelli P, Greenwood RJ, Rothwell JC. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. *Clin Neurophysiol.* (2006) 117:1641–59. doi: 10.1016/j.clinph.2006.01.016
10. Bastani A, Jaberzadeh S, Barker A, Freeston I, Jalinous R, Jarratt J, et al. A higher number of TMS-elicited MEP from a combined hotspot improves intra- and inter-session reliability of the upper limb muscles in healthy individuals. *PLoS ONE.* (2012) 7:e47582. doi: 10.1371/journal.pone.0047582
11. Christie A, Fling B, Crews RT, Mulwitz LA, Kamen G. Reliability of motor-evoked potentials in the ADM muscle of older adults. *J Neurosci Methods.* (2007) 164:320–4. doi: 10.1016/j.jneumeth.2007.05.011
12. ter Braack EM, de Goede AA, van Putten MJAM. Resting motor threshold, MEP and TEP variability during daytime. *Brain Topogr.* (2019) 32:17–27. doi: 10.1007/s10548-018-0662-7
13. Hassanzahraee M, Zoghi M, Jaberzadeh S. Longer transcranial magnetic stimulation intertrial interval increases size, reduces variability, and improves the reliability of motor evoked potentials. *Brain Connect.* (2019) 9:770–6. doi: 10.1089/brain.2019.0714

14. Hendricks HT, Zwarts MJ, Plat EF, Van Limbeek J. Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. *Arch Phys Med Rehabil.* (2002) 83:1303–8. doi: 10.1053/apmr.2002.34284
15. Hendricks HT, Pasman JW, Van Limbeek J, Zwarts MJ. Motor evoked potentials of the lower extremity in predicting motor recovery and ambulation after stroke: a cohort study. *Arch Phys Med Rehabil.* (2003) 84:1373–9. doi: 10.1016/s0003-9993(03)00237-5
16. Lim JY, Oh M-K, Park J, Paik N-J. Does measurement of corticospinal tract involvement add value to clinical behavioral biomarkers in predicting motor recovery after stroke? *Neural Plast.* (2020) 2020:8883839. doi: 10.1155/2020/8883839
17. Koski L, Mernar TJ, Dobkin BH. Immediate and long-term changes in corticomotor output in response to rehabilitation: correlation with functional improvements in chronic stroke. *Neurorehabil Neural Repair.* (2004) 18:230–49. doi: 10.1177/1545968304269210
18. Edwardson MA, Lucas TH, Carey JR, Fetz EE. New modalities of brain stimulation for stroke rehabilitation. *Exp Brain Res.* (2013) 224:335–58. doi: 10.1007/s00221-012-3315-1
19. Dodd KC, Nair VA, Prabhakaran V. Role of the contralesional vs. Ipsilesional hemisphere in stroke recovery. *Front Hum Neurosci*. (2017) 11:469. doi: 10.3389/fnhum.2017.00469
20. Du J, Yang F, Hu J, Hu J, Xu Q, Cong N, et al. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. *NeuroImage Clin.* (2019) 21:101620. doi: 10.1016/j.nicl.2018.101620
21. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain.* (2006) 130:170–80. doi: 10.1093/brain/awl333
22. Singh N, Saini M, Kumar N, Srivastava MVP, Mehndiratta A. Evidence of neuroplasticity with robotic hand exoskeleton study for post-stroke rehabilitation: a randomized controlled trial. *J NeuroEng Rehabil.* (2021) 18:76. doi: 10.1186/s12984-021-00867-7
23. Jena U, Liepert J, Dettmers C. Two different reorganization patterns after rehabilitative therapy : an exploratory study with fMRI and TMS Two different reorganization patterns after rehabilitative therapy : An exploratory study with fMRI and TMS. Neuroimage. (2016) 31:710–20. doi: 10.1016/j.neuroimage.2005.12.035
24. Dong Y, Winstein CJ, Albistegui-Dubois R, Dobkin BH. Evolution of fMRI activation in the perilesional primary motor cortex and cerebellum with rehabilitation training-related motor gains after stroke: a pilot study. *Neurorehabil Neural Repair.* (2007) 21:412–28. doi: 10.1177/1545968306298598
25. Ramos-Murguialday A, Broetz D, Rea M, Läer L, Yilmaz Ö, Brasil FL, et al. Brain-machine interface in chronic stroke rehabilitation: a controlled study. *Ann Neurol.* (2013) 74:100–8. doi: 10.1002/ana.23879
26. Schaechter JD, Kraft E, Hilliard TS, Dijkhuizen RM, Benner T, Finklestein SP, et al. *Motor Recovery and Cortical Reorganization after Constraint-Induced Movement Therapy in Stroke Patients: A Preliminary Study | Enhanced Reader*. Available online at: https://journals.sagepub.com/doi/10.1177/154596830201600403?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed& (accessed May 13, 2021).
27. Yamada N, Kakuda W, Senoo A, Kondo T, Mitani S, Shimizu M, et al. Functional cortical reorganization after low-frequency repetitive transcranial magnetic stimulation plus intensive occupational therapy for upper limb hemiparesis: evaluation by functional magnetic resonance imaging in poststroke patients. *Int J Stroke.* (2013) 8:422–9. doi: 10.1111/ijs.12056
28. Small SL, Hlustik P, Noll DC, Genovese C, Solodkin A. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. *Brain.* (2002) 125:1544–57. doi: 10.1093/brain/awf148
29. Takahashi CD, Der-Yeghiaian L, Le V, Motiwala RR, Cramer SC. Robot-based hand motor therapy after stroke. *Brain.* (2008) 131:425–37. doi: 10.1093/brain/awm311
30. Wolf SL, Sahu K, Bay RC, Buchanan S, Reiss A, Linder S, et al. The HAAPI (Home Arm Assistance Progression Initiative) trial: a novel robotics delivery approach in stroke rehabilitation. *Neurorehabil Neural Repair.* (2015) 29:958–68. doi: 10.1177/1545968315575612
31. Kuthiala N, Bhasin A, Sharma R, Padma Srivastava MV, Senthil Kumran S, Sharma S, et al. rTMS and CIMT for neurofunctional recovery in chronic stroke. *Int J Neurorehabil.* (2020) 7:6. doi: 10.37421/ijn.2020.7.378
32. McIntyre A, Viana R, Janzen S, Mehta S, Pereira S, Teasell R. Systematic review and meta-analysis of constraint-induced movement therapy in the hemiparetic upper extremity more than six months post stroke. *Top Stroke Rehabil.* (2012) 19: 499–513. doi: 10.1310/tsr1906-499
33. Calabrò RS, Naro A, Leo A, Bramanti P. Usefulness of robotic gait training plus neuromodulation in chronic spinal cord injury: a case report. *J Spinal Cord Med.* (2017) 40:118–21. doi: 10.1080/10790268.2016.1153275
34. Kang Y, Park H, Kim H, Lim T, Ku J, Cho S, et al. Upper extremity rehabilitation of stroke: facilitation of corticospinal excitability using virtual mirror paradigm. *J Neuroeng Rehabil.* (2012) 9:71. doi: 10.1186/1743-0003-9-71
35. Hu XL, Tong KY, Li R, Xue JJ, Ho SK, Chen P. The effects of electromechanical wrist robot assistive system with neuromuscular electrical stimulation for stroke rehabilitation. *J Electromyogr Kinesiol.* (2012) 22:431–9. doi: 10.1016/j.jelekin.2011.12.010
36. Hu XL, Tong RKY, Ho NSK, Xue JJ, Rong W, Li LSW. Wrist rehabilitation assisted by an electromyography-driven neuromuscular electrical stimulation robot after stroke. *Neurorehabil Neural Repair.* (2015) 29:767–76. doi: 10.1177/1545968314565510
37. Liao W, Wu C, Hsieh Y, Lin K, Chang W. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial. *Clin Rehabil.* (2012) 26:111–20. doi: 10.1177/0269215511416383
38. Lee M-J, Lee J-H, Lee S-M. Effects of robot-assisted therapy on upper extremity function and activities of daily living in hemiplegic patients: a single-blinded, randomized, controlled trial. *Technol Heal Care.* (2018) 26:659–66. doi: 10.3233/THC-181336
39. Scobbie L, McLean D, Dixon D, Duncan E, Wyke S. Implementing a framework for goal setting in community based stroke rehabilitation: a process evaluation. *BMC Health Serv Res.* (2013) 13:190. doi: 10.1186/1472-6963-13-190
40. Volpe BT, Ferraro M, Lynch D, Christos P, Krol J, Trudell C, et al. Robotics and other devices in the treatment of patients recovering from stroke. *Curr Atheroscler Rep.* (2004) 6:314–9. doi: 10.1007/s11883-004-0064-z
41. Cho KH, Hong M-R, Song W-K. Upper limb robotic rehabilitation for chronic stroke survivors: a single-group preliminary study. *J Phys Ther Sci.* (2018) 30:580–3. doi: 10.1589/jpts.30.580

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.

frontiers in Neurology

STUDY PROTOCOL
published: 08 September 2021
doi: 10.3389/fneur.2021.710640

Korean Model for Post-acute Comprehensive rehabilitation (KOMPACT): The Study Protocol for a Pragmatic Multicenter Randomized Controlled Study on Early Supported Discharge

*Won Kee Chang[1], Won-Seok Kim[1], Min Kyun Sohn[2], Sungju Jee[2], Yong-Il Shin[3], Sung-Hwa Ko[3], Minsu Ock[4], Hyun Joo Kim[5] and Nam-Jong Paik[1]**

[1] Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea, [2] Department of Rehabilitation Medicine, Chungnam National University College of Medicine, Chugnam National University Hospital, Daejeon, South Korea, [3] Department of Rehabilitation Medicine, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, Pusan, South Korea, [4] Department of Preventive Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea, [5] Department of Nursing Science, Shinsung University, Dangjin, South Korea

OPEN ACCESS

Edited by:
Stephanie Clarke,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

Reviewed by:
S. Santana,
University of Aveiro, Portugal
Birgitta Langhammer,
Oslo Metropolitan University, Norway

***Correspondence:**
Nam-Jong Paik
njpaik@snu.ac.kr

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 16 May 2021
Accepted: 09 August 2021
Published: 08 September 2021

Citation:
Chang WK, Kim WS, Sohn MK, Jee SJ, Shin YI, Ko SH, Ock MS, Kim HJ and Paik NJ (2021) Korean Model for Post-acute Comprehensive rehabilitation (KOMPACT): The Study Protocol for a Pragmatic Multicenter Randomized Controlled Study on Early Supported Discharge. Front. Neurol. 12:710640. doi: 10.3389/fneur.2021.710640

Introduction: Early supported discharge (ESD) is a transitional care model aimed at facilitating post-acute stroke patients' discharge to home. Previous studies have demonstrated that ESD provides equivalent patient and caregiver outcomes with superior cost-effectiveness compared to conventional rehabilitation (CR). This study intends to examine the feasibility of ESD in Korea.

Methods and Analysis: This study is designed as a multicenter assessor-blinded, randomized controlled trial. Ninety post-acute stroke patients with mild to moderate disability (modified Rankin Scale 1–3) will be recruited from three university hospitals (30 patients per hospital) in Korea and allocated to either the ESD group or the CR group in a 1:1 ratio. Patients in the ESD group will receive individualized discharge planning and goal setting, a 4-week home-based rehabilitation program, and liaison service to community-based resources by a multidisciplinary team. Patients in the CR group will receive rehabilitation practices according to their current hospital policy.

Outcomes: The primary outcome is the Korean version of the modified Barthel Index, and the primary endpoint was post-onset 3 months. Clinical outcomes, patient/caregiver reported outcomes, and socioeconomic outcomes will be measured at baseline, 1 month after discharge, 2 months after discharge, and 3 months after onset.

Discussion: The efficacy and cost-effectiveness of ESD can vary according to the healthcare system and sociocultural aspects. To establish ESD as an alternative transitional care model for post-acute stroke patients in Korea, its feasibility needs to be examined in prior. This study will add evidence on the applicability of ESD in Korea.

Ethical Considerations: The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number B-2012/654-308). The study protocol was registered at ClinicalTrials.gov (Identifier NCT04720820). Disseminations will include submission to peer-reviewed journals and presentations at conferences.

Keywords: stroke, transitional care, early supported discharge, randomized controlled trials, quality of life, Korea

INTRODUCTION

Stroke is a significant global healthcare problem, accounting for the second largest disease burden (1) and major health service costs (2). The numbers of both post-stroke survivors and associated healthcare costs are expected to increase in the future (3), which will lead to a strong need for the establishment of an efficient and effective transitional stroke care model.

Early supported discharge (ESD) is an approach that aims to accelerate the home discharge of post-acute stroke patients by providing an equivalent level of rehabilitation services in the patient's home setting by a specialized multidisciplinary team (4, 5). A recent meta-analysis study has shown that a well-organized ESD can reduce long-term dependency and admission to institutional care of stroke patients as well as reduce the length of hospital stay (6). However, studies on ESD have mostly been conducted in European countries (7–12), Canada (13), and Australia (14), and the effectiveness of ESD can vary in non-European countries due to differences in medical systems and costs, allocation of rehabilitation resources, and cultural aspects (15). Thus, the applicability of the ESD model in Asian countries, namely Korea, remains unclear and requires further validation.

This study aims to examine the effectiveness and economic impact of ESD in post-acute stroke patients in Korea by comparing it with conventional rehabilitation (CR) through a multi-center assessor-blinded randomized controlled trial.

MATERIALS AND METHODS

Study Design

This study is designed as a multi-center assessor-blinded, randomized controlled trial. Patients will be recruited from three national university hospitals in Korea: Seoul National University Bundang Hospital (Seongnam-si, Gyeonggi-do, Korea), Chungnam National University Hospital (Jung-gu, Daejeon, Korea), and Pusan National University Yangsan Hospital (Yangsan-si, Gyeongsangnam-do, Korea). **Figure 1** shows an overall flowchart of the proposed study.

Aim and Primary Hypothesis

This study aims to examine the effectiveness of ESD services in stroke patients with mild to moderate disability in Korea and establish it as an alternative to conventional rehabilitation services.

The primary hypothesis of the study is that the functional outcome of the patients in the ESD group would be non-inferior to those in the CR group, which was based on previous results of ESD trials (9, 13, 14). Producing equivalent functional outcomes with possibly reduced healthcare-related costs will prove that ESD is a feasible option for patients with stroke.

Recruitment, Randomization, and Group Allocation

Patients will be screened for eligibility when referred to the rehabilitation department during acute stroke inpatient treatment. Eligible patients will be informed and enrolled by the study team. After the patient is enrolled, the patient will undergo baseline evaluation by the assessor and will be randomly allocated by the coordinator into either the ESD group or the CR group in a 1:1 ratio (total 30 patients per hospital). Randomization sequences were computer-generated using mixed block sizes of two and four, without stratification by the institution's biostatistician who is independent of the study team and will be managed by the coordinator in an opaque-sealed envelope at each study site. The patients' allocated group will be informed to the study team by the coordinator after the baseline evaluation is done. Patients' follow-up arrangements are managed by the study coordinator.

Blinding

All evaluations (except for the ESD program satisfaction questionnaires) will be performed at each hospital by designated occupational therapist who is independent from the ESD team. The assessor will be blinded to the patients' intervention group throughout the study.

Eligibility

This study aims to recruit acute stroke patients with mild to moderate disabilities who can be directly discharged to home after acute stroke treatment at the hospital. Major inclusion criteria are as follows: age $>$ 20 years, planned to be discharged to home within 30 days from onset, initial modified Rankin Scale score 1–3, functional ambulation category score 3 or above, and no deficit of consciousness. Major exclusion criteria are as follows: transient ischemic attack, medically unstable, psycho-behavioral problems, or severe cognitive deficits that hinder participation in the ESD service. The detailed inclusion and exclusion criteria are listed in **Table 1**.

Interventions

The ESD team at each hospital is comprised of a rehabilitation physiatrist, a physiotherapist, an occupational therapist, and a social worker (optional) who have experience in stroke patient care. The ESD service consists of individualized discharge

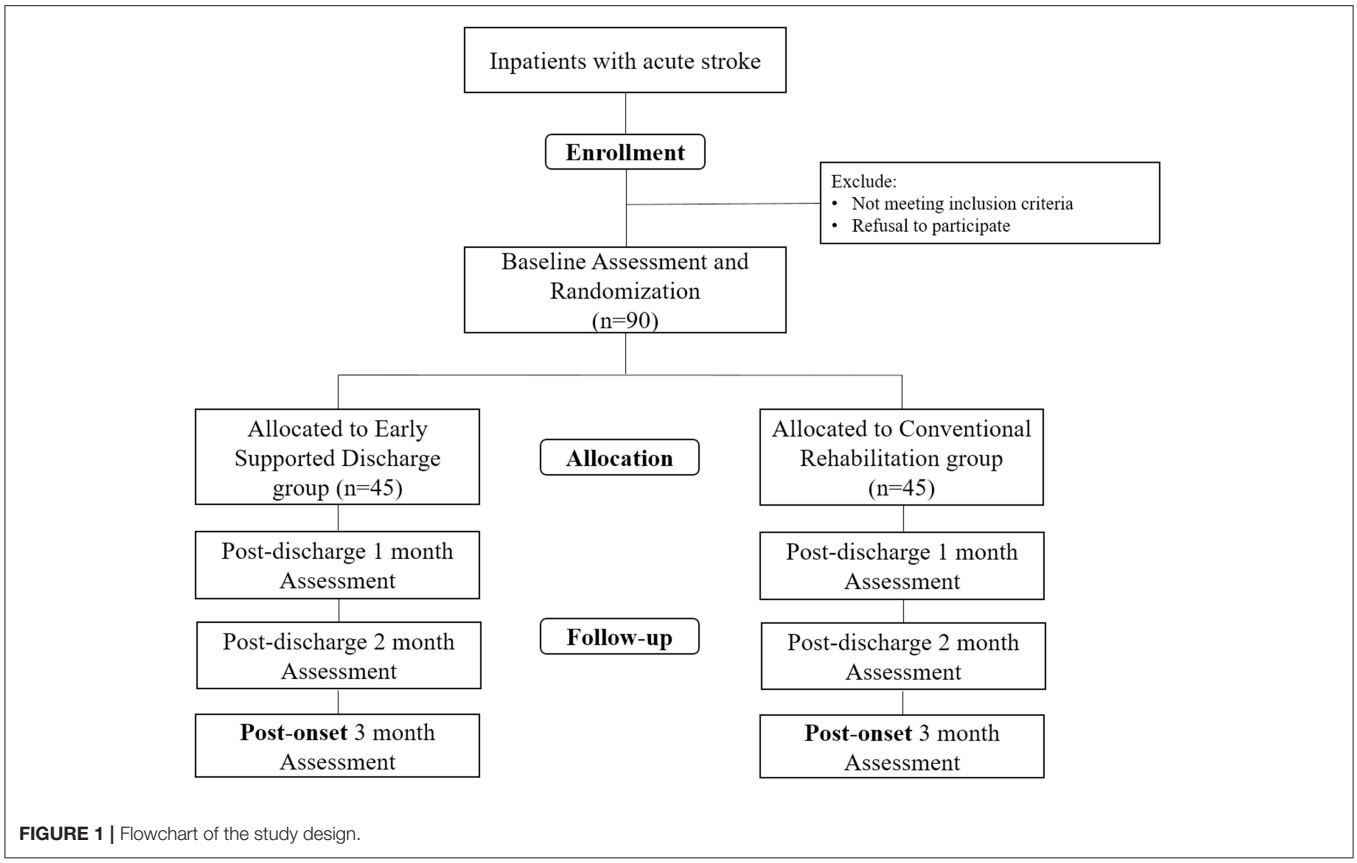


FIGURE 1 | Flowchart of the study design.

planning and goal setting, 4-weeks of home-based tailor-made rehabilitation program, including at least 30 min of visiting physical therapy (PT) and occupational therapy (OT) sessions each at the patients' homes per week, additional PT, OT, and speech therapy (ST) at the hospital outpatient settings if needed, and liaison service to community-based resources as required. The team will discuss each patient's ESD program biweekly and modify the ESD program, if necessary. ESD programs will be set to meet patients' needs, with emphasis on adjusting to community living (16).

Patients in the CR group will receive current practices on post-acute stroke patients regarding discharge planning and follow-up rehabilitation services. Patients will receive outpatient-based PT, OT, and ST after discharge, if needed. Referral to community-based resources will be done according to the current hospital policy.

Safety of the Health Professionals and the Patients

To secure the safety of health professionals during home rehabilitation services, ESD team will visit the patients' home in team of two or more people. Also the patients' caregiver will be mandatory to stay at home during the visit. ESD services will be terminated if there is significant risk to the team regarding safety. To minimize the risk of COVID-19 infection, ESD team will use personal protective equipment such as gloves and masks during the home rehabilitation services. The ESD services will be provided in accordance with the Korean government and the hospital's infection control policies.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria
1. Patient who is admitted with clinical diagnosis of stroke
2. Patient who will be discharged to home within 30 days from onset
3. Patient who lives within 30-min distance from the discharged hospital with caregiver
4. Patient who's initial functional status is (measured within 14 days from onset)
1) Mild to moderate disability (mRS score 1–3)
2) Able to walk of transfer with on-man assist (FAC 3 or above)
3) No deficit of consciousness (K-NIHSS 1a, 1b, and 1c score 0)
Exclusion criteria
1. Patient who had TIA
2. Patient who is medically unstable
3. Patient who has indwelling catheter
4. Patient who's oral food intake is prohibited
5. Patient who has uncontrolled pain (with usage of NSAIDs or Opioids)
6. Patient who has psychobehavioral problems
7. Patient who has severe cognitive deficit (K-MMSE <15)
8. Patient who is unable to participate post-stroke rehabilitation program

mRS, modified Rankin Scale; K-MBI, Korean version of modified Barthel Index; FAC, Functional Ambulation Category; K-NIHSS, Korean version of the National Institute of Health Stroke Scale; TIA, Transient Ischemic Attack; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; K-MMSE, Korean version of the Mini-Mental State Exam.

Measures

There are several types of outcome measures in this study: clinical outcomes, patient and caregiver reported outcomes, and socioeconomic outcomes. Measures will be evaluated at baseline, 1 month after discharge, 2 months after discharge (if necessary), and 3 months after onset. Since the length of hospital stay is expected to be different in both groups (6), we have set the primary endpoint as 3 months after onset. The detailed outcome measures and evaluation timetable are shown in **Table 2**.

Primary Outcome

The primary outcome of this study is the Korean version of the Modified Barthel Index (K-MBI) (17). The K-MBI is a scale consisting of 10 items that measure the ability to perform activities of daily living (ADL). The K-MBI is widely used to assess the degree of function in stroke patients, and the score ranges from 0 to 100, with higher scores indicating better function of the patient.

Secondary Outcomes—Clinical Outcomes

Clinical secondary outcomes include the modified Rankin Scale, Korean version of Instrumental Activities of Daily Living, fall experience, readmission, and mortality rates.

The modified Rankin Scale (mRS) is a clinician-reported ordinal scale that measures global disability. mRS is widely used to evaluate the gross functional outcomes of stroke patients (18). mRS ranges from 0 to 6 with 0 indicating no symptoms at all and 6 indicating death.

The Korean version of Instrumental Activities of Daily Living (K-IADL) measures a person's ability to perform activities that are required to live independently in the community (19). The K-IADL consists of 11 items (shopping, mode of transportation, ability to handle finances, housekeeping, preparing food, ability to use a telephone, responsibility for own medication, recent memory, hobbies, watching television, and fixing around the house). K-IADL ranges from 0 to 33, with lowerr scores indicating better ability.

Fall experience, readmission, and mortality rates are outcomes that are related to the safety and long-term dependency of community-dwelling post-stroke patients. Patients will be asked whether they had experienced a fall or serious fall-related injury, which is defined as an injury that requires medical treatment as a consequence of a fall (20). Readmission and mortality rates will be monitored by questioning the patient or caregiver at each follow-up schedule.

Secondary Outcomes—Patient/Caregiver Reported Outcomes

The Patient Health Questionnaire-9 (PHQ-9) is a brief 9-item depression module used for screening depression (21). The

TABLE 2 | Timetable and measures to be made.

Measures	Screening	Baseline	1 months	2months+	3 months
Primary outcome					
modified Barthel Index (K-MBI)		√	√		√
Secondary outcomes—clinical					
modified Rankin Scale (mRS)	√	√	√		√
Instrumental Activities of Daily Living (K-IADL)			√		√
Fall experience			√		√
Readmission rate			√		√
Mortality rate			√		√
Secondary outcomes—patient reported outcomes					
Patient Health Questionnaire-9 (PHQ-9)		√	√		√
Reintegration to Normal Living Index (K-RNLI)			√		√
Stroke Impact Scale 3.0 (K-SIS)			√		√
EuroQoL-5D-5L (EQ-5D-5L)		√	√		√
Zarit Burden Interview (K-ZBI 22)			√		√
ESD Program satisfaction questionnaires*			√		√
Secondary outcomes—socioeconomic					
Length of Hospital stay			√		
Direct cost (Hospital cost, Home-based rehabilitation cost)			√	√	√
Indirect cost (Transportation cost, Caregiver cost)			√	√	√
Productivity loss					√
Other measures					
Demographic/Social information	√	√			
Medical History	√	√			
ESD program participation rate	√				

**Early Supported Discharge group only.*

+Measurement can be skipped if the time interval between 2 months after discharge and 3 months after onset is <2 weeks.

PHQ-9 score ranges from 0 to 27, with higher scores indicating more severe depressive symptoms.

The Korean version of the Reintegration to Normal Living Index (K-RNLI) assesses the consequences of disease on the restoration of normal life with 11 domains scored using a visual analog scale (22).

The Korean version of the Stroke Impact Scale 3.0 (K-SIS) is used to identify patients' needs in multiple dimensions regarding health-related quality of life (HRQoL) (23). The scale consists of nine domains with each domain score ranging from 0 to 100. Higher scores indicate a better quality of life.

EuroQoL-5D-5L (EQ-5D-5L) is a globally used self-reported health status measure with five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The Korean version of the Zarit Burden Interview (K-ZBI 22) is the most widely used instrument for measuring caregiver burden (24). This scale contains 22-items and has 5 subscales assessing the subjective burden of caregivers: general strain, isolation, disappointment, emotional involvement, and environment. All items are scored on a scale from 1 to 4, with higher scores indicating a higher caregiver burden.

Secondary Outcomes—Socioeconomic

The length of hospital stay will be obtained from electronic medical records (EMR). Both the total number of bed days and the number of days after randomization will be documented.

Direct cost includes the cost of hospital admission, outpatient clinic visits, and rehabilitation therapy (both home-based and outpatient-based). The cost generated at the study-site hospital will be acquired from EMR, while costs occurring at other hospitals or clinics will be obtained using a patient questionnaire. *Indirect cost* consists of transportation cost for visiting a hospital or clinic, caregiver cost (if a caregiver is employed to help the patient), and cost of modifying home to assist ADL (for example, installing a handrail on the wall to assist transfer). Indirect costs will be obtained using patient questionnaires.

Productivity loss will be calculated based on the human capital approach (25) determined by calculating the average monthly working hours and the average monthly wage obtained with the patient questionnaire.

Data Collection and Management

Data from all patients will be collected by research team members and entered into iCReaT (http://icreat.nih.go.kr), a web-based clinical research and trial database management program developed by the Korea Centers for Disease Control and Prevention. The coordinating investigator will have access to the final study dataset, and the anonymized dataset will be available upon reasonable request to the corresponding author.

Sample Size Estimation

The sample size of this study was estimated based on our primary hypothesis. The non-inferiority margin was defined as 50% of the changes in MBI scores from baseline to 3 months after onset from a previous ESD trial (14). With a non-inferiority margin of 6.2 and standard deviation of 10.6, the minimum sample size determined using PASS 2020 (NCSS, LLC. Kaysville, Utah, USA) was 37 patients in each group after applying a 5% probability of type 1 error and 80% statistical power. Allowing 18% of attrition per group, a total of 90 patients will be required for the study.

Statistical Analysis

For the statistical analysis, the Student *t*-test or Mann-Whitney *U*-test will be used to analyze numeric variables according to the parametricity of the distribution. Chi-squire test will be used to analyze categorical variables. Subgroup analysis based on the baseline mRS scores (1–3) will be performed if there are sufficient participants in all three subgroups. For primary analysis, both the intent-to-treat (ITT) approach and per-protocol analysis approach will be applied. If the dropout rate exceeds 20% of the total patients in the final stage, ITT-based analysis will be performed after multiple imputations of missing data. $P < 0.05$ will be considered as statistically significant. The data will be analyzed using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

DISCUSSION

ESD is currently considered an acceptable, cost-effective transitional care model for post-acute stroke patients in Europe, Canada, and Australia (6). However, the feasibility of ESD needs to be examined in the healthcare system environment of Korea, since the applicability of ESD depends on the healthcare system, stroke-related cost, and cultural aspect of the country it is implemented (15).

The healthcare system of Korea offers inpatient medical services at a relatively low cost with good accessibility compared to other developed countries (26) thus, the ESD program might not be an attractive option for stroke patients with moderate to severe disabilities. Therefore, we chose the target population of stroke patients with mild to moderate disabilities, which has been proven to have benefitted from ESD service (16). Another aspect that needs to be mentioned is the cultural perception of caregiving in Korea. It has been speculated that filial piety and familism of Asian culture have a positive effect on reducing caregiving burden (27), which can be advantageous in reducing the potential risk of increased caregiver burden caused by ESD (14).

The primary hypothesis of this study was set to test the non-inferiority of functional outcomes in patients undergoing ESD, compared with CR. This was based on previous studies (9, 12–14), and the results showed no significant difference in functional outcomes between the groups. Moreover, considering that our target population is post-acute stroke patients with mild to moderate disabilities, we expect the ability to perform ADL at our primary endpoint, 3 months after onset, will not be significantly different in both groups.

Current post-acute stroke rehabilitation in Korea is highly dependent on inpatient rehabilitation, resulting in a long hospital stay for stroke patients (28, 29). Since the economic burden of stroke in Korea is increasing (30) with productivity loss accounting for the largest portion (31), a search for a new model of post-acute stroke transitional care that could facilitate patients' reintegration to the community is essential.

In this study, we plan to investigate the impact of ESD on various dimensions; not only the functional outcomes and economic efficiency but also the social and cultural aspects. Sociocultural aspect is an important factor when implementing ESD into existing stroke care system (32). By assessing the impact of ESD in various aspects, our results will provide comprehensive information on its applicability.

In conclusion, this study aimed to examine the feasibility of ESD in post-acute patients with mild to moderate disability by comparing its efficacy and socioeconomic impact with the current rehabilitation system. This study provides evidence on the applicability of ESD in Korea.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number B-2012/654-308). The study protocol was registered at ClinicalTrials.gov (Identifier NCT04720820). Written informed consent to participate in this study will be provided by the patients and/or their legal guardians.

AUTHOR CONTRIBUTIONS

WC, W-SK, MS, SJ, Y-IS, S-HK, MO, HK, and N-JP conceived the study and designed the study protocol. The draft of the manuscript was written by WC and revised by W-SK, MS, SJ, Y-IS, S-HK, and N-JP. All authors contributed to the manuscript and approved the submitted version.

FUNDING

This work was supported by the Research Program funded by the Korea National Institute of Health (2020ER630601).

REFERENCES

1. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2197–223. doi: 10.1016/S0140-6736(12)61689-4
2. Evers SMAA, Struijs JN, Ament AJHA, Van Genugten MLL, Jager JC, Van Den Bos GAM. International comparison of stroke cost studies. *Stroke.* (2004) 35:1209–15. doi: 10.1161/01.STR.0000125860.48180.48
3. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, et al. Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ.* (2019) 20:107–34. doi: 10.1007/s10198-018-0984-0
4. Langhorne P, Taylor G, Murray G, Dennis M, Anderson C, Bautz-Holter E, et al. Early supported discharge services for stroke patients: a meta-analysis of individual patients' data. *Lancet.* (2005) 365:501–6. doi: 10.1016/S0140-6736(05)17868-4
5. Langhorne P, Widen-Holmqvist L, Taylor G, Murray G, Askim T, Dennis M, et al. Early supported discharge after stroke. *J Rehabil Med.* (2007) 39:103–8. doi: 10.2340/16501977-0042
6. Langhorne P, Baylan S. Early supported discharge services for people with acute stroke. *Cochr Datab Systemat Rev.* (2017) 2017:CD000443. doi: 10.1002/14651858.CD000443.pub4
7. Rudd AG, Wolfe CDA, Tilling K, Beech R. Randomised controlled trial to evaluate early discharge scheme for patients with stroke. *Br Med J.* (1997) 315:1039–44. doi: 10.1136/bmj.315.7115.1039
8. Bautz-Holter E, Sveen U, Rygh J, Rodgers H, Wyller TB. Early supported discharge of patients with acute stroke: a randomized controlled trial. *Disabil Rehabil.* (2002) 24:348–55. doi: 10.1080/09638280110093677
9. Donnelly M, Power M, Russell M, Fullerton K. Randomized controlled trial of an early discharge rehabilitation service: the belfast community stroke trial. *Stroke.* (2004) 35:127–33. doi: 10.1161/01.STR.0000106911.96026.8F
10. Fjærtoft H, Rohweder G, Indredavik B. Stroke unit care combined with early supported discharge improves 5-year outcome: a randomized controlled trial. *Stroke.* (2011) 42:1707–11. doi: 10.1161/STROKEAHA.110.601153
11. Hofstad H, Gjelsvik BEB, Næss H, Eide GE, Skouen JS. Early supported discharge after stroke in Bergen (ESD Stroke Bergen): three and six months results of a randomised controlled trial comparing two early supported discharge schemes with treatment as usual. *BMC Neurol.* (2014) 14:1–10. doi: 10.1186/s12883-014-0239-3
12. Santana S, Rente J, Neves C, Redondo P, Szczygiel N, Larsen T, et al. Early home-supported discharge for patients with stroke in Portugal: a randomised controlled trial. *Clin Rehabil.* (2017) 31:197–206. doi: 10.1177/0269215515627282
13. Mayo NE, Wood-Dauphinee S, Côté R, Gayton D, Carlton J, Buttery J, et al. There's no place like home: an evaluation of early supported discharge for stroke. *Stroke.* (2000) 31:1016–23. doi: 10.1161/01.STR.31.5.1016
14. Anderson C, Rubenach S, Mhurchu CN, Clark M, Spencer C, Winsor A. Home or hospital for stroke rehabilitation? results of a randomized controlled trial. *Stroke.* (2000) 31:1024–31. doi: 10.1161/01.STR.31.5.1024
15. Haussen DC, Yavagal DR. Stroke: consensus on evidence-based implementation of early supported discharge. *Nat Rev Neurol.* (2011) 7:482–3. doi: 10.1038/nrneurol.2011.128
16. Fisher RJ, Gaynor C, Kerr M, Langhorne P, Anderson C, Bautz-Holter E, et al. A consensus on stroke: early supported discharge. *Stroke.* (2011) 42:1392–7. doi: 10.1161/STROKEAHA.110.606285
17. Jung HY, Park BK, Shin HS, Kang YK, Pyun SB, Paik NJ, et al. Development of the Korean Version of Modified Barthel Index (K-MBI): multi-center Study for Subjects with Stroke. *Ann Rehabil Med.* (2007) 31:283–97.
18. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: implications for stroke clinical trials - a literature review and synthesis. *Stroke.* (2007) 38:1091–6. doi: 10.1161/01.STR.0000258355.23810.c6
19. Kang S, Choi SH, Lee B, Kwon J, Na D, Han SH. The reliability and validity of the Korean Instrumental Activities of Daily Living (K-IADL). *J Korean Neurol Assoc.* (2002) 20:8–14.
20. Bergland A, Wyller TB. Risk factors for serious fall related injury in elderly women living at home. *Injury Prev.* (2004) 10:308–13. doi: 10.1136/ip.2003.004721
21. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 46202:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
22. Daneski K, Coshall C, Tilling K, Wolfe CDA. Reliability and validity of a postal version of the Reintegration to Normal Living Index, modified for use with stroke patients. *Clin Rehabil.* (2003) 17:835–9. doi: 10.1191/0269215503cr686oa
23. Choi SU, Lee HS, Shin JH, Ho SH, Koo MJ, Park KH, et al. Stroke impact scale 3.0: reliability and validity evaluation of the Korean version. *Ann Rehabil Med.* (2017) 41:387–93. doi: 10.5535/arm.2017.41.3.387
24. Elmståhl S, Malmberg B, Annerstedt L. Caregiver's burden of patients 3 years after stroke assessed by a novel caregiver burden scale. *Archiv Phys Med Rehabil.* (1996) 77:177–82. doi: 10.1016/S0003-9993(96)90164-1
25. Drummond MF, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. Toronto, ON: Oxford University Press (1997).
26. Lee KS. Development and reconsideration of Korea Healthcare System. *Health Pol Manag.* (2013) 23:303–13. doi: 10.4332/KJHPA.2013.23.4.303
27. Lai DWL. Filial piety, caregiving appraisal, and caregiving Burden. *Res Aging.* (2010) 32:200–23. doi: 10.1177/0164027509351475

28. Kang JH, Bae HJ, Choi YA, Lee SH, Shin HI. Length of hospital stay after stroke: a Korean nationwide study. *Ann Rehabil Med.* (2016) 40:675–81. doi: 10.5535/arm.2016.40.4.675
29. Kim WS, Bae HJ, Lee HH, Shin HI. Status of rehabilitation after ischemic stroke: a Korean nationwide study. *Ann Rehabil Med.* (2018) 42:528–35. doi: 10.5535/arm.2018.42.4.528
30. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive summary of stroke statistics in Korea 2018: a report from the epidemiology research council of the Korean Stroke Society. *J Stroke.* (2019) 21:42–59. doi: 10.5853/jos.2018.03125
31. Cha YJ. The economic burden of stroke based on South Korea's national health insurance claims database. *Int J Health Pol Manag.* (2018) 7:904–9. doi: 10.15171/ijhpm.2018.42
32. Mas MÀ, Inzitari M. A critical review of Early Supported Discharge for stroke patients: from evidence to implementation into practice. *Int J Stroke.* (2015) 10:7–12. doi: 10.1111/j.1747-4949.2012.00950.x

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.

frontiers in Neurology

STUDY PROTOCOL
published: 09 September 2021
doi: 10.3389/fneur.2021.712512

Effects of Radial Extracorporeal Shock Wave Therapy on Flexor Spasticity of the Upper Limb in Post-stroke Patients: Study Protocol for a Randomized Controlled Trial

Tao Fan[1,2†], Xiangying Zhou[1†], Peichen He[1], Xiaojia Zhan[1], Peng Zheng[1], Rong Chen[1], Rongdong Li[1], Rihui Li[1], Mingyang Wei[1], Xue Zhang[1] and Guozhi Huang[1,2]*

[1] Department of Rehabilitation Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, China, [2] School of Rehabilitation Medicine, Southern Medical University, Guangzhou, China

OPEN ACCESS

Edited by:
Won-Seok Kim,
Seoul National University Bundang Hospital, South Korea

Reviewed by:
Le Li,
Northwestern Polytechnical University, China
Yingchun Zhang,
University of Houston, United States

***Correspondence:**
Guozhi Huang
drhuang66@163.com

[†] These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 21 May 2021
Accepted: 03 August 2021
Published: 09 September 2021

Citation:
Fan T, Zhou X, He P, Zhan X, Zheng P, Chen R, Li R, Li R, Wei M, Zhang X and Huang G (2021) Effects of Radial Extracorporeal Shock Wave Therapy on Flexor Spasticity of the Upper Limb in Post-stroke Patients: Study Protocol for a Randomized Controlled Trial. Front. Neurol. 12:712512. doi: 10.3389/fneur.2021.712512

Background: Flexor spasticity of the upper limb is common in poststroke patients and seriously affects the recovery of upper limb function. However, there are no standard management protocols for this condition. Radial extracorporeal shock wave therapy (rESWT) is widely used for various diseases, some studies reported the effects of ESWT on reducing spasticity, but the mechanism of ESWT to reduce spasticity by affecting the excitability of stretch reflex or non-neural rheological components in spastic muscles or both is not yet clear. A large randomized controlled trial with comprehensive evaluation indicators is still needed. The study is to observe the effect of rESWT on flexor spasticity of the upper limb after stroke and explore its mechanism.

Methods: A prospective, randomized, double-blind controlled trial is to be performed. One hundred participants will be recruited from the Inpatient Department of Zhujiang Hospital. Eligible patients will be randomly allocated to either receive three sessions of active rESWT (group A) or sham-placebo rESWT (group B) with 3-day intervals between each session. Assessment will be performed at baseline and at 24 h after each rESWT (t1, t2, and t3). The primary assessment outcome will be the Modified Ashworth Scale, and other assessments include surface electromyography, MyotonPRO digital muscle function evaluation, and infrared thermal imaging. All data will be analyzed using intention-to-treat principles. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and nonresponses. Per protocol, analyses will also be performed on the participants who complete other assessments. Statistical analysis will be performed using SPSS software (version 20.0) and the significance level set at $p < 0.05$.

Discussion: This trial aims to analyze the application of rESWT for the management of spasticity after stroke *via* appropriate assessments. We hypothesized that after receiving active rESWT, patients would show greater improvement of upper limb muscles compared with patients within the sham-placebo group.

The rESWT would be an alternative to traditional methods, and the results of this study may provide support for the further study of potential mechanisms.

Clinical Trial Registration: www.chictr.org.cn, identifier: ChiCTR1800016144.

Keywords: extracorporeal shock wave therapy, stroke, hemiplegia, spasticity, neurorehabilitation

BACKGROUND

Spasticity is a form of muscle hypertonia that results in the pyramidal tract when corticoreticulospinal fibers (extrapyramidal tract) are damaged, which gives an upper motor neuron syndrome due to a lesion of the central nervous system (brain and/or spinal cord) (1). After central nervous system injury, the inhibition of cerebral cortex and other higher centers is lost, and the excitability of γ-motor neurons is enhanced so that the excitability and sensitivity of muscle spindle are increased. Through the α-γ loop, the α-motor neurons in the anterior horn of the spinal cord are overexcited, resulting in an excessive increase in the stretch reflex. Continuous contractions of spasmodic muscles can lead to contracture, pain, limited joint movement, and joint deformity (2). Flexor spasticity is common in poststroke patients with upper limb dysfunction, and uncontrolled spasticity often leads to secondary complications such as pain and contractures (3) while placing a significant mental and financial burden on the patient, caregivers, and society (4). The mechanisms underlying this disorder may be due to the hyperexcitable stretch reflexes caused by the imbalance of supraspinal inhibitory and excitatory inputs after the upper motor neuron lesion (1) and also involve the changes in muscle properties (5, 6) (e.g., stiffness, fibrosis, and atrophy), which is referred as intrinsic hypertonia. Aggressive and appropriate spasticity management contributes to motor relearning and function recovery during chronic stages (4, 7). Currently, mainstream interventions for upper limb hypertonia include stretching, oral anti-spasticity medications, focal botulinum toxin (BTX) injections, and surgical treatment (7–10). However, the treatment methods mentioned earlier have advantages or drawbacks in their effectiveness and safety (8, 11–13). For example, BTX injection therapy is more effective but invasive and more expensive. Surgical treatment is more traumatic, and the risk is higher.

An extracorporeal shock wave is defined as a sequence of single sonic pulses with high peak pressure (14, 15), which can cause energy gradient differences and torsional tension between tissues of different densities through energy conversion and transmission, and form a cavitation effect, which induces a biological effect (16). During the past few decades, extracorporeal shock wave lithotripsy (17) has been widely used and has evolved to be standard therapy used for urinary calculi due to its excellent efficacy, non-invasiveness, and lack of obvious complications. At present, extracorporeal shock wave therapy (ESWT) has also been widely used for the treatment of various neurological and musculoskeletal diseases (18, 19), such as cerebral palsy (20), multiple sclerosis (21), tendinopathy (22), chronic tennis elbow (23), and nonunion of long bone fracture (24). Recently, several studies (25–27) have indicated that ESWT could be used for decreasing hypertonia in strokes. However, only a few convincing studies have been published; a systematic review (28) in 2020 evaluated the scientific reliability and methodological quality of recent clinical trials according to their level of evidence and found that among enrolled 17 studies, only seven studies obtained Sackett's grading system's highest level 1 of evidence (studies scoring 6–10). A most recent overview (29) in 2021 concluded that an ESWT effectively reduced spasticity after stroke without adverse effects, but the mechanism of action of ESWT on spasticity muscles and standard parameters of ESWT (regarding frequency, energy flux density, location, and total ESWT sessions) in poststroke spasticity remained unclear. Therefore, a prospective large-sample randomized, double-blind controlled trial with a comprehensive assessment method is needed to further confirm its efficacy and explore the underlying mechanism of ESWT on spasticity. There are two types of ESWT: focused extracorporeal shock wave therapy (fESWT) and radial extracorporeal shock wave therapy (rESWT). According to differences of mechanical properties in fESWT and rESWT and combine the study outcomes of Wu et al. (30), which was the only one to directly compare the effect of rESWT and fESWT so far, we chose rESWT device for the management of upper limb spasticity after stroke in this study.

The Modified Ashworth Scale (MAS) (31, 32) is the most widely used clinical scale to grade spasticity and shows high inter- and intra-rater reliability for the assessment of muscle tone of upper extremities. H reflex can objectively evaluate changes in the excitability of α-motor neurons before and after treatment. Motor nerve conduction velocity (MCV) is a diagnostic technique used to assess peripheral nerve conduction function. By detecting the MCV of the median nerve before and after rESWT intervention, we can observe whether the peripheral nerve has been damaged and determine the safety of the ESWT procedure. Surface electromyography (sEMG) can reflect the overall situation of muscle activity by placing surface electrodes on the muscle to collect electrical signals (33). The sEMG indexes of root mean square (RMS), integrated electromyogram (iEMG), and co-contraction ratio (CR) (34–36) can be used to assess muscle spasms objectively

Abbreviations: AE, adverse event; BM, musculus biceps brachii; BTX, botulinum toxin; CR, co-contraction ratio; CRFs, Case report forms; DMC, Data Monitoring Committee; EC, Ethics Committee; EMG, Electromyography; ESWT, Extracorporeal shock wave therapy; fESWT, focused extracorporeal shock wave therapy; H-max, the maximal amplitude of H-reflex; iEMG, Integrated electromyogram; IRT, infrared thermal imaging; MAS, Modified Ashworth Scale; MCV, motor nerve conduction velocity; MIVC, maximum isometric voluntary contraction; M-max, the maximal amplitude of M-response; rESWT, radial extracorporeal shock wave therapy; RMS, root mean square; sEMG, surface electromyography; TM, musculus triceps brachii.

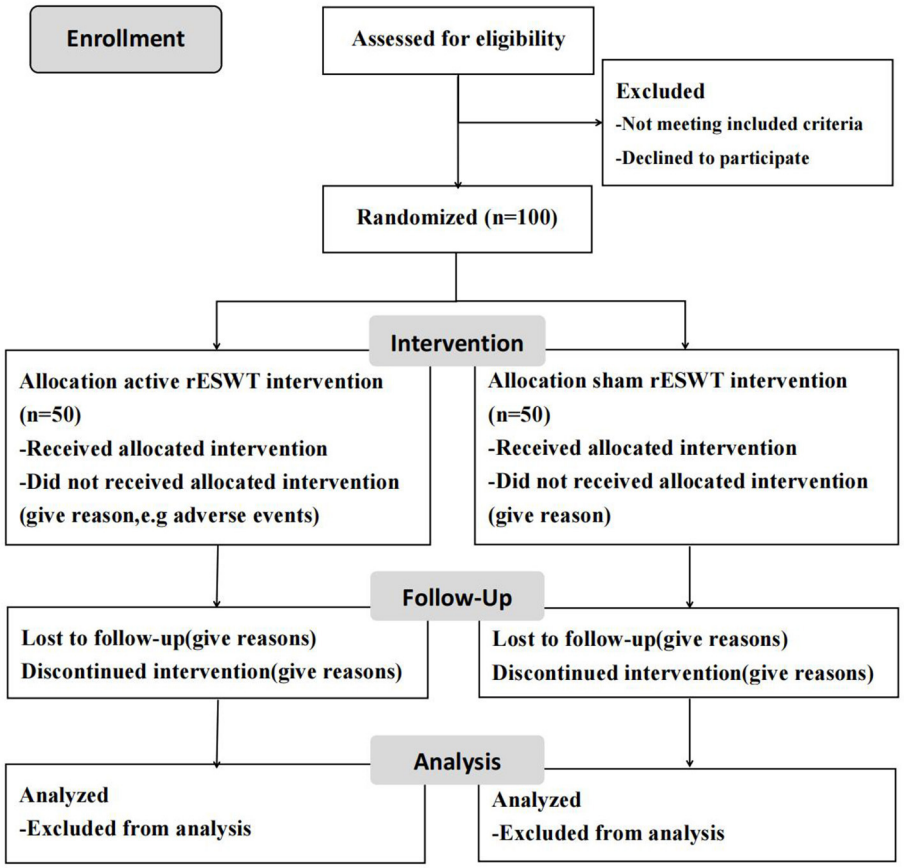


FIGURE 1 | CONSORT flow diagram of study.

and quantitatively. The MyotonPRO digital muscle function assessment system is a new non-invasive instrument that can be used to evaluate the functional status of skeletal muscles and biological soft tissue. It can quantitatively measure muscle tension, elasticity, stiffness, and other functional conditions (37, 38). A previous study by Dymarek et al. (39) has shown that ESWT can improve trophic conditions of spastic muscles. The infrared thermal imaging (IRT) system detects local trophic condition changes in spasmodic muscles of the upper limbs, which are associated with blood microcirculation and surface temperature distribution (40, 41). The assessment techniques mentioned earlier can reflect the changes of upper limb spasm, muscle tension, nerve excitability, muscle elasticity, and surface temperature of stroke patients from different perspectives and can comprehensively reflect the effects of ESWT from multiple perspectives. Therefore, this trial is designed to use the assessment techniques mentioned earlier to examine the efficacy (rESWT can relieve upper limb spasticity after stroke) and safety (rESWT has no harm to nerve, muscle, and other tissues and organs) of rESWT for the treatment of upper limb spasticity after stroke.

METHODS/DESIGN

Trial Design

This study is a prospective, double-blind, and randomized controlled trial that conformed to Standard Protocol Items of the Recommendations for Interventional Trials guidelines (42) (Additional file 1). The flow diagram of the study to be followed in this study is shown in **Figure 1**. The participants are observed during their hospital stay and are randomly assigned to either receive three rounds of treatment with active rESWT (group A) or sham-placebo rESWT (group B). Assessments including MAS, H reflex, MCV, sEMG, myotonometer, and IRT are to be performed at baseline and at 24 h after intervention.

Study Setting

The study setting is the Department of Rehabilitation Medicine at the Zhujiang Hospital of Southern Medical University, Guangzhou, China. The first patient was recruited on October 18, 2018, and the recruitment was planned to be completed within 3 years.

Patient and Public Involvement

To have scientifically rigorous clinical trials and reliable results, patients in this trial will not be involved in the design, recruitment, or conduction of the study. After the last visit, the patients will be informed by the study's physician of the results in the form of pictures and text.

Inclusion Criteria

Participants will be qualified for inclusion when they meet the following criteria: (1) meeting the "criteria for the diagnosis of cerebrovascular diseases" adopted by the Fourth Academic Conference on Cerebrovascular Diseases in 1995 (43) and confirmed using computed tomography or magnetic resonance imaging examination of the head; (2) age between 35 and 75 years old, with a first episode > 1 month and being in a stable clinical condition; (3) the presence of hemiplegic or hemiparesis with elbow joint spasticity grade > 1, determined by MAS (31); (4) no obvious cognitive impairment; and (5) the informed consent form being completed by the patient.

Exclusion Criteria

The exclusion criteria are as follows: (1) having received oral antispasmodic drugs, BTX injections, and local block or surgical treatments for decreasing spasticity; (2) fixed elbow joint muscle contracture; (3) uncontrolled hypertension; (4) patients with chronic heart failure, malignant arrhythmia, and other severe organic heart diseases; (5) patients with a pacemaker and other electronic implants; (6) the presence of coagulation dysfunction; (7) patients with local infections and skin rupture; and (8) refusal to participate in this study.

Interventions

Active Radial Extracorporeal Shock Wave Therapy Intervention (Group A): An rESW device (Power Shocker LGT-2510A, Guangzhou Longest Science & Technology Co., Ltd., China) was used for shock wave therapy. Study participants were treated in the supine position on the area of the biceps brachii, the flexor carpi radialis, and the pronator teres muscle after their affected side has been marked and the skin has been cleaned by soaking with alcohol.

The coupling gel as a contact medium is evenly applied onto the treatment probe to reduce tissue resistance, and a medium- to high-intensity pressure was applied to keep the probe close to each muscle belly. The following protocol is to be used: 2,000 shots, an energy flux density of 0.03 mJ/mm^2, a pressure of 0.2 MPa (two bars), and a frequency of 8 Hz is delivered to each marked position, for a total of three rounds of treatment, once in 3 days.

Sham Radial Extracorporeal Shock Wave Therapy Intervention (Group B): The protocol to be used is the same as that of "group A," except that pressure is one bar and no coupling gel is used on the treatment site, whereas a thick layer of gauze is placed between the skin and the probe instead, with no pressure applied.

The physiotherapist who is to perform the intervention should have received standardized training and must be familiar with the process and details of the intervention. The patients are all required to undergo the same routine therapeutic program (including common physical therapy and occupational therapy).

TABLE 1 | Definitions of MAS for grading muscle spasticity.

Grade	Modified ashworth scale (28)	Values
0	No increase in muscle tone;	0
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension;	1
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remaining (less than half) range of motion;	2
2	More marked increase in muscle tone through most of the range of motion, but affected part easily moved;	3
3	Considerable increase in muscle tone, passive movement difficult;	4
4	Affected part(s) rigid in flexion or extension.	5

For convenience of statistical analysis, a Modified Ashworth Scale grade 1+ is to be substituted with a value of 2, and grade 2, 3 and 4 are matched to 3, 4, and 5, respectively.

Outcome Measures

Primary Outcome Measure: Modified Ashworth Scale

The scale is graded in six stages, ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension). For the convenience of statistical analysis, a MAS grade of 1+ is to be substituted with a value of 2, whereas grades 2, 3, and 4 are to be substituted with values of 3, 4, and 5, respectively **Table 1**.

(1) Recovery: Muscle tension had completely returned to normal;
(2) Obvious effect: The muscle tension had not returned to normal, but muscle tension had decreased by two levels;
(3) Effective: Muscle tension had decreased by 1 level;
(4) Inefficacy: No change in muscle tone pre- and posttreatment.

Secondary Outcome Measures

Electromyography (EMG), surface electromyography (sEMG), MyotonPRO digital muscle function evaluation system, and infrared thermal imaging (IRT) are to be used for the evaluation.

1. **H reflex**: H reflex of the median nerve is to be detected using the Schwarzer topas EMG system (Natus Medical Incorporated, Pleasanton, CA, USA). The recording must be conducted from the flexor carpi radialis as follows: the recording electrode is to be placed at the mid-upper 1/3 junction of the medial humeral epicondyle and the radial styloid process line, the reference electrode is to be placed at the tendon, the ground electrode is to be placed at the olecranon, and the stimulation electrode is to be placed at the median nerve proximally to the elbow. The maximal amplitude of H-reflex (H-max) and M-response (M-max) are to be recorded. The H-max/M-max value, which can reflect the excitability change of the α-motor neuron, is to be calculated to detect changes in response to the effect of rESWT on the spasmodic muscle.

2. **Motor Nerve Conduction Velocity**: The same apparatus is to be used, but the electrodes are to be placed differently. The recording electrodes must be placed on the abductor pollicis brevis muscle belly, and the stimulating electrode must be placed on the median nerve at wrist and elbow level to record distal motor latency, MCV, and amplitude. This assessment is aimed at determining whether rESWT causes nerve injury and evaluating its safety.
3. **Root-Mean-Square Value**: An sEMG recording is to be obtained using bipolar Ag/AgCl surface electrodes (MyoMove, Northam Electric Co., Ltd., Shanghai, China) for the sEMG assessment. The patient is to be treated while in a sitting position. The electrodes are to be placed on the fullest part of the upper limbs muscle belly. The locations at which the stimulating and recording electrodes are to be placed must be rubbed with 70% alcohol to reduce skin impedance. Electrode placement is to be done as recommended by Surface EMG Non-invasive Muscle Assessment and the International Society of Electrophysiology and Kinesiology. With the upper limbs of a patient comfortably placed on the treatment table, the resting sEMG activity of the musculus biceps brachii (BM) and flexor carpi radialis are to be measured under stable and static conditions for 30 s at a time. Also, the RMS of biceps brachii and flexor carpi radialis is calculated. RMS can be used to objectively and quantitatively evaluate the condition of muscle spasms, with a higher value indicating a more severe muscle spasm.
4. **Integrated Electromyogram and Co-contraction Ratio**: The patient is seated with the upper body fixed to the seat with a wide nylon strap. The elbow of the patient is at a 45° flexed position and wrist in a neutral position, and the hand holds the handle of the arm strength test joystick of Biodex System 3® dynamometer (Biodex Medical Systems, Shirley, NY, USA). The electrodes are to be placed on the muscle belly of BM and musculus triceps brachii (TM). Training is to be performed for 1 min before the assessment to help patients familiarize themselves with the process. During the test, the patients are to be asked to stretch the elbow joint with maximum strength for 10 s to measure maximum isometric voluntary contraction (MIVC) of TM (44). The iEMG and CR of BM and TM are to be recorded for 20 and 5 s before and after contraction, respectively, as the basic control. The test is to be carried out three times, with an interval of 5 min between each application, and the maximum value is to be recorded. The assessment includes the iEMG of the BM and TM when the elbow is stretched for MIVC, and then the CR is calculated. The iEMG value can reflect the total amount of muscle discharge per unit time and is mainly used to analyze the contraction characteristics of muscles per unit time. CR refers to the proportion of antagonist muscles during the process of active muscle contraction (34), although it is well known that increased synergistic contraction of antagonistic muscles is a common phenomenon in stroke patients. The decrease of CR within MIVC of the elbow indicates a reduction in the strength of the biceps tendon.

$$CR = \frac{\text{iEMG of BM}}{\text{iEMG of BM} + \text{iEMG of TM}} \times 100\%$$

5. **MyotonPRO Digital Muscle Function Assessment System**: The MyotonPRO system (Muomeetria Ltd., Tallinn, Estonia, EU) performs a noninvasive measurement of the functional state of skeletal muscles and biological soft tissues, which can quantitatively assess the functional status of muscle tension and elasticity (45, 46). The patient is asked to completely relax while lying in the supine position on a mat, with the forearm in the mid position and the elbow joint extended (if the muscles cannot be fully extended, the forearm is supported

TABLE 2 | Flow chart of the study.

Items/Time points	Enrollment	Allocation	Post-allocation			
	-t1	**Baseline**	*t1*	*t2*	*t3*	
Basic medical history	×					
Eligibility screen	×					
Informed consent	×					
Allocation(Group A/Group B)		×				
Intervention(Group A/Group B)		×				
Assessments	MAS		×	×	×	×
	H reflex		×			×
	MCV		×			×
	RMS		×	×	×	×
	iEMG		×	×	×	×
	CR		×	×	×	×
	MyotonPRO		×	×	×	×
	IRT		×	×	×	×

Group A, active rESWT; Group B, sham-placebo rESWT; MAS, Modified Ashworth Scale; MCV, Motor nerve conduction velocity; RMS, Root mean square value; iEMG, Integrated electromyogram; CR, co-contraction ratio; IRT, Infrared Thermal Imaging; t1/ t2/ t3, at 24 hours after the first/ second/ third radial extracorporeal shock wave therapy.

on both sides to maintain the forearm neutral position). The measurement point of the BM is tested perpendicular to the skin surface. Measurement is taken once every 1 min, for three times in total, and the average is obtained. The parameters required are (47): F—natural damped oscillation frequency (hertz) to describe muscle tension; C—Creep is the ratio of muscle relaxation time to deformation time, also called Deborah number; R—Muscle internal mechanical pressure release time (millisecond); and C and R reaction to the viscoelasticity of the muscle.

6. **Infrared Thermal Imaging**: A non-invasive and non-contact infrared thermal imaging system (Baotonghua Medical Devices Co., Ltd. Chongqing, China) is to be used to detect changes in local trophic conditions related to blood microcirculation and surface temperature distribution. The instrument has a thermal sensitivity of 0.1 °C. Before measurement, all clothes covering the area to be examined must be removed, and the patients are allowed to adapt to the room for 15–20 min. The room is to be kept quiet with a temperature ranging from 22 to 27 °C and relative humidity below 45%. Then, a thermovision camera is positioned perpendicular to the area of the biceps surface on the anterior side of the arm at a distance of 1 m. The IRT value is obtained in degrees Celsius. The lower the surface temperature, the worse local blood circulation and trophic conditions of muscles.

Participants

Patients with flexor spasticity of the upper limb after stroke (**Table 2**).

Recruitment

Direct recruitment from Zhujiang Hospital.

Sample Size Calculation

The known effectiveness of poststroke spasticity treatment using conventional methods is 64.5%, whereas preliminary experiments with ESWT have shown expected effectiveness of 80%, with two-tailed tests of a significance level of $\alpha = 0.05$ and $\beta = 0.1$, which is expected to fall off at a rate of 10%, using professional software Advisor nQuery sample size estimation, for a sample size of 45 cases in each group, which can be considered as a loss rate of approximately 10%. Therefore, for this study, a sample size of 50 cases in each group was decided on, with a total sample size of 100 cases.

Randomization

Eligible patients are to be numbered sequentially based on enrollment sequence and randomly assigned to group A (active rESWT) or group B (sham-placebo rESWT), with a total of 50 patients in each. Random numbers are to be generated using a computer software program run by an external statistician. Each of the random numbers and the group assignment are to be written on a piece of paper and enclosed in a sealed envelope.

Blinding

This study uses a double-blinded design, in which interventions are performed by one physiotherapist and patients are evaluated by another physician who is unaware of the treatment or grouping. Neither of them will participate in the subsequent data analysis.

After the statistical judgment is completed, unblinding will be performed to expose the experimental group and the control group. In general, emergency unblinding is not considered.

Data Collection Methods

The evaluation index is to be collected before and after treatment is performed on all patients, with raw data recorded on case report forms (CRFs) in a timely, complete, accurate, and clear manner. To improve subject compliance, subjects who can complete the entire procedure in accordance with the protocol are to be provided with additional rehabilitation assessments and rehabilitation recommendations. If a participant chooses to withdraw, they will be asked to provide reasons, and the reasons for withdrawal are to be recorded.

Data Management

An EPIDATA 3.2 database will be used to manage data, for which input and proofreading will be performed by two researchers independently, leading to double data entry and storage.

Statistical Methods

The primary comparisons for MAS will be made using repeated measures mixed-effect model with terms of treatment, time, and corresponding baseline values as covariates. We will first examine the intervention by time interaction and then proceed to the main effects model with only group and time.

Repeated analysis of variance with *post-hoc* test will be used to compare changes between active rESWT intervention and sham rESWT intervention groups from baseline to the end of follow-up when data are normally distributed, and the Mann–Whitney U-test will be used when data are not normally distributed. A chi-square test will be used for dichotomous variables.

In secondary analyses, repeated measures mixed model will also be used to examine the associations between treatments and repeated measures outcomes. Additionally, linear regression and/or logistic regression analyses will be used to assess the associations between treatments and changes or increases in outcomes from baseline to the end of follow-up in univariate and multivariate modeling adjusted for relevant covariates.

All data will be analyzed using intention-to-treat principles. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses. Per protocol analyses will also be performed in the participants who complete other assessments, including Hmax/Mmax, MCV, RMS, iEMG, CR, MyotonPRO, and IRT. Statistical analysis will be performed using SPSS software (version 20.0) and the significance level set at $p < 0.05$.

Data and Safety Monitoring

Original CRFs will be archived and stored with corresponding subject codes after the completion of data entry and review. A Data Monitoring Committee (DMC), composed of clinicians and

biostatisticians, without any competing interests, will monitor the safety and progress of the trial.

Harm and Audit

The researchers are obliged to take necessary measures to protect the safety of the subjects. The subjects are informed that there may be adverse events (AEs) such as pain and hematomas during and after ESWT through oral notification and informed consent form. If an AE occurs during the trial, the investigator should take appropriate measures, record it in the CRF, and explain whether it has a correlation with the intervention. The incidence of AEs between groups A and B should be compared after the trial. If serious adverse events occur during the clinical trials, the investigator should immediately take appropriate treatment measures and report to the sponsor, the Ethics Committee (EC), and DMC in a timely manner.

During the trial, Tao Fan will be responsible for communicating with relevant parties (such as other investigators, trial participants, journals, and regulatory authorities) if there is a need for subsequent modification of important experimental protocols, and any modification of the trial protocol should be approved by the EC. The EC and DMC will periodically review the experimental behavior to safeguard the rights of the subjects involved in the clinical trial, to ensure the accuracy and completeness of the test records and reported data, and to ensure consistency with the protocol approved. If serious adverse events caused by interventions occur during the trial, the EC has the right to propose a modification of the trial protocol or even terminate the trial.

Trial Status

This is the second version of the study protocol dated October 20, 2017. This trial was registered on May 14, 2018. The first patient was recruited on October 18, 2018. At the time of manuscript submission, a total of 50 patients have been recruited, and we hope to complete recruitment within 3 years. After patient recruitment is completed, all data will be statistically analyzed, and a research article will be written and submitted.

Additional File

Additional file 1: Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist: recommended items to be addressed in a clinical trial protocol and related documents.*

DISCUSSION

Stroke survivors with spasticity suffer substantial mental, physical, and financial stress. Effective spasticity treatment will likely increase their functioning and their health-related quality of life. Clinical studies (48–50) have shown that ESWT may improve the muscle spasm of stroke patients without serious adverse reactions. A meta-analysis (51) found that adding the ESWT to conventional therapy provides an additional benefit for reducing upper limb spasticity, and the results may be optimal given the ESWT at the subacute phase, but the mechanism remains unclear. Many studies conducted in recent years have been investigating the biological effects of ESWT (52–55). In the past, the mechanism by which ESWT acts on musculoskeletal diseases was assumed to be mechanical decomposition, just like extracorporeal shock wave lithotripsy. However, further clinical observations and experimental results have suggested that ESWT can promote neovascularization, the release of growth factors, the differentiation of mesenchymal stem cells, and the production of endogenous nitric oxides (15, 56, 57), which can decrease the intrinsic stiffness of connective tissue, increase muscle elongation, improve tissue microcirculation, and change the formation of neuromuscular junctions of the peripheral nervous system (55, 58, 59), to achieve encouraging clinical results.

We know that poststroke spasticity is related to the hyperexcitability of stretch reflexes and the changes in muscle properties (60). There are a few hypotheses that attempt to explain the effect of ESWT reducing spasticity. Daliri et al. (48) reported a significant improvement of the wrist flexor muscles spasticity assessed by the α-motor neuron excitability and the H-reflex (H-max/M-max value) of post-ESWT after stroke. However, some studies (61, 62) found that the effect of ESWT did not relate to α-motor neuron excitability. The hypothesis on spinal cord excitability seems to be weak, which adds some support to the hypothesis that ESWT affects periphery biomechanical properties of the hypertonic muscles. Lee et al. (63) assessed the effect of a single session of ESWT on patients with stroke by an ultrasonographic assessment on gastrocnemius before the treatment and 30 min and 1 and 4 weeks after treatment, and they found that the mean scores of Achilles tendon length, muscle thickness, and pennation angle were decreased, whereas muscle fascicle length increased in the ESWT group at any follow-up time. The study showed that muscular architecture parameters related to muscle fiber mechanics were improved after ESWT. Also, this may be due to the mechanical vibration of ESWT reducing intrinsic stiffness of connective tissue and promoting the local release of angiogenetic factors and growth factors, resulting in the addition of sarcomere and increased muscle length. Furthermore, ESWT can induce nitric oxides, which seem to play an important role in spasticity relieving mechanisms through involving in the formation of neuromuscular junction formation in the peripheral nervous system and in physiological functions of the central nervous system (15, 59). A new study by Leng et al. (64) applied passive torque measurement combined with biomechanical modeling, myotonometer measurements, and electrical impedance myography to assess the changes of muscle properties induced by ESW in the spastic wrist joint, then concluded that both the neural and peripheral components played a role in muscle spasticity, and ESWT may be more effective in addressing the peripheral component of spasticity muscle.

Based on the propagation pattern and device of the waves, ESWT can be classified as fESWT and rESWT. There are some common mechanisms of biological action for fESWT and rESWT, but they also differ in penetration depth and other physical properties related to clinical effect. rESWT lacks

the characteristic features of shock waves, such as short rise-time, high peak pressure, and non-linearity (65). In addition, rESWT had a more superficial effect compared with focused shock waves that penetrated and can focus their energies much deeper into the tissue (16). Compared with fESWT, which can penetrate and focus its energies more rapid and much deeper into the tissue (pressure increasing under 10 ns, reaching 100–1,000 bars with absorption to 12 cm), the pressure of rESWT increases slowly and has a more superficial effect (pressure increasing up to 5 μs, reaching 1–10 bars and absorbed to 3 cm). Wu et al. (30) compared the effect of fESWT and rESWT for the treatment of spastic equinus in patients with stroke; they concluded that the effect of rESWT was superior to the fESWT in improving the ankle passive range of motion and plantar contact area during gait, whereas both of them showed similar improvement in the spasticity of the gastrocnemius muscle; there was no significant difference in changes for MAS scores between the two groups. Other significant differences of rESWT and fESWT in the clinical application effects are still being observed.

Through the use of new assessment techniques, this trial is designed to generate a considerable amount of outcome data to clarify its effects on the neural and peripheral contribution of muscle spasticity and provide strong supporting evidence for the effectiveness of rESWT for the management of spasticity after stroke. We hypothesize that after active rESWT, patients will show greater improvement in upper limb muscles compared with patients who have received sham-placebo rESWT treatment. rESWT would be an attractive alternative to traditional methods, and the results could provide guidance and support for the further study of potential mechanisms.

Our study also has some limitations. First, this study is a single-center clinical study, which was slow to collect subjects. Second, the rESWT interference only three sessions due to limited length of hospital stay, which may affect clinical curative during the treatment phase. Third, the follow-up time of this study is short due to the short hospital stay of the patients.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the Zhujiang Hospital of Southern Medical University has approved our study (Reference Number: 2017-KFYXK-003). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study protocol. TF is responsible for this study. GH conceived and developed the study design. XYZ and RC drafted the trial protocol and prepared the manuscript. PCH, PZ, and MYW revised the protocol. XJZ, RDL, RHL, and XZ are responsible for data acquisition and analyses. All authors have read and approved the final manuscript.

FUNDING

Guangdong Provincial Science and Technology Department self-financing fund science and technology plan project (2017ZC0121). This research project has been peer-reviewed by the Guangdong Provincial Science and Technology Department and has been approved for set up, but there is no fund sponsorship from it for this project.

ACKNOWLEDGMENTS

We thank the Department of Biostatistics, School of Public Health, Southern Medical University for statistical advice. We also thank all patients who will be participating in this study.

REFERENCES

1. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. *Brain Inj.* (2013) 27:1093–105. doi: 10.3109/02699052.2013.804202
2. Malhotra S, Pandyan AD, Rosewilliam S, Roffe C, Hermens H. Spasticity and contractures at the wrist after stroke: time course of development and their association with functional recovery of the upper limb, *Clin Rehabilit.* (2011) 25:184–91. doi: 10.1177/0269215510381620
3. Marciniak C. Poststroke hypertonicity: upper limb assessment and treatment. *Top Stroke Rehabil.* (2011) 18:179–94. doi: 10.1310/tsr1803-179
4. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. *Neurology.* (2013) 80:45–52. doi: 10.1212/WNL.0b013e3182764c86
5. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *Lancet Neurol.* (2007) 6:725–33. doi: 10.1016/S1474-4422(07)70193-X
6. Dietz V, Trippel M, Berger W. Reflex activity and muscle tone during elbow movements in patients with spastic paresis. *Ann Neurol.* (1991) 30:767–79. doi: 10.1002/ana.410300605
7. Li S. Spasticity, motor recovery, and neural plasticity after stroke. *Front Neurol.* (2017) 8:120. doi: 10.3389/fneur.2017.00120
8. Francisco GE, Mcguire JR. Poststroke spasticity management. *Stroke.* (2012) 43:3132–6. doi: 10.1161/STROKEAHA.111.639831
9. Bethoux F. Spasticity management after stroke. *Phys Med Rehabil Clin N Am.* (2015) 26:625–39. doi: 10.1016/j.pmr.2015.07.003
10. Sandrini G, Baricich A, Cisari C, Paolucci S, Smania N, Picelli A. Management of spasticity with onabotulinumtoxinA: practical guidance based on the italian real-life post-stroke spasticity survey. *Funct Neurol.* (2018) 33:37–43. doi: 10.11138/FNeur/2018.33.1.037
11. Landau W M. Oral antispastic drugs in nonprogressive neurologic diseases: a systematic review. *Neurology.* (2005) 64:1989–90. doi: 10.1212/WNL.64.11.1989-b
12. Baizabal-Carvallo JF, Jankovic J, Feld J. Flu-like symptoms and associated immunological response following therapy with botulinum toxins. *Neurotox Res.* (2013) 24:298–306. doi: 10.1007/s12640-013-9400-9
13. Salazar AP, Pinto C, Ruschel MJ, Figueiro B, Lukrafka JL, Pagnussat AS. Effectiveness of static stretching positioning on post-stroke upper-limb spasticity and mobility: systematic review with meta-analysis. *Ann Phys Rehabil Med.* (2019) 62:274–82. doi: 10.1016/j.rehab.2018.11.004

14. Ogden JA, Toth-Kischkat A, Schultheiss R. Principles of shock wave therapy. *Clin Orthop Relat Res.* (2001) 387:8–17. doi: 10.1097/00003086-200106000-00003
15. Mariotto S, de Prati AC, Cavalieri E, Amelio E, Marlinghaus E, Suzuki H. Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. *Curr Med Chem.* (2009) 16:2366–72. doi: 10.2174/092986709788682119
16. Speed C, A. systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. *Br J Sports Med.* (2014) 48:1538–42. doi: 10.1136/bjsports-2012-091961
17. Drach G W, Dretler S, Fair W, Finlayson B, Gillenwater J, Griffith D, et al. Report of the United States cooperative study of extracorporeal shock wave lithotripsy. *J Urol.* (1986) 135:1127–33. doi: 10.1016/S0022-5347(17)46015-0
18. Wang C J. Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res.* (2012) 7:11. doi: 10.1186/1749-799X-7-11
19. Korakakis V, Whiteley R, Tzavara A, Malliaropoulos N. The effectiveness of extracorporeal shockwave therapy in common lower limb conditions: a systematic review including quantification of patient-rated pain reduction. *Br J Sports Med.* (2018) 52:387–407. doi: 10.1136/bjsports-2016-097347
20. Corrado B, Di Luise C, Servodio I C. Management of muscle spasticity in children with cerebral palsy by means of extracorporeal shockwave therapy: a systematic review of the literature. *Dev Neurorehabil.* (2019) 24:1–7. doi: 10.1080/17518423.2019.1683908
21. Marinelli L, Mori L, Solaro C, Uccelli A, Pelosin E, Curra A, et al. Effect of radial shock wave therapy on pain and muscle hypertonia: a double-blind study in patients with multiple sclerosis. *Mult Scler.* (2015) 21:622–9. doi: 10.1177/1352458514549566
22. Mani-Babu S, Morrissey D, Waugh C, Screen H, Barton C. The effectiveness of extracorporeal shock wave therapy in lower limb tendinopathy: a systematic review. *Am J Sports Med.* (2015) 43:752–61. doi: 10.1177/0363546514531911
23. Chung B, Wiley J, Rose M. Long-term effectiveness of extracorporeal shockwave therapy in the treatment of previously untreated lateral epicondylitis. *Clin J Sport Med.* (2005) 15:305–12. doi: 10.1097/01.jsm.0000179137.69598.7e
24. Haffner N, Antonic V, Smolen D, Slezak P, Schaden W, Mittermayr R, et al. Extracorporeal shockwave therapy (ESWT) ameliorates healing of tibial fracture non-union unresponsive to conventional therapy. *Injury.* (2016) 47:1506–13. doi: 10.1016/j.injury.2016.04.010
25. Li T Y, Chang C Y, Chou Y C, Chen L C, Chu H Y, Chiang S L, et al. Effect of radial shock wave therapy on spasticity of the upper limb in patients with chronic stroke: a prospective, randomized, single blind, controlled trial. *Medicine (Baltimore).* (2016) 95:e3544. doi: 10.1097/MD.0000000000003544
26. Radinmehr H, Nakhostin A N, Naghdi S, Olyaei G, Tabatabaei A. Effects of one session radial extracorporeal shockwave therapy on post-stroke plantarflexor spasticity: a single-blind clinical trial. *Disabil Rehabil.* (2017) 39:483–90. doi: 10.3109/09638288.2016.1148785
27. Kim Y, Shin J, Yoon J, Kim Y, Lee S. Usefulness of radial extracorporeal shock wave therapy for the spasticity of the subscapularis in patients with stroke: a pilot study. *Chin Med J.* (2013) 126:4638–43.
28. Dymarek R, Ptaszkowski K, Ptaszkowska L, Kowal M, Sopel M, Taradaj J, Rosińczuk J. Shock waves as a treatment modality for spasticity reduction and recovery improvement in post-stroke adults - current evidence and qualitative systematic review. *Clin Interv Aging.* (2020) 15:9–28. doi: 10.2147/CIA.S221032
29. Opara J, Taradaj J, Walewicz K, Rosińczuk J, Dymarek R. The current state of knowledge on the clinical and methodological aspects of extracorporeal shock waves therapy in the management of post-stroke spasticity-overview of 20 years of experiences. *J Clin Med.* (2021) 10:261. doi: 10.3390/jcm10020261
30. Wu YT, Chang CN, Chen Y M, Hu GC. Comparison of the effect of focused and radial extracorporeal shock waves on spastic equinus in patients with stroke: a randomized controlled trial. *Eur J Phys Rehabil Med.* (2018) 54:518–25. doi: 10.23736/S1973-9087.17.04801-8
31. Bohannon R W, Smith M B. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* (1987) 67:206–7. doi: 10.1093/ptj/67.2.206
32. Meseguer-Henarejos A B, Sanchez-Meca J, Lopez-Pina J A, et al. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. *Eur J Phys Rehabil Med.* (2018) 54:576–90. doi: 10.23736/S1973-9087.17.04796-7
33. Cram J R. The history of surface electromyography. *Appl Psychophysiol Biofeedback.* (2003) 28:81–91. doi: 10.1023/A:1023802407132
34. Hammond M, Fitts S, Kraft G, Nutter P, Trotter M, Robinson L. Co-contraction in the hemiparetic forearm: quantitative EMG evaluation. *Arch Phys Med Rehabil.* (1988) 69:348–51.
35. Liang M, Dou Z, Wen H, Jiang L, Wang Q, Xiong W, et al. Correlation between the changes of surface electromyographic signals of elbow flexor and extensor and motor function in stroke patients. *National Medical Journal of China.* (2014) 94:1304–8.
36. Poon D, Chan H. Hyperactive stretch reflexes, co-contraction, and muscle weakness in children with cerebral palsy. *Dev Med Child Neurol.* (2009) 51:128–35. doi: 10.1111/j.1469-8749.2008.03122.x
37. Davidson MJ, Bryant AL, Bower WF, Frawley HC. Myotonometry reliably measures muscle stiffness in the thenar and perineal muscles. *Physiother Can.* (2017) 69:104–12. doi: 10.3138/ptc.2015-85
38. Chuang L L, Wu C Y, Lin K C. Reliability, validity, and responsiveness of myotonometric measurement of muscle tone, elasticity, and stiffness in patients with stroke. *Arch Phys Med Rehabil.* (2012) 93:532–40. doi: 10.1016/j.apmr.2011.09.014
39. Dymarek R, Taradaj J, Rosinczuk J. Extracorporeal shock wave stimulation as alternative treatment modality for wrist and fingers spasticity in poststroke patients: a prospective, open-label, preliminary clinical trial. *Evid Based Complement Alternat Med.* (2016) 2016:4648101. doi: 10.1155/2016/4648101
40. Pereira C B, Czaplik M, Blanik N, Rossaint R, Blazek V, Leonhardt S. Contact-free monitoring of circulation and perfusion dynamics based on the analysis of thermal imagery. *Biomed Opt Express.* (2014) 5:1075–89. doi: 10.1364/BOE.5.001075
41. Neves EB, Vilaca-Alves J, Rosa C, Reis VM. Thermography in Neurologic Practice. *Open Neurol J.* (2015) 9:24–7. doi: 10.2174/1874205X01509010024
42. Agha RA, Altman DG, Rosin D. The SPIRIT 2013 statement–defining standard protocol items for trials. *Int J Surg.* (2015) 13:288–91. doi: 10.1016/j.ijsu.2014.12.007
43. Chinese Academic Conference of Diseases. Criteria for the diagnosis of cerebrovascular diseases. *Chin J Neurol.* (1996) 6:379–81.
44. Boettcher C E, Ginn K A, Cathers I. Standard maximum isometric voluntary contraction tests for normalizing shoulder muscle EMG. *J Orthop Res.* (2008) 26:1591–7. doi: 10.1002/jor.20675
45. Chuang L L, Lin K C, Wu C Y, Chang C W, Chen H C, Yin H P, et al. Relative and absolute reliabilities of the myotonometric measurements of hemiparetic arms in patients with stroke. *Arch Phys Med Rehabil.* (2013) 94:459–66. doi: 10.1016/j.apmr.2012.08.212
46. Agyapong-Badu S, Warner M, Samuel D, Stokes M. Measurement of ageing effects on muscle tone and mechanical properties of rectus femoris and biceps brachii in healthy males and females using a novel hand-held myometric device. *Arch Gerontol Geriatr.* (2016) 62:59–67. doi: 10.1016/j.archger.2015.09.011
47. Schneider S, Peipsi A, Stokes M, Knicker A, Abeln V. Feasibility of monitoring muscle health in microgravity environments using Myoton technology. *Med Biol Eng Comput.* (2015) 53:57–66. doi: 10.1007/s11517-014-1211-5
48. Daliri SS, Forogh B, Emami Razavi SZ, Ahadi T, Madjlesi F, Ansari NN. A single blind, clinical trial to investigate the effects of a single session extracorporeal shock wave therapy on wrist flexor spasticity after stroke. *NeuroRehabilitation.* (2015) 36:67–72. doi: 10.3233/NRE-141193
49. Taheri P, Vahdatpour B, Mellat M, Ashtari F, Akbari M. Effect of extracorporeal shock wave therapy on lower limb spasticity in stroke patients. *Arch Iran Med.* (2017) 20:338–43.
50. Xiang J, Wang W, Jiang W, Qian Q. Effects of extracorporeal shock wave therapy on spasticity in post-stroke patients: A systematic review and meta-analysis of randomized controlled trials. *J Rehabil Med.* (2018) 50:852–9. doi: 10.2340/16501977-2385
51. Cabanas-Valdés R, Serra-Llobet P, Rodriguez-Rubio P R, López-De Celis C, Llauró-Fores M, Calvo-Sanz J. The effectiveness of extracorporeal shock wave therapy for improving upper limb spasticity and functionality in stroke patients: a systematic review and meta-analysis. *Clin Rehabil.* (2020) 34:1141–56. doi: 10.1177/0269215520932196
52. D'Agostino M, Craig K, Tibalt E, Respizzi S. Shock wave as biological therapeutic tool: From mechanical stimulation to recovery

and healing, through mechanotransduction. *Int J Surg.* (2015) 24:147–53. doi: 10.1016/j.ijsu.2015.11.030
53. Yang W, He Y, Gan L, Zhang F, Hua B, Yang P, Guo T. Cardiac shock wave therapy promotes arteriogenesis of coronary micrangium, and ILK is involved in the biomechanical effects by proteomic analysis. *Sci Rep-Uk.* (2018) 8:1814. doi: 10.1038/s41598-018-19393-z
54. Mattyasovszky S G, Langendorf E K, Ritz U, Schmitz C, Schmidtmann I, Nowak T E, et al. Exposure to radial extracorporeal shock waves modulates viability and gene expression of human skeletal muscle cells: a controlled *in vitro* study. *J Orthop Surg Res.* (2018) 13:75. doi: 10.1186/s13018-018-0779-0
55. Henk V D W, Inge V D A, Hans V S. Zwerver J. ESWT for tendinopathy: technology and clinical implications. *Knee Surg Sports Traumatol Arthrosc.* (2013) 21:1451–8. doi: 10.1007/s00167-012-2009-3
56. Rinella L, Marano F, Paletto L, Fraccalvieri M, Annaratone L, Castellano I, et al. Extracorporeal shock waves trigger tenogenic differentiation of human adipose-derived stem cells. *Connect Tissue Res.* (2018) 59:561–73. doi: 10.1080/03008207.2018.1424147
57. Seabaugh K A, Thoresen M, Giguere S. Extracorporeal Shockwave Therapy Increases Growth Factor Release from Equine Platelet-Rich Plasma *In Vitro*. *Front Vet Sci.* (2017) 4:205. doi: 10.3389/fvets.2017.00205
58. Kisch T, Wuerfel W, Forstmeier V, Liodaki E, Stang F H, Knobloch K, et al. Repetitive shock wave therapy improves muscular microcirculation. *J Surg Res.* (2016) 201:440–5. doi: 10.1016/j.jss.2015.11.049
59. Kenmoku T, Nemoto N, Iwakura N, Ochiai N, Uchida K, Saisu T, et al. Extracorporeal shock wave treatment can selectively destroy end plates in neuromuscular junctions. *Muscle Nerve.* (2018) 57:466–72. doi: 10.1002/mus.25754
60. Mukherjee A, Chakravarty A. Spasticity mechanisms - for the clinician. *Front Neurol.* (2010) 1:149. doi: 10.3389/fneur.2010.00149
61. Manganotti P, Amelio E. Long-term effect of shock wave therapy on upper limb hypertonia in patients affected by stroke. *Stroke.* (2005) 36:1967–71. doi: 10.1161/01.STR.0000177880.06663.5c
62. Santamato A, Micello M, Panza F, Fortunato F, Logroscino G, Picelli A, et al. Extracorporeal shock wave therapy for the treatment of poststroke plantar-flexor muscles spasticity: a prospective open-label study. *Top Stroke Rehabil.* (2014) 21:S17–24 doi: 10.1310/tsr21S1-S17
63. Lee C, Lee S, Yoo J, Lee S. Ultrasonographic evaluation for the effect of extracorporeal shock wave therapy on gastrocnemius muscle spasticity in patients with chronic stroke. *PMR.* (2019) 11:363–71. doi: 10.1016/j.pmrj.2018.08.379
64. Leng Y, Lo W, Hu C, Bian R, Xu Z, Shan X. Li L.The effects of extracorporeal shock wave therapy on spastic muscle of the wrist joint in stroke survivors: evidence from neuromechanical analysis. *Front Neurosci.* (2020) 14:580762. doi: 10.3389/fnins.2020.580762
65. Cleveland RO, Chitnis PV, McClure SR. Acoustic field of a ballistic shock wave therapy device. *Ultrasound Med Biol.* (2007) 33:1327–35. doi: 10.1016/j.ultrasmedbio.2007.02.014

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 October 2021
doi: 10.3389/fneur.2021.744732

A Retrospective Study on Statins and Post-stroke Patients: What About Functional Outcome and Follow-Up in a Stroke Rehabilitation Cohort?

Chiara Mele[1], Giorgio Maggioni[2], Andrea Giordano[3], Clara Lunardon[2], Francesca Balsamo[2], Alessandra Mazzone[3] and Caterina Pistarini[4]*

[1] Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy, [2] Neurorehabilitation Division, Istituti Clinici Scientifici Maugeri SPA SB, Institute of Veruno, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Novara, Italy, [3] Bioengineering Division, Istituti Clinici Scientifici Maugeri SPA SB, Institute of Veruno, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Novara, Italy, [4] Department of Physical and Rehabilitation Medicine, Istituti Clinici Scientifici Maugeri SPA SB, Institute of Genoa Nervi, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Genoa, Italy

Objective: Statins exert pleiotropic effects by influencing several mechanisms, including synaptogenesis, neurogenesis, cerebral flow regulation, and angiogenesis. Results from *in vitro* and animal models suggest that statins could have beneficial effect on functional recovery and outcome after stroke events. However, results in human studies are still controversial. The aim of our study was to evaluate the role of statin in influencing functional outcome and subsequent clinical follow-up in a large cohort of post-stroke rehabilitation patients.

Methods: This retrospective study consecutively enrolled 413 adult patients with stroke event, admitted to the division of Neurorehabilitation of the IRCCS ICS Maugeri, Veruno (Italy), for an individual rehabilitation program between 2015 and 2017. Follow-up lasted 3–5 years after discharge. Demographic data, etiology, classification, and anatomical site of stroke lesion, functional assessment, use and duration of statin therapy, and death during hospitalization were collected at baseline and on discharge. Clinical data on subsequent follow-up were also evaluated, considering these as variables: stroke recurrence, bone fractures, cardiovascular complications, and death.

Results: In our cohort, 177 patients (42.9%) were prescribed statin therapy, of whom 50 (28.2%) before the stroke event and 127 (71.8%) at the beginning of the rehabilitation process. The use and type of statin therapy as well as the duration of treatment were not associated with recovery and functional outcome, regardless of confounders including sex, age, etiology, and site of stroke lesion, and initial functional level. For what concern post-discharge clinical follow-up, the use of statin therapy was significantly associated with a lower risk of bone fractures (OR = 0.095, CI 95%: 0.012–0.743, $p = 0.01$) independently from age, sex, initial and final functional level, and comorbidities.

Conclusions: The use of statins does not seem to influence the functional outcome in post-stroke patients. However, they could exert a protective role against bone fractures during post-discharge follow-up, suggesting further evaluation on this topic.

Keywords: statin, stroke, disability, functional outcome, follow-up

OPEN ACCESS

Edited by:
Giorgio Scivoletto, Santa Lucia Foundation (IRCCS), Italy

Reviewed by:
Federico Rea, University of Milano-Bicocca, Italy
Tomas Tesar, Comenius University, Slovakia

****Correspondence:***
Chiara Mele
chiara.mele1989@gmail.com

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *20 July 2021*
Accepted: *23 September 2021*
Published: *21 October 2021*

Citation:
Mele C, Maggioni G, Giordano A, Lunardon C, Balsamo F, Mazzone A and Pistarini C (2021) A Retrospective Study on Statins and Post-stroke Patients: What About Functional Outcome and Follow-Up in a Stroke Rehabilitation Cohort? Front. Neurol. 12:744732. doi: 10.3389/fneur.2021.744732

INTRODUCTION

Statins, also known as HMG-CoA reductase inhibitors, represent a widely used class of cholesterol-lowering medications, able to reduce morbidity and mortality in individuals at high risk of cardiovascular diseases (1). Several randomized clinical trials demonstrated that statin prevents stroke in patients with cardiovascular risk factors and in survivors of first stroke (2, 3).

Stroke events are often associated with short- and long-term disability including immobilization, gait and balance impairment, cognitive deficits, and increased risk of falling and bone fractures (4, 5).

Results from animal models suggested that statins could have beneficial effects on functional and clinical outcomes in post-stroke patients (6–10). Studies on mouse models of acute stroke demonstrated that statin therapy is able to reduce infarct volume and functional disability, enhancing neurological function, synaptogenesis, angiogenesis, and migration of neuronal progenitor cells in the infarct region (6–10). Several pleiotropic properties of statin, including antithrombotic, antioxidant, anti-inflammatory, and neuroprotective effects, probably mediate these benefits (11). However, evidences from clinical studies investigating the effects of statins on post-stroke neurological and functional outcomes are conflicting, and several potential confounders often complicate the interpretation of results (12–16).

Stroke represents also a major risk factor for osteoporosis and bone fractures, which can negatively affect functional recovery, thus increasing disability and mortality risk (5, 17). An interesting beneficial effect of statins on bone metabolism has been documented. The potential association between statins and bone health was described by Mundy et al. (18). The authors observed that statins promote bone formation, through increasing the production of bone morphogenic protein-2 (BMP-2) in mouse bone cells. More recent studies reported that statin could exert anabolic and antiresorptive effects by reducing osteoclast formation and preserving osteoblasts (19–21). Even in this context, results of clinical studies are conflicting (22–27). In fact, several observational studies in humans reported a lower risk of bone fractures in patients treated with statins (22–24), whereas a cohort study in Japanese population observed an inverse association between statin use and bone mineral density (BMD) (26).

To date, it is unclear whether the use of statins in humans can actually improve functional outcome and reduce the risk of bone fractures. Therefore, the aim of our study was to evaluate the role of statins in influencing the functional outcome, the subsequent clinical follow-up, and the risk of fractures in a large cohort of post-stroke rehabilitation patients.

MATERIALS AND METHODS

Study Design and Population

In this observational retrospective study, we included all patients with stroke consecutively admitted to the division of Early Intensive Neurorehabilitation Unit of the IRCCS ICS Maugeri of Veruno, Italy, between January 1, 2015 and December 31, 2017. Collection and analysis of clinical data were performed after approval by the ethics committee of ICS Maugeri and in accordance with the ethical standards laid down in the Declaration of Helsinki. Participants, or authorized representatives, signed a written informed consent before admission to Neurorehabilitation unit.

The inclusion criteria were the following: (1) age $\geq$ 18 years, (2) diagnosis of stroke on presentation, (3) admission to a hospital emergency department within 24 h of injury, (4) admission within 1 month from the injury to the rehabilitation unit to continue clinical care and rehabilitation program, (5) up to 2 months of observation in the rehabilitation setting, and (6) availability of clinical information on post-discharge follow-up.

Exclusion criteria were pre-existing neurological diseases and/or functional disability and pregnancy.

Variables, Data Sources, and Measurements

From patients' hospital electronic records, age at occurrence of stroke event, sex, etiology and anatomical site of stroke lesion, comorbidities, functional assessments, use and duration of statin therapy, death during hospitalization were collected at baseline, during the rehabilitation workup and on discharge. Clinical data on post-discharge follow-up were also evaluated.

Stroke Classifications

Strokes were primarily classified into the two main types: ischemic or hemorrhagic. Stroke type and location were assessed using radiological imaging including computed tomography (CT) and/or magnetic resonance imaging (MRI).

The ischemic stroke subtypes were determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (28), which includes five categories: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-artery occlusion (lacune), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology. Diagnoses are based on clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state. Ischemic stroke events were also classified into four categories according to the brain territory involved using the Oxfordshire Community Stroke Project (OCSP) (29): (1) total anterior circulation infarct (TACI), (2) partial anterior circulation infarct (PACI), (3) posterior circulation infarct (POCI), or lacunar infarct (LACI) based on their maximum neurological defects.

Hemorrhagic strokes were classified according to the type and location of bleeding: (1) typical intracerebral hemorrhage, (2) atypical intracerebral hemorrhage, (3) subarachnoid hemorrhage (SAH).

Comorbidities

Comorbidity at the time of admission to our neurorehabilitation unit was assessed with the Cumulative Illness Rating Scale Geriatric Version (CIRS-G) (30). CIRS-G is a valid instrument in younger and elderly patients (31). The score differentiates among 14 organ systems. Every comorbidity of a patient was assigned to

one of the organ systems and rated from 1 (mild comorbidity) to 4 (extremely severe comorbidity).

Rehabilitation Outcome and Follow-Up

Rehabilitation outcomes were evaluated through the Functional Independence Measure (FIM) scale, an 18-item measurement tool that explores the physical, psychological, and social function of an individual (32, 33). The tool is used to assess the patient's level of disability as well as change in patient status in response to rehabilitation or medical intervention (34). FIM scale was evaluated on admission and at discharge.

All patients were followed up from 3 to 5 years after discharge. Data about the occurrence of bone fractures, stroke recurrence, cardiovascular (CV) complications, and death were collected.

Statistical Analysis

Values are expressed as median and interquartile range (IQR) or absolute number and percentage. Data were tested for normality of distribution with the Shapiro–Wilk test and log-transformed when needed in order to correct for skewness. Mann–Whitney and chi-square tests were used for comparisons between groups. Multiple linear regression analysis was used to evaluate the predictive role of the use and duration of statin therapy on functional outcome, adjusted for age, sex, etiology and site of stroke lesion, initial functional level and comorbidities. A multinomial regression model was also used to evaluate the association between the post-discharge bone fractures occurrence and the use of statin therapy. A value of $p < 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS Statistics 21 (IBM Corporation, Somers, NY, USA).

RESULTS

A total of 413 adult patients with stroke event were consecutively admitted to our Neurorehabilitation Unit for an individual rehabilitation program from January 2015 to December 2017.

Clinical characteristics, functional outcome, and follow-up data of the whole population are summarized in **Table 1**. Most of patients (85.5%) were over 65 years of age at the time of stroke event. Male sex was more prevalent than female (54.5 vs. 45.5%).

Overall, an ischemic lesion was detected in 341 patients (82.6%) whereas a hemorrhagic lesion in 72 patients (17.4%). As regard the localization of the stroke lesion, most patients (41.2%) presented multiple site lesions, with basal ganglia (31.4%) being the most involved. According to the TOAST classification, the most prevalent ischemic stroke etiology was the small-artery occlusion (33.7%), followed by cardioembolism and large-artery atherosclerosis (28.4 and 26.7%, respectively). According to OCSP classification, the brain territory most frequently involved in ischemic lesions was LACI (43.7%). In case of hemorrhagic lesions, atypical intracerebral hemorrhages were the most represented (51.4%).

Approximately half of the patients (42.9%) were prescribed statin therapy, of whom 50 (28.2%) before the stroke event and 127 (71.8%) at the beginning of the rehabilitation process. The most prescribed statin was atorvastatin (85.9%), followed by simvastatin (11.3%), and rosuvastatin (2.8%). There were no severe drug-related toxic effects during hospitalization and statin therapy was continued for the entire course of the hospital stay in the rehabilitation unit and after discharge.

Death during rehabilitative hospitalization was observed in 31 patients (7.5%).

For what concern post-discharge follow-up, stroke recurrence was observed in 42 patients (10.2%), bone fracture in 16 patients (3.9%), cardiovascular complications in 13 patients (3.1%) and death in two cases.

Comparison analyses were conducted between patients with and without statin therapy (**Table 1**). As expected, statin therapy was more frequently prescribed in ischemic stroke than in hemorrhagic events ($\chi^2 = 17.3$, $p < 0.0001$). No significant differences were found between the two groups in terms of demographic, clinical, and functional outcomes, whereas patients using statin therapy had a significant lower prevalence of bone fractures during post-discharge follow-up compared with those who were not using statin therapy ($\chi^2 = 9.1$, $p = 0.002$).

By analyzing functional outcome and post-discharge follow-up in patients treated with statin subgrouped according to the beginning of treatment, no significant differences were found in terms of FIM and post-discharge complications between patients who started statin therapy before stroke event and patients who started treatment at the beginning of rehabilitation process (**Table 2**).

Associative Analyses

Multiple linear regression analysis was conducted to evaluate the predictive role of the use of statin therapy on functional outcome. The use and type of statin therapy were not associated with the recovery and functional outcome in terms of FIM total score T1, regardless of confounders including age, sex, etiology and site of stroke lesion, initial functional level expressed as basal FIM and comorbidities (CIRS-G) (**Supplementary Table 1**). A secondary analysis was performed in the subgroup of statin users to evaluate the association between the duration of statin treatment and functional outcome. Also, the duration of treatment did not represent a predictor of recovery and functional outcome, independently from the potential confounding variables mentioned above (**Supplementary Table 2**). Basal FIM (FIM total score T0) emerged as the only independent predictor of recovery and functional outcome among the included variables.

For what concern post-discharge clinical follow-up, the use of statin therapy, in particular atorvastatin, was significantly associated with a lower risk of bone fractures (OR = 0.095, CI 95%: 0.012–0.743, and $p = 0.01$) independently from age, sex, initial and final functional level, and comorbidities (**Table 3**).

DISCUSSION

The results of our study show that the use and type of statin therapy as well as the duration of treatment were not significantly associated with the recovery and functional outcome in terms of FIM, regardless of confounders including sex, age, etiology, and site of stroke lesion, initial functional level, and comorbidities.

TABLE 1 | Clinical, rehabilitation, and follow-up characteristics of the population as a whole and subdivided into two groups according to the use or not of statin therapy.

Variables		Whole population ($n = 413$)	Statin ($n = 177$, 42.9%)	No statin ($n = 236$, 57.1%)	*p*-value
Age (years), *median* (*IQR*)		78 (69–84)	78 (71–83)	79 (69–84)	0.27
Sex	M	225 (54.5%)	100 (56.5%)	125 (53.0%)	0.47
	F	188 (45.5%)	77 (43.5%)	111 (47.0%)	
Statin—active substance	Simvastatin	–	20 (11.3%)	–	–
	Atorvastatin	–	152 (85.9%)	–	–
	Rosuvastatin	–	5 (2.8%)	–	–
Type of lesion	**Ischemic**	341 (82.6%)	**162 (91.5%)**	**179 (75.8%)**	**<0.0001**
	Haemorrhagic	72 (17.4%)	**15 (8.5%)**	**57 (24.2%)**	
TOAST (*for ischaemic stroke only*)	Large-artery atherosclerosis	91 (26.7%)	48 (29.6%)	42 (23.5%)	0.20
	Cardioembolism	97 (28.4%)	40 (24.7%)	56 (31.3%)	0.18
	Small-artery occlusion	115 (33.7%)	58 (35.8%)	53 (29.6%)	0.22
	Other etiology	34 (10.0%)	16 (9.9%)	24 (13.4%)	0.31
	Undetermined	4 (1.2%)	0 (0.0%)	4 (2.2%)	0.06
OCSP (*for ischaemic stroke only*)	TACI	86 (25.2%)	36 (22.2%)	50 (27.9%)	0.23
	PACI	49 (14.4%)	29 (17.9%)	20 (11.2%)	0.09
	POCI	57 (16.7%)	24 (14.8%)	33 (18.4%)	0.37
	LACI	149 (43.7%)	73 (45.1%)	76 (42.5%)	0.63
Haemorrhagic stroke etiology	Typical ICH	24 (33.3%)	5 (33.3%)	19 (33.3%)	1.00
	Atypical ICH	37 (51.4%)	8 (53.3%)	29 (50.9%)	0.86
	SAH	11 (15.3%)	2 (13.4%)	9 (15.8%)	0.81
Location	Frontal lobe	22 (5.3%)	8 (4.5%)	14 (5.9%)	0.53
	Parietal lobe	33 (8.0%)	16 (9.0%)	17 (7.2%)	0.49
	Temporal lobe	11 (2.7%)	1 (0.6%)	10 (4.2%)	0.06
	Occipital lobe	11 (2.7%)	4 (2.3%)	7 (3.0%)	0.66
	Cerebellum	19 (4.6%)	7 (4.0%)	12 (5.1%)	0.59
	Basal Ganglia	130 (31.4%)	62 (35.0%)	68 (28.8%)	0.18
	Brain stem	17 (4.1%)	9 (5.1%)	8 (3.4%)	0.39
	Multiple	170 (41.2%)	70 (39.5%)	100 (42.4%)	0.56
CIRS-G, *median* (*IQR*)	Total score	18 (13–22)	17 (14–21)	18 (13–22)	0.73
	Severity index	1.3 (0.9–1.6)	1.3 (1.0–1.6)	1.3 (0.9–1.6)	0.42
FIM, *median* (*IQR*)	Total score T0	52 (33–74)	52 (28–73)	53 (37–75)	0.24
	Total score T1	82 (51–106)	82 (52–105)	82 (51–107)	0.69
	Δ total score	19 (8–35)	20 (10–34)	18 (7–35)	0.24
	Motor score T0	25 (16–43)	24 (14–43)	25 (17–44)	0.35
	Motor score T1	55 (30–74)	52 (29–73)	55 (32–75)	0.86
	Δ motor score	16 (6–30)	17 (8–31)	16 (6–30)	0.34
	Cognitive score T0	27 (16–33)	27 (15–33)	27 (18–33)	0.49
	Cognitive score T1	30 (22–34)	30 (21–34)	30 (22–34)	0.78
	Δ cognitive score	1 (0–4)	1 (0–4)	1 (0–3)	0.19
Death during hospitalization		31 (7.5%)	14 (7.9%)	17 (7.2%)	0.79
Post-discharge follow-up	Stroke recurrence	42 (10.2%)	16 (9.0%)	26 (11.0%)	0.51
	Bone fractures	16 (3.9%)	**1 (0.6%)**	**15 (6.4%)**	**0.002**
	CV complications	13 (3.1%)	4 (2.3%)	9 (3.8%)	0.37
	Death	2 (0.5%)	0 (0.0%)	2 (0.8%)	0.22

Data are expressed as median and interquartile range (IQR) or absolute number and percentage. Comparison between groups were performed with χ^2 or Mann–Whitney tests. TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct; ICH, intracerebral hemorrhage; T0 on admission to neurorehabilitation, T1 at discharge; CV, cardiovascular; TOAST, Trial of Org 10172 in Acute Stroke Treatment; OCSP, Oxfordshire Community Stroke Project; SAH, subarachnoid hemorrhage; CIRS-G, Cumulative Illness Rating Scale-Geriatric; FIM, Functional Independence Measure scale.
Significant differences are shown in bold characters.

TABLE 2 | Rehabilitative and follow-up characteristics of patients treated with statin subdivided into two groups according to the beginning of treatment: patients who started statin therapy before stroke even and patients who started treatment at the beginning of rehabilitation process.

Variables		Statin before stroke ($n = 50$)	Statin during rehabilitation ($n = 127$)	*p*-value
CIRS-G, *median* (*IQR*)	Total score	19 (15–22)	17 (13–20)	0.11
	Severity index	1.4 (1.1–1.6)	1.3 (1.0–1.6)	0.87
FIM, *median* (*IQR*)	Total score T0	53 (32–72)	52 (28–73)	0.99
	Total score T1	78 (60–103)	83 (52–107)	0.95
	Δ total score	19 (8–38)	21 (11–34)	0.79
	Motor score T0	24 (15–43)	24 (14–43)	0.82
	Motor score T1	49 (33–70)	54 (29–75)	0.78
	Δ motor score	17 (8–30)	17 (8–31)	0.81
	Cognitive score T0	29 (19–33)	27 (13–32)	0.59
	Cognitive score T1	30 (24–33)	30 (20–34)	0.40
	Δ cognitive score	1 (0–3)	1 (0–4)	0.87
Death during hospitalization		4 (8.0%)	10 (7.9%)	0.91
Post-discharge follow-up	Stroke recurrence	2 (4.0%)	14 (11.0%)	0.26
	Bone fractures	0 (0.0%)	1 (0.8%)	0.11
	CV complications	1 (2.0%)	3 (2.4%)	0.88
	Death	0 (0.0%)	0 (0.0%)	–

Data are expressed as median and interquartile range (IQR) or absolute number and percentage. Comparison between groups were performed with χ^2 or Mann–Whitney tests. T0 on admission to neurorehabilitation, T1 at discharge.

TABLE 3 | Multinomial regression model evaluating the negative association between statin therapy and bone fractures.

Covariates		Bone fractures		
		OR	**CI 95%**	***p*-value**
Age		1.014	0.963–1.068	0.59
Sex	M	0.785	0.347–4.064	0.78
	F	1	–	Reference
CIRS-G total score		0.929	0.836–1.033	0.18
FIM total score T0		1.004	0.962–1.048	0.86
FIM total score T1		1.018	0.988–1.050	0.24
Statin therapy	Yes	**0.095**	**0.012–0.743**	**0.01**
	No	1	–	Reference

Dependent variable: bone fractures (No = 0, Yes = 1), covariates: age, sex, CIRS-G total score, FIM total score T0 and T1, statin therapy (No = 0, Yes = 1).
TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct; ICH, Intracerebral hemorrhage; T0 on admission to neurorehabilitation, T1 at discharge.
Significant differences are shown in bold characters.

However, during post-discharge clinical follow-up, statin users were found to be at lower risk of developing bone fractures.

Despite currently available treatment options for stroke events, patients often face the prospect of substantial post-stroke disability that could influence the occurrence of other clinical complications and impact quality of life (35). Randomized controlled trials demonstrated that statins are able to prevent ischemic stroke in high-risk patients and in survivors of first stroke (2, 3). More recently, some evidences suggest that statin therapy could improve rehabilitation and functional outcomes after both ischemic and hemorrhagic stroke (12, 15, 16). Animal stroke models showed that statins have microvascular and neuroprotective properties. In mice, pre-treatment with high-dose statin enhances an upregulation of endothelial nitric oxide synthase (eNOS), thus promoting cerebral blood flow and a reduction of infarct volume, and improving neurological function (7, 36). In mice with embolic stroke, low atorvastatin doses are able to induce the expression of vascular endothelial growth factor (VEGF), thus promoting neovascularization, and improve neurological function by enhancing synaptogenesis and proliferation of neural progenitor cells (10). Neuroprotective effects of statins, including antioxidative, anti-inflammatory, angiogenic, neurogenic, and antiapoptotic properties, have also been demonstrated in animals with hemorrhagic stroke (37). All these findings led to hypothesized that statin administration may positively influence cerebral repair after injury acting on neurogenesis and angiogenesis (7, 9, 10, 16, 36).

However, evidences from clinical studies evaluating the effects of statins on stroke rehabilitation and functional outcome are conflicting, and the interpretation of results is often difficult because of small sample size, possible bias, and confounders (12–16). Whereas several observational studies observed a decreased mortality rate or improved functional outcomes in patients treated with statins, these beneficial effects were not demonstrated in other studies (13–16, 38–40). Also, results from randomized controlled trials and meta-analysis were not univocal (12, 41–43). With the aim of clarifying this issue, we evaluated the

possible role of statins in influencing the functional outcome in terms of FIM in a large cohort of stroke patients with different etiology, by using a multinomial logistic regression analysis in order to eliminate the effect of possible confounders including age, sex, etiology and site of stroke lesion, initial functional level, and comorbidities.

It is important to point out that most of previous studies used modified Rankin scale (mRS) to evaluate functional outcome. The mRS is a single-item scale for assessing levels of functional independence among stroke survivors. It is used to categorize level of functional independence with reference to pre-stroke activities rather than on observed performance of a specific task (44). Our study evaluated functional outcome using FIM that represents a widely accepted functional assessment measure applied during inpatient rehabilitation (44, 45). The FIM is an 18-item ordinal scale, used with all diagnoses within a rehabilitation population and measures independent performance in self-care, sphincter control, transfers, locomotion, communication, and social cognition (45). With respect to mRS, FIM addresses a greater number of items and an accurate evaluation of several aspects both in motor and cognitive functions.

In contrast to our expectation that statin treatment has a significant beneficial effect on functional outcome after stroke, our results show that the use and type of statin therapy as well as the duration of treatment did not significantly influence the recovery and functional outcome, in agreement with other previous clinical studies (38, 40, 42). Despite the well-known pleiotropic effects of statins and its potential role in influencing rehabilitation and functional outcome in animal models, in clinical practice patients generally have many potential individual and clinical factors that could influence rehabilitation, thus masking the effect of statins. Moreover, most of clinical studies, including ours, evaluated only a short-term functional outcome. Therefore, further clinical trials and experimental model data will be required to elucidate the potential role and effect of statin treatment on short-term and long-term functional outcome.

Our study also evaluated post-discharge clinical follow-up lasted 3–5 years after discharge in terms of stroke recurrence, bone fractures, CV complications, and death. Our results suggest that statin users were at lower risk of developing bone fractures. Many evidences suggest that stroke represent a major risk factor for bone fracture and osteoporosis, as it induces immobilization, balance impairment, gait disability, and increases fall risk (5, 17). Fractures can further impair functional recovery, increasing disability, and mortality risk in these patients (4, 46). Several studies hypothesized a further pleiotropic effect of statins in reducing osteoporosis and bone fractures, but controversial results have been reported (22–27). The potential source of the conflicting results could be related to many factors including ethnicity, the individual predisposition to develop osteoporosis, as well as dosage and duration of statin therapy. A meta-analysis of Jin et al. (47) that included studies on general population showed that statin therapy is significantly associated with a decreased risk of overall fractures. Recently, Lin et al. (24), in a retrospective study specifically focused on stroke patients, reported that statin therapy is able to decrease the risk of osteoporosis and bone fractures of about 30% with a dose effect-relationship. However, these studies did not consider comorbidities as well as the initial and final functional level, which could represent potential confounders. Our results show that the use of statin therapy, and in particular atorvastatin, was significantly associated with a lower risk of bone fractures in post-stroke patients, independently from age, sex, initial and final functional level, and comorbidities, suggesting a potential intrinsic effect of the statin molecule on bone metabolism. The mechanisms underlying the relationship between statins, osteoporosis, and bone fractures have not yet been elucidated. *In vitro* and *in vivo* studies demonstrated that statins increase expression of BMP-2, which has a key role in the processes of bone formation, promote osteogenic activity, and simultaneously inhibit osteoblast activity through different molecular pathways (19–21).

Our study has several limitations, which should be pointed out. First, the retrospective nature of the study does not allow us to draw any conclusion about the mechanisms involved in the negative association between statin and bone metabolism. Second, we did not assess all the individual risk factors that could influence the lack of association between statin use and functional outcome.

In conclusion, in our cohort of post-stroke patients, the use of statins does not seem to influence the functional outcome. However, they could exert a protective role against bone fractures during post-discharge follow-up, suggesting further evaluation on this topic.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Istituti Clinici Scientifici Salvatore Maugeri, IRCCS, Veruno. The patients/participants, or their authorized representatives, provided a written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM designed the study and drafted the manuscript. GM and AG interpreted the results and contributed to the discussion. CL and FB collected and analyzed data. AM contributed to analyse data and reviewed the manuscript. CP reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.744732/full#supplementary-material

REFERENCES

1. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* (2016) 316:2008–24. doi: 10.1001/jama.2015.15629
2. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* (2005) 366:1267–78. doi: 10.1016/S0140-6736(05)67394-1
3. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* (2006) 355:549–59. doi: 10.1056/NEJMoa061894
4. Huo K, Hashim SI, Yong KL, Su H, Qu QM. Impact and risk factors of post-stroke bone fracture. *World J Exp Med.* (2016) 6:1–8. doi: 10.5493/wjem.v6.i1.1
5. Callaly EL, Ni Chroinin D, Hannon N, Sheehan O, Marnane M, Merwick A, et al. Falls and fractures 2 years after acute stroke: the North Dublin Population Stroke Study. *Age Ageing.* (2015) 44:882–6. doi: 10.1093/ageing/afv093
6. Cimino M, Balduini W, Carloni S, Gelosa P, Guerrini U, Tremoli E, et al. Neuroprotective effect of simvastatin in stroke: a comparison between adult and neonatal rat models of cerebral ischemia. *Neurotoxicology.* (2005) 26:929–33. doi: 10.1016/j.neuro.2005.03.009
7. Amin-Hanjani S, Stagliano NE, Yamada M, Huang PL, Liao JK, Moskowitz MA. Mevastatin, an HMG-CoA reductase inhibitor, reduces stroke damage and upregulates endothelial nitric oxide synthase in mice. *Stroke.* (2001) 32:980–6. doi: 10.1161/01.STR.32.4.980
8. Sironi L, Cimino M, Guerrini U, Calvio AM, Lodetti B, Asdente M, et al. Treatment with statins after induction of focal ischemia in rats reduces the extent of brain damage. *Arterioscler Thromb Vasc Biol.* (2003) 23:322–7. doi: 10.1161/01.ATV.0000044458.23905.3B
9. Berger C, Xia F, Maurer MH, Schwab S. Neuroprotection by pravastatin in acute ischemic stroke in rats. *Brain Res Rev.* (2008) 58:48–56. doi: 10.1016/j.brainresrev.2007.10.010
10. Chen J, Zhang ZG, Li Y, Wang Y, Wang L, Jiang H, et al. Statins induce angiogenesis, neurogenesis, and synaptogenesis after stroke. *Ann Neurol.* (2003) 53:743–51. doi: 10.1002/ana.10555
11. Vaughan CJ. Prevention of stroke and dementia with statins: effects beyond lipid lowering. *Am J Cardiol.* (2003) 91:23B—9B. doi: 10.1016/S0002-9149(02)03270-8
12. Biffi A, Devan WJ, Anderson CD, Cortellini L, Furie KL, Rosand J, et al. Statin treatment and functional outcome after ischemic stroke: case-control and meta-analysis. *Stroke.* (2011) 42:1314–9. doi: 10.1161/STROKEAHA.110.605923
13. Reeves MJ, Gargano JW, Luo Z, Mullard AJ, Jacobs BS, Majid A, et al. Effect of pretreatment with statins on ischemic stroke outcomes. *Stroke.* (2008) 39:1779–85. doi: 10.1161/STROKEAHA.107.501700
14. Arboix A, García-Eroles L, Oliveres M, Targa C, Balcells M, Massons J. Pretreatment with statins improves early outcome in patients with first-ever ischaemic stroke: a pleiotropic effect of statins or a beneficial effect of hypercholesterolemia? *BMC Neurol.* (2010) 10:47. doi: 10.1186/1471-2377-10-47
15. Silva Marques J, Ennis G, Venade G, João Soares R, Monteiro N, Gomes A. Association of statins with functional outcome and 30-day mortality in patients with intracerebral hemorrhage. *Cureus.* (2021) 13:e14421. doi: 10.7759/cureus.14421
16. Ní Chróinín D, Callaly EL, Duggan J, Merwick Á, Hannon N, Sheehan Ó, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. *Stroke.* (2011) 42:1021–9. doi: 10.1161/STROKEAHA.110.596734
17. Carda S, Cisari C, Invernizzi M, Bevilacqua M. Osteoporosis after stroke: a review of the causes and potential treatments. *Cerebrovasc Dis.* (2009) 28:191–200. doi: 10.1159/000226578
18. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, et al. Stimulation of bone formation *in vitro* and in rodents by statins. *Science.* (1999) 286:1946–9. doi: 10.1126/science.286.5446.1946
19. Monjo M, Rubert M, Ellingsen JE, Lyngstadaas SP. Rosuvastatin promotes osteoblast differentiation and regulates SLCO1A1 transporter gene expression in MC3T3-E1 cells. *Cell Physiol Biochem.* (2010) 26:647–56. doi: 10.1159/000322332
20. Yamashita M, Otsuka F, Mukai T, Otani H, Inagaki K, Miyoshi T, et al. Simvastatin antagonizes tumor necrosis factor-alpha inhibition of bone morphogenetic proteins-2-induced osteoblast differentiation by regulating Smad signaling and Ras/Rho-mitogen-activated protein kinase pathway. *J Endocrinol.* (2008) 196:601–13. doi: 10.1677/JOE-07-0532
21. Ahn KS, Sethi G, Chaturvedi MM, Aggarwal BB. Simvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, suppresses osteoclastogenesis induced by receptor activator of nuclear factor-κB ligand through modulation of NF-κB pathway. *Int J Cancer.* (2008) 123:1733–40. doi: 10.1002/ijc.23745
22. Helin-Salmivaara A, Korhonen MJ, Lehenkari P, Junnila SY, Neuvonen PJ, Ruokoniemi P, et al. Statins and hip fracture prevention–a population based cohort study in women. *PLoS One.* (2012) 7:e48095. doi: 10.1371/journal.pone.0048095
23. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. *JAMA.* (2000) 283:3205–10. doi: 10.1001/jama.283.24.3205
24. Lin SM, Wang JH, Liang CC, Huang HK. Statin use is associated with decreased osteoporosis and fracture risks in stroke patients. *J Clin Endocrinol Metab.* (2018) 103:3439–48. doi: 10.1210/jc.2018-00652
25. LaCroix AZ, Cauley JA, Pettinger M, Hsia J, Bauer DC, McGowan J, et al. Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med.* (2003) 139:97–104. doi: 10.7326/0003-4819-139-2-200307150-00009
26. Wada Y, Nakamura Y, Koshiyama H. Lack of positive correlation between statin use and bone mineral density in Japanese subjects with type 2 diabetes. *Arch Intern Med.* (2000) 160:2865. doi: 10.1001/archinte.160.18.2865
27. Peña JM, Aspberg S, MacFadyen J, Glynn RJ, Solomon DH, Ridker PM. Statin therapy and risk of fracture: results from the JUPITER randomized clinical trial. *JAMA Intern Med.* (2015) 175:171–7. doi: 10.1001/jamainternmed.2014.6388
28. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
29. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet.* (1991) 337:1521–6. doi: 10.1016/0140-6736(91)93206-O
30. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc.* (1968) 16:622–6. doi: 10.1111/j.1532-5415.1968.tb02103.x
31. Hudon C, Fortin M, Vanasse A. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. *J Clin Epidemiol.* (2005) 58:603–8. doi: 10.1016/j.jclinepi.2004.10.017
32. Linacre JM, Heinemann JW, Wright BD, Granger CV, Hamilton BB. The structure and stability of the functional independence measure. *Arch Phys Med Rehabil.* (1994) 75:127–32. doi: 10.1016/0003-9993(94)90384-0
33. Mackintosh S. Functional independence measure. *Aust J Physiother.* (2009) 55:65. doi: 10.1016/S0004-9514(09)70066-2
34. Heinemann AW, Linacre JM, Wright BD, Hamilton BB, Granger C. Relationships between impairment and physical disability as measured by the functional independence measure. *Arch Phys Med Rehabil.* (1993) 74:566–73. doi: 10.1016/0003-9993(93)90153-2
35. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol Res Pract.* (2020) 2:17. doi: 10.1186/s42466-020-00060-6
36. Endres M, Laufs U, Huang Z, Nakamura T, Huang P, Moskowitz MA, et al. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A.* (1998) 95:8880–5. doi: 10.1073/pnas.95.15.8880
37. Chen CJ, Ding D, Ironside N, Buell TJ, Elder LJ, Warren A, et al. Statins for neuroprotection in spontaneous intracerebral hemorrhage. *Neurology.* (2019) 93:1056–066. doi: 10.1212/WNL.0000000000008627
38. Elkind MS, Flint AC, Sciacca RR, Sacco RL. Lipid-lowering agent use at ischemic stroke onset is associated with decreased mortality. *Neurology.* (2005) 65:253–8. doi: 10.1212/01.WNL.0000171746.63844.6a
39. Aslanyan S, Weir CJ, McInnes GT, Reid JL, Walters MR, Lees KR. Statin administration prior to ischaemic stroke onset and survival: exploratory

evidence from matched treatment-control study. *Eur J Neurol.* (2005) 12:493–8. doi: 10.1111/j.1468-1331.2005.01049.x
40. Miedema I, Uyttenboogaart M, Koopman K, De Keyser J, Luijckx GJ. Statin use and functional outcome after tissue plasminogen activator treatment in acute ischaemic stroke. *Cerebrovasc Dis.* (2010) 29:263–7. doi: 10.1159/000275500
41. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol.* (2007) 6:961–9. doi: 10.1016/S1474-4422(07)70250-8
42. Montaner J, Chacón P, Krupinski J, Rubio F, Millán M, Molina CA, et al. Simvastatin in the acute phase of ischemic stroke: a safety and efficacy pilot trial. *Eur J Neurol.* (2008) 15:82–90. doi: 10.1111/j.1468-1331.2007.02015.x
43. Goldstein LB, Amarenco P, Zivin J, Messig M, Altafullah I, Callahan A, et al. Statin treatment and stroke outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke.* (2009) 40:3526–31. doi: 10.1161/STROKEAHA.109.557330
44. Silva SM, Brandão TCP, Silva FPD, Buchalla CM. Identification of categories of the International Classification of Functioning, Disability and Health in functional assessment measures for stroke survivors: a systematic review. *Disabil Rehabil.* (2020) 42:156–62. doi: 10.1080/09638288.2018.1496149
45. Gillen G. Functional independence measure. In: Gillen G, editor. *Cognitive and Perceptual Rehabilitation.* St. Louis, MO: Mosby (2009). p. 1–31.
46. Cummings SR, Eastell R. Risk and prevention of fracture in patients with major medical illnesses: a mini-review. *J Bone Miner Res.* (2016) 31:2069–72. doi: 10.1002/jbmr.3030
47. Jin S, Jiang J, Bai P, Zhang M, Tong X, Wang H, et al. Statin use and risk of fracture: a meta-analysis. *Int J Clin Exp Med.* (2015) 8:8269–75.

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

CLINICAL TRIAL
published: 29 October 2021
doi: 10.3389/fneur.2021.745618

Immediate Effect of Dry Needling at Myofascial Trigger Point on Hand Spasticity in Chronic Post-stroke Patients: A Multicenter Randomized Controlled Trial

Zengqiao Zhang[1,2†], Wu Wang[3†], Yongjia Song[2†], Tianjun Zhai[2], Yan Zhu[3], Liming Jiang[1], Qunfeng Li[1], Lei Jin[4], Kunpeng Li[2] and Wei Feng[1,2*]*

[1] Department of Rehabilitation, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2] School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [3] Department of Neurological Rehabilitation, Shanghai Second Rehabilitation Hospital, Shanghai, China, [4] Department of Rehabilitation, Shanghai Hudong Hospital, Shanghai, China

OPEN ACCESS

Edited by:
Won-Seok Kim,
Seoul National University Bundang Hospital, South Korea

Reviewed by:
Pengxu Wei,
National Research Center for Rehabilitation Technical Aids, China
Areerat Suputtitada,
Chulalongkorn University, Thailand

***Correspondence:**
Kunpeng Li
xyfyli@163.com
Wei Feng
fwginger@126.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *22 July 2021*
Accepted: *30 September 2021*
Published: *29 October 2021*

Citation:
Zhang Z, Wang W, Song Y, Zhai T, Zhu Y, Jiang L, Li Q, Jin L, Li K and Feng W (2021) Immediate Effect of Dry Needling at Myofascial Trigger Point on Hand Spasticity in Chronic Post-stroke Patients: A Multicenter Randomized Controlled Trial. Front. Neurol. 12:745618. doi: 10.3389/fneur.2021.745618

Background: Hand spasticity after stroke influences the rehabilitation of hand function. Immediate and effective relief of spasticity potentially creates conditions for later rehabilitation training, which has far-reaching significance in the smooth transition of patients to the recovery period.

Objective: To evaluate the immediate effect of dry needling (DN) at myofascial trigger point on hand spasticity in stroke patients.

Methods: This was a prospective, evaluator blind, multicenter, randomized controlled study. A total of 210 participants were randomly divided into DN group (DN, $N = 70$), sham dry needling group (SDN, $N = 70$), and control group ($N = 70$). Participants in the DN group were treated with DN at myofascial trigger point five times (30 min each time) every week for 4 weeks. Subjects in the SDN group were manipulated the same way as in the DN group, except that the acupuncture site was located in the area adjacent to the myofascial trigger point, which constituted a SDN. Routine rehabilitation treatment was performed for participants in the two groups and in the control group. The primary evaluation index was the immediate effect of hand spasticity relief. Secondary evaluation indicators included the cumulative effect of hand spasticity relief from baseline to week 4, and the changes in flexion angles of the wrist, thumb, and fingers 2–5 in the rest position before, immediately after, and 4 weeks after intervention.

Results: The immediate effective rate of spasticity relief (thumb, fingers 2–5, and wrist) of patients with different degrees of spasticity in the DN group was higher than that in the control and SDN groups (thumb, $\chi^2 = 55.833$, $P < 0.001$; fingers 2–5, $\chi^2 = 68.096$, $P < 0.001$; wrist, $\chi^2 = 49.180$, $P < 0.001$) ($P < 0.05$). The effective rate of spasticity relief from baseline to 4 weeks in the DN group exceeded that in the control group and SDN groups (thumb, $\chi^2 = 8.806$, $P = 0.012$; fingers 2–5, $\chi^2 = 8.087$, $P = 0.018$; and wrist, $\chi^2 = 8.653$, $P = 0.013$) ($P < 0.05$). No difference in immediate and cumulative effect was found between the control group and SDN group. The change of joints flexion angles in

resting position before and after each treatment in the DN group was higher than that in the control and SDN groups ($P < 0.05$), but it was not significantly different between the control group and SDN group. At 4 weeks, although the change in the DN group was higher than that in the control group and SDN group, this difference was not statistically significant ($P > 0.05$).

Conclusion: Dry needling can relieve varying degrees of hand spasticity instantly in post-stroke.

Trial Registration: www.chictr.org.cn, ChiCTR1900022379.

Keywords: stroke, hand spasticity, dry needling, myofascial trigger point, immediate effect

INTRODUCTION

Stroke is a common disease that has seen an unprecedented rise in incidence, disability, and mortality (1). In spite of the declining mortality of stroke over the years, the disability rate is still soaring (2). The predominant association between physical disability and muscle spasticity delay the recovery time of limb function of patients (3). The incidence of spasticity can reach 42.6% in the chronic phase (>3 months post-stroke) (4). And there are different strategies by which spasticity can obstruct the improvement of hand function. As such, treating spasticity is a crucial approach to post-stroke management. In most cases, management of hypertonia occupies the majority of each rehabilitation session, and this reduces therapeutic efficiency greatly. This process is so distressing that patients consider discontinuing treatment, underscoring the need for immediate spasm relief, which is a prerequisite for rehabilitation of hand function with subsequent therapeutic approaches.

Conventional therapies for post-stroke spasticity primarily comprise physical therapy, surgical intervention, and pharmacotherapy (5). Physical therapy has demonstrated promising results in the management of post-stroke patients with limb spasticity. However, corresponding standards or clinical guidelines to guide the implementation of physical therapy, such as frequency or duration, are lacking. In addition, the majority of physical therapy interventions take a long duration, resulting in poor patient compliance and greatly reduced treatment efficacy (5). Although pharmacotherapy exerts some beneficial effects in post-stroke patients with limb spasticity, prolonged use of anti-spasmodics poses a risk of adverse effects and drug resistance; also, the high cost limits their application (6, 7). Surgical intervention can be a reliable option for post-stroke patients with severe spasticity; however, surgical treatment currently has few clinical applications because it is associated with high risk, numerous complications, and inaccurate effects (8). Therefore, a facile, cost-effective, and effective method is needed to offer immediate spasm relief and set the stage for rehabilitation training.

The DN technique was first put forward by Janet Travell in the 1940s. The American Physical Therapy Association (APTA) defined DN as a common intervention approach that entails the penetration of the skin with thin needles at the myofascial trigger point, muscle, and connective tissue to relieve musculoskeletal pain and dyskinesia (9). In recent years, mounting evidence supports a role for dry acupuncture at myofascial trigger points in improving dystonia in patients with neurological diseases (10). Although DN had a positive effect on lower limb spasticity in stroke patients, it had a negative effect on upper limb spasticity (11, 12). However, these results are derived from studies with low quality. Therefore, further high-quality studies are needed to confirm or refute the effect of DN on spasticity at the trigger point.

In our previous clinical practice, we found that the myofascial trigger point was repeatedly touched between the first metacarpal bone and the second metacarpal bone in post-stroke patients with hand spasticity. Dry needling (DN) at this myofascial trigger point elicited immediate relief from spasm, but a robust randomized controlled trial to provide further supportive evidence was lacking. In the present work, we performed a multicenter, prospective, randomized controlled trial to further evaluate the immediate efficacy of DN at myofascial trigger point in post-stroke patients with hand spasticity.

MATERIALS AND METHODS

Study Design

This prospective, multicenter, three-arm, randomized controlled clinical trial was performed in line with the criteria of relevant trial guidelines and was approved by the Institutional Review Board and the Ethical Committee (2018-IRBQYYS). We registered the clinical trial on the Chinese clinical trial registry (ChiCTR1900022379) before the enrolment of the first participant.

Participants

Participants were recruited from the Seventh People's Hospital Affiliated with the Shanghai University of traditional Chinese medicine, Shanghai Second rehabilitation hospital, and Shanghai Hudong hospital through the web platform, outpatient, and inpatient clinical poster advertisements.

The Inclusion Criteria Were as Follows

① Clinically diagnosed with stroke (13); ② Brunnstrom stages ranged from II to IV; ③ spasticity of the hand [Modified Ashworth Scale (MAS) score 1^{+}-3); ④ aged between 50 and 70 years; ⑤ could understand the content of the scale and cooperate

with the evaluation and treatment; ⑥ agreed to engage in the trial and signed the informed consent.

The Exclusion Criteria Were as Follows

① Secondary Parkinson's disease; ② aphasia, conscious, or cognitive impairment; ③ severe bleeding tendency or infection of treatment site; ④ received other related treatment in the past 3 months; ⑤ other causes of hand spasticity; ⑥ combined with muscle contracture or joint deformity; ⑦ pregnant and lactating women; ⑧ fear of acupuncture or fainting.

Researchers in our team selected the qualified participants according to the relevant standards. Eligible participants were informed of the research plan and signed informed consent after preliminary screening were further assessed by a therapist.

Randomization and Masking

Eligible participants were allocated in a 1:1:1 ratio. Nine randomized groups were stratified in three hospitals. The random sequence was performed using a computer-generated code generated using SAS software version 9.4 (SAS Institute) with a random seed of 2,118 generated centrally at the Clinical Trials Center of Shanghai Seventh People's hospital. The generated random sequence was kept by a specially designated person. The clinical research coordinator recorded the information of participants, obtained random numbers, and determined their allocation. The research assistant screened and recruited participants and assigned them random numbers in the entire research process. The evaluator of the results was responsible for recording the scale data. All rehabilitation therapists, outcome assessors, and statisticians were blind to group assignment.

Study Interventions

All interventions were performed by practitioners with relevant legal qualifications and extensive clinical experience.

Dry Needling Group

Participants in this group were treated with DN at myofascial trigger point five times a week (30 min each time) for 4 weeks. In addition, they were given routine rehabilitation therapy at the same frequency and intensity as the control group.

The location of myofascial trigger point: The patient remained seated or supine, with the doctor standing on the patient's side. Briefly, the operator's thumb and the area between the first metacarpal bone and the second metacarpal bone on the back of the patient's hand were disinfected with a 75% alcohol cotton ball. Subsequently, the operator applied unidirectional pressure from the distal end to the proximal end in the area between the first metacarpal bone and the second metacarpal bone on the dorsal side of the patient's palm with the sterilized screw surface of the thumb. In this process, the operator touched the cord like nodules, and the patient would feel an obvious pain. Deep pressure led to distal referred pain, which is the myofascial trigger point (**Figure 1**).

Method of needling: After routine disinfection, the operator swiftly penetrated a sterile needle (0.3 mm * 25 mm) vertically into the myofascial trigger point. The success criteria of acupuncture were local pain, distal finger pain, and finger twitch. The needle was kept for 30 min following the induction of a convulsive reaction.

Sham Dry Needling Group

Participants in this group received sham dry acupuncture five times a week (30 min each time) for 4 weeks. The acupuncture needle was inserted 2 mm lateral to myofascial trigger point to a depth of 2 mm without manual stimulation (14). In addition, subjects received routine rehabilitation therapy at the same frequency and intensity as the control group.

Control Group

The participants in this group received routine rehabilitation treatment, including recumbent position, neurodevelopmental treatment, and activities of daily living (ADL) treatment, five times a week for 4 weeks. The participants were also given routine anti-stroke treatment.

Outcome Measures

Primary Outcome Measurement

The primary outcome was the immediate effect of DN at myofascial trigger point on thumb spasticity relief. The spasticity grade of flexor muscles was assessed with MAS before and immediately after each treatment. Treatment was considered effective when MAS score was reduced by at least one grade.

Secondary Outcome Measures

Secondary outcomes included the immediate effect of DN at myofascial trigger point on fingers 2–5 and wrist spasticity relief, the cumulative effect of hand (thumb, fingers 2–5, and wrist) spasticity relief from baseline to week 4, and changes of the flexion angles of the wrist, thumb (metacarpophalangeal joint, interphalangeal joint), and fingers 2–5 (metacarpophalangeal joint, proximal interphalangeal joint, distal interphalangeal joint) of the affected hand before and right after each treatment and at the end of 4-week intervention. Participants were asked to adopt a natural position during the assessments. In this study, joint angle was measured at the condition that patients were in a supine position with their arms placed on both sides of body, elbow stretched, and palm up. Then fix the protractor so that its axis was aligned with the center of the joint. In addition, subgroup analysis was performed to provide further evidence for our findings.

Statistical Analyses

The purpose of this study was to explore whether there was any difference in the effective rate of immediate relief in post-stroke patients with hand spasticity among the DN group, the sham dry needling (SDN) group, and the control group. According to our preliminary study, the effective rates of immediate remission of thumb spasm after each treatment were assumed to be 55% (control group), 80% (DN group), and 50% (SDN group), respectively. Herein, assuming a dropout rate of 20%, the allowable error of 5%, and the test power of 90%, we needed a sample size of 210 (70 in each group).

Descriptive statistics were performed on the baseline characteristics of patients. Student *t*-test or one-way ANOVA

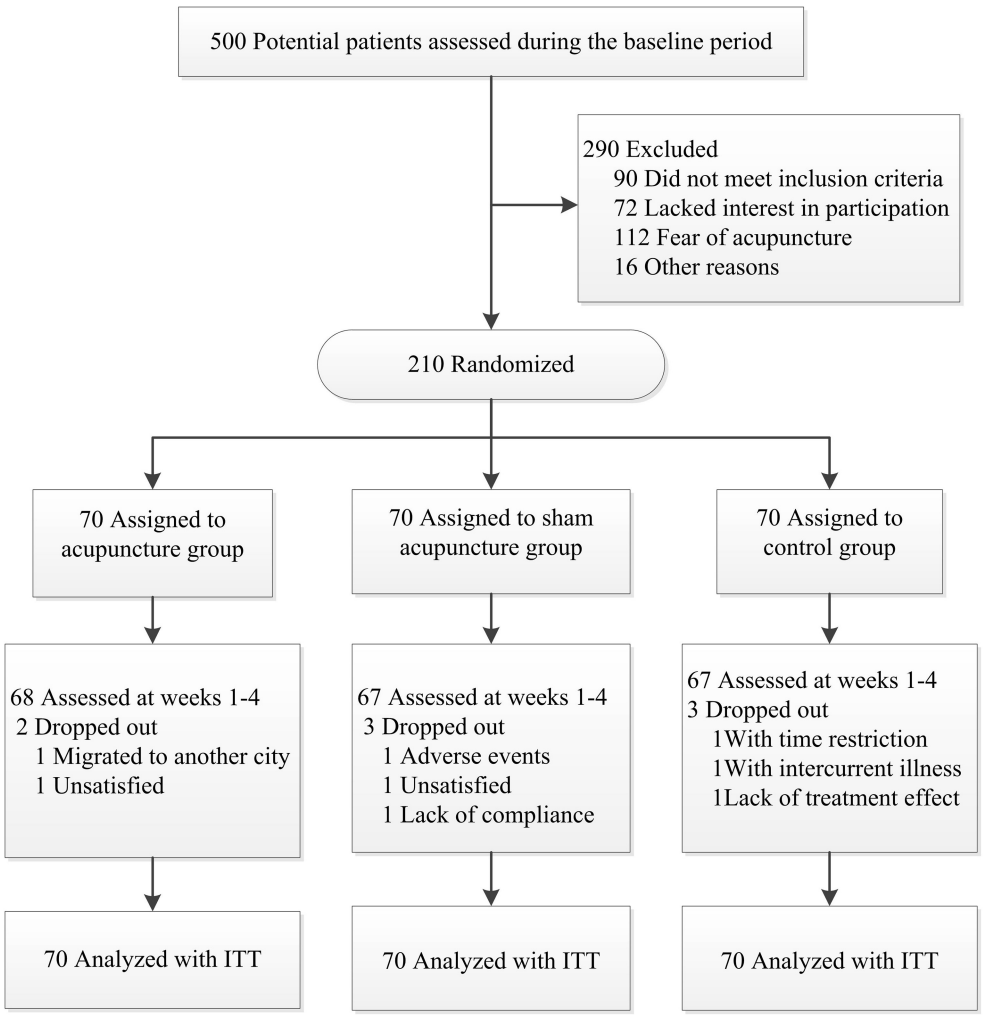


FIGURE 1 | Flowchart of the screening, enrollment, and randomization.

were applied for those who fit a normal distribution to continuous variables, whereas Kruskal–Wallis *H*-test was used for others. For categorical variables, the chi-square test or Fisher exact test were used. *P*-value <0.05 denoted statistical significance. Notably, to avoid type I error when performing multiple comparisons, adjusted *P*-value was calculated as *P*-value of 0.05 divided by the number of comparisons.

RESULTS

Study Participants

After screening 500 subjects, 290 were eligible for inclusion, but we ended up enrolling 210 participants since some did not meet inclusion criteria (90 patients) or lacked interest in participation (72 patients), feared acupuncture (112 patients), or other reasons (16 patients). **Figure 2** present a flow chart of patient screening, enrollment, and randomization. Baseline characteristics of the randomized patients were well-balanced in the three treatment groups (**Table 1**). There was no significant difference in baseline characteristics among the three groups.

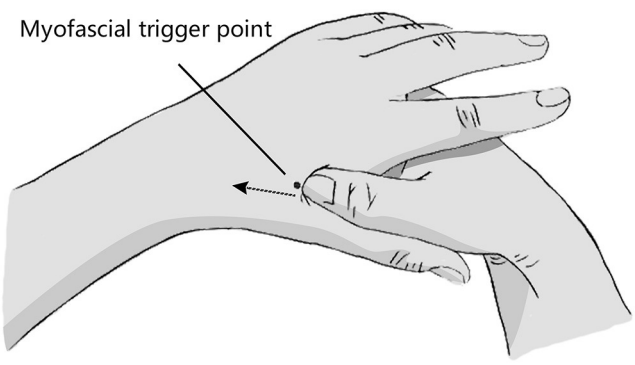


FIGURE 2 | The location of myofascial trigger point.

Primary Outcome

According to the MAS, the effective rate of thumb spasticity relief from baseline to after each treatment in the DN group was

TABLE 1 | Baseline characteristics.

Characteristics	DN group ($n = 70$)	SDN group ($n = 70$)	CON group ($n = 70$)	χ^2	*P*
Age, mean (SD), years	66.17 (9.84)	62.97 (11.53)	65.07 (8.50)	1.837	0.162
Gender, No (%)					
Female	23 (32.90)	26 (37.10)	22 (31.40)	0.553	0.758
Male	47 (67.10)	44 (62.90)	48 (68.60)		
Duration of illness, mean (SD), month	12.67 (3.09)	13.41 (2.98)	12.54 (3.04)	1.662	0.192
MAS score[§], No (%)					
1+	37 (52.90)	31 (44.30)	36 (51.40)	1.378	0.848
2	26 (37.10)	29 (41.40)	26 (37.10)		
3	7 (10.00)	10 (14.30)	8 (11.40)		
Types of stroke, No (%)					
Cerebral ischemic stroke	52 (74.30)	46 (65.70)	47 (67.10)	1.381	0.501
Cerebral hemorrhagic stroke	18 (25.70)	24 (34.30)	23 (32.90)		
Affected limb, No (%)					
Left	34 (48.60)	33 (47.10)	37 (52.90)	0.495	0.781
Right	36 (51.40)	37 (52.90)	33 (47.10)		

DN, dry needling; SDN, sham dry needling; CON, control.

[§]MAS, Modified Ashworth Scale, The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 4 at each joints, with higher scores indicating more severe spasticity; P-value of <0.05 was considered significant.

TABLE 2 | Effective rate of thumb spasticity relief from baseline to after each treatment.

Group	*N*	Effective cases	Effective rate (%)[γ]	χ^2	*P*-value
DN	**70**	67	95.71	55.833	<0.001
SDN	**70**	30	42.86※		
CON	**70**	29	41.43※#		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.

[γ]Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.

※ *Statistically significant difference from DN group.*

[#]No statistical significance as compared to SDN group; P-value of <0.05 was considered significant.

higher than that in control and SDN groups ($\chi^2 = 55.833$, $P < 0.001$) (**Table 2**); however, no significant difference was reported between the control group and SDN group.

Secondary Outcomes

Effective Rate of Spasticity Relief From Baseline to After Each Treatment in Fingers 2–5 and Wrist

According to the MAS, the effective rate of fingers 2–5 and wrist spasticity relief from baseline to after each treatment in the DN group was higher than that in control and SDN groups (fingers 2–5, $\chi^2 = 68.096$, $P < 0.001$; wrist, $\chi^2 = 49.180$, $P < 0.001$) (**Table 3**); however, no significant difference was reported between the control group and SDN group.

Subgroup Analysis of the Immediate Effective Rate of Different Degrees of Hand Spasticity

The immediate effective rate of thumb spasticity relief (**Table 4**) of patients with different degrees of spasticity in the DN group was higher than that in the control and SDN groups (1+, $\chi^2 = 8.682$, $P = 0.013$; 2, $\chi^2 = 35.533$, $P < 0.001$; 3, $P = 0.001$), however, no significant difference was reported between the control group and SDN group. This tendency was also seen in fingers 2–5 (**Table 5**) and wrist (**Table 6**).

The Effective Rate of Spasticity Relief From Baseline to Four Weeks

According to the MAS, the effective rate of spasticity relief from baseline to 4 weeks in the DN group was higher than that in control and SDN groups (thumb, $\chi^2 = 8.806$, $P = 0.012$; fingers 2–5, $\chi^2 = 8.087$, $P = 0.018$; and wrist, $\chi^2 = 8.653$, $P = 0.013$) (**Table 7**); however, no significant difference was found between the control group and SDN group.

Changes of Joint Angles of Hand in Rest Position

Mean rank of joint angle change in hand rest position from baseline to after each treatment in the DN group were 148.97, 163.59, 160.28, 170.07, 169.27, and 169.91 at the wrist, MCP and IP of the thumb, MCP, DIP, and the PIP of the fingers 2–5, respectively; the corresponding changes in the control group were 85.38, 76.44, 78.53, 72.20, 72.34, 73.06 and 82.15, 76.48, 77.69, 74.23, 74.89, 73.53 in the SDN group. There was statistical significance in the DN group compared to the control group and SDN group, while $P > 0.05$ for comparisons between the control group and SDN group (**Table 8**). At 4 weeks, although the mean rank of the DN group was higher than that of the control group and SDN group, the difference was not statistically significant ($P > 0.05$), except for the comparison between the DN group and SDN group in the proximal interphalangeal joint of the fingers 2–5 ($P = 0.026$) (**Table 9**).

TABLE 3 | Effective rate of spasticity relief from baseline to after each treatment in fingers 2–5 and wrist.

Sites	Group	*N*	Effective cases	Effective rate (%)[γ]	χ^2	*P*-value
Fingers 2–5 flexor spasticity	DN	70	69	98.57	68.096	<0.001
	SDN	70	29	41.43[※]		
	CON	70	26	37.14[※#]		
Wrist flexor spasticity	DN	70	64	91.43	49.180	<0.001
	SDN	70	28	40.00[※]		
	CON	70	29	41.43[※#]		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.
[γ]*Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.*
[※]*Statistically significant difference from DN group.*
[#]*No statistical significance as compared to SDN group. P-value of <0.05 was considered significant.*

TABLE 4 | Immediate effective rate of thumb spasticity relief in patients with different degree of spasticity.

MAS score[§]	Group	*N*	Effective cases	Effective rate (%)[γ]	χ^2	*P*-value
1+	DN	37	36	97.30	8.682	0.013
	SDN	31	24	77.42[※]		
	CON	36	26	72.22[※#]		
2	DN	26	20	76.92	35.533	<0.001
	SDN	29	4	13.79[※]		
	CON	26	2	7.69[※#]		
3	DN	7	6	85.71	NA	0.001[η]
	SDN	10	1	10.00[※]		
	CON	8	1	12.50[※#]		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.
[§]*MAS, Modified Ashworth Scale, The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 4 at each joints, with higher scores indicating more severe spasticity.*
[γ]*Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.*
[※] *Statistically significant difference from DN group.*
[#]*No statistical significance as compared to SDN group; P-value of < 0.05 was considered significant.*
[η]*Fisher's exact test.*
NA, Not Available.

TABLE 5 | Immediate effective rate of fingers 2–5 spasticity relief in patients with different degree of spasticity.

MAS score[§]	Group	*N*	Effective cases	Effective rate (%)[γ]	χ^2	*P*-value
1+	DN	37	37	100.00	20.342	<0.001
	SDN	31	22	70.97[※]		
	CON	36	20	55.56[※#]		
2	DN	26	22	84.62	32.625	<0.001
	SDN	29	5	17.24[※]		
	CON	26	5	19.23[※#]		
3	DN	7	7	100.00	NA	<0.001[η]
	SDN	10	2	20.00[※]		
	CON	8	1	12.50[※#]		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.
[§]*MAS, Modified Ashworth Scale, The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 4 at each joints, with higher scores indicating more severe spasticity.*
[γ]*Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.*
[※]*Statistically significant difference from DN group.*
[#]*No statistical significance as compared to SDN group.*
P-value of <0.05 was considered significant.
[η]*Fisher's exact test.*
NA, Not Available.

TABLE 6 | Immediate effective rate of wrist spasticity relief in patients with different degree of spasticity.

MAS score[§]	Group	*N*	Effective cases	Effective rate (%)[γ]	χ^2	*P*-value
1+	DN	37	35	94.59	10.114	0.006
	SDN	31	21	67.74[※]		
	CON	36	24	66.67[※#]		
2	DN	26	17	65.38	16.09	<0.001
	SDN	29	6	20.69[※]		
	CON	26	5	19.23[※#]		
3	DN	7	5	71.43	NA	0.004[η]
	SDN	10	1	10.00[※]		
	CON	8	0	0.00[※#]		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.
[§]MAS, Modified Ashworth Scale, The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 4 at each joints, with higher scores indicating more severe spasticity.
[γ]Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.
[※]Statistically significant difference from DN group.
[#]No statistical significance as compared to SDN group; P-value of <0.05 was considered significant.
[η]Fisher's exact test.
NA, Not Available.

TABLE 7 | Effective rate of spasticity relief from baseline to week 4.

Sites	Group	*N*	Effective cases[γ]	Effective rate(%)[≠]	χ^2	*P*-value
Thumb flexor spasticity	DN	70	55	78.57	8.806	0.012
	SDN	70	41	58.57[※]		
	CON	70	40	57.14[※#]		
Fingers 2–5 flexor spasticity	DN	70	57	81.43	8.087	0.018
	SDN	70	43	61.43[※]		
	CON	70	44	62.86[※#]		
Wrist flexor spasticity	DN	70	54	77.14	8.653	0.013
	SDN	70	39	55.71[※]		
	CON	70	40	57.14[※#]		

N, number of cases included in each group; DN, dry needling; SDN, sham dry needling; CON, control.
[≠]Intention-to-Treat Analysis, 2 dropped out in DN group, 3 dropped out in SDN group, 3 dropped out in control group.
[γ]Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.
[※] Statistically significant difference from DN group.
[#]No statistical significance as compared to SDN group; P-value of <0.05 was considered significant.

Adverse Events

No serious adverse events requiring withdrawal were reported across the three groups (**Table 10**).

DISCUSSION

The immediate efficacy of DN at the trigger point in the treatment of hand spasticity after stroke has been evaluated. In our clinical trial, DN could effectively relieve different degrees of hand spasticity in patients with stroke after each treatment. It also reduced the flexion angle of joints (wrist joint, thumb, and fingers 2–5) in the rest position of the hand. The results of this study showed that the effective rate of spasticity relief (immediate or 4 weeks) in the SDN group was equivalent to that in the control group. We speculated that this might be related to the distinctive location and manipulation of myofascial trigger points. Acupuncture at the non-myofascial trigger points was difficult to produce curative effect, excluding the placebo effect caused by acupuncture behavior itself. By discontinuing the intervention after 4 weeks, some level of cumulative effect was realized although it was not significant. Considering that the intervention cycle is too short, we speculate that it takes a certain time for the accumulation of stimulation effect before it reaches levels that produce best treatment effects. Because the curative effect of acupuncture is a gradual accumulation process, that is, the therapeutic effect improves gradually as the treatment course of acupuncture increases, this is termed as accumulation of post acupuncture effect. Based on previous research, we plan to increase the acupuncture and needle retention time, prolong the observation period, explore the time-effect relationship in acupuncture, longitudinally study the whole action cycle of acupuncture, and determine a more reasonable treatment

TABLE 8 | Change of joint flexion angles in resting position before and after each treatment.

Joint	Group	Median (*P25*, *P75*)	Mean rank[γ]	Kruskal–Wallis *H*-test	
				H	*P*-value
Wrist	DN	31.50 (17.25, 40.25)	148.97	58.133	<0.001
	SDN	0.00 (0.00, 26.25)	82.15[※]		
	CON	0.00 (0.00, 27.25)	85.38[※#]		
MCP of thumb	DN	20.00 (15.00, 25.00)	163.59	101.389	<0.001
	SDN	0.00 (0.00, 9.25)	76.48[※]		
	CON	0.00 (0.00, 9.25)	76.44[※#]		
IP of thumb	DN	39.00 (30.00, 53.00)	160.28	90.427	<0.001
	SDN	0.00 (0.00, 30.00)	77.69[※]		
	CON	0.00 (0.00, 28.00)	78.53[※#]		
MCP of fingers 2–5	DN	22.00 (17.00, 28.00)	170.07	125.889	<0.001
	SDN	0.00 (0.00, 8.25)	74.23[※]		
	CON	0.00 (0.00, 7.25)	72.2[※#]		
PIP of fingers 2–5	DN	42.00 (36.00, 52.00)	169.27	122.796	<0.001
	SDN	0.00 (0.00, 26.25)	74.89[※]		
	CON	0.00 (0.00, 25.25)	72.34[※#]		
DIP of fingers 2–5	DN	35.00 (33.00, 51.00)	169.91	125.233	<0.001
	SDN	0.00 (0.00, 22.00)	73.53[※]		
	CON	0.00 (0.00, 24.00)	73.06[※#]		

DN, dry needling; SDN, sham dry needling; CON, control; MCP, metacarpophalangeal joint; IP, interphalangeal joint; DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint.
[γ]Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.
[※] Statistically significant difference from DN group.
[#]No statistical significance as compared to SDN group; P-value of <0.05 was considered significant.

TABLE 9 | Change of joint flexion angles in resting position from baseline to week 4.

Joint	Group	Median (*P25*, *P75*)	Mean rank[γ]	Kruskal–Wallis *H*-test	
				H	*P*-value
Wrist	DN	14.50 (4.25, 30.00)	119.78[#ϕ]	6.108	0.047
	SDN	8.00 (0.00, 29.00)	98.67[ϕ]		
	CON	8.00 (0.00, 26.00)	98.05		
MCP of thumb	DN	10.00 (5.00, 14.00)	117.38	4.209	0.122
	SDN	8.50 (0.00, 12.00)	99.39		
	CON	6.00 (0.00, 13.00)	99.74		
IP of thumb	DN	26.50 (5.75, 30.00)	120.79[#ϕ]	6.965	0.031
	SDN	23.00 (0.00, 29.00)	98.06[ϕ]		
	CON	23.00 (0.00, 29.00)	97.65		
MCP of fingers 2–5	DN	10.00 (5.00, 13.00)	116.38	3.513	0.173
	SDN	8.00 (0.00, 14.00)	100.95		
	CON	8.00 (0.00, 13.00)	99.17		
PIP of fingers 2–5	DN	25.00 (17.75, 30.00)	121.84[ϕ]	8.004	0.018
	SDN	20.00 (0.00, 26.00)	95.28[※]		
	CON	20.00 (0.00, 28.00)	99.38[#]		
DIP of fingers 2–5	DN	24.50 (18.75, 26.25)	117.9	5.022	0.081
	SDN	21.00 (0.00, 25.25)	95.72		
	CON	22.00 (0.00, 27.00)	102.88		

DN, dry needling; SDN, sham dry needling; CON, control; MCP, metacarpophalangeal joint; IP, interphalangeal joint; DIP, distal interphalangeal joint; PIP, proximal interphalangeal joint.
[γ]Bonferroni correction was used for multiple comparisons between groups, $\alpha = 0.05/3 = 0.017$.
[※] Statistically significant difference from DN group.
[#]No statistical significance as compared to SDN group.
[ϕ]No statistical significance as compared to CON group; P-value of <0.05 was considered significant.

TABLE 10 | Adverse events related to treatment.

Adverse event[a]	Participant, No (%)		
	DN ($n = 70$)	SDN ($n = 70$)	CON ($n = 70$)
Overall	1 (1.43)	2 (2.86)	0
Severe adverse events	0	0	0
Subcutaneous hematoma	1 (1.43)	1 (1.43)	0
Fainting	0	0	0
Sharp pain	0	1 (1.43)	0
Instrument fracture	0	0	0
Sticking of needle	0	0	0

a: Adverse events were analyzed in all participants who received treatment. Adverse events were counted by type rather than frequency in the same participant. Adverse events with different types occurring in a single participant were defined as independent adverse events. An adverse event with multiple occurrences in a single participant was defined as 1 adverse event. DN, dry needling; SDN, sham dry needling; CON, control.

scheme. DN treatment primarily reduces muscle tension to relieve limb spasms and create conditions for later rehabilitation training. These effects are beneficial to patients to develop in the direction of separation and coordination, and to allow their smooth transition to the recovery period.

Emerging evidence has implicated DN in the management of muscle spasticity in nervous system diseases, including spastic quadriplegia and post-stroke spasticity. The meta-analysis of Fernández-de-Las-Peñas et al. (11) found that the effect of DN on spasticity was mainly in the lower extremities, though the effect on related pain and motor function was inconclusive in the short-term follow-up. Elsewhere, Ghannadi et al. (15) found that deep DN exerts short-term effects by reducing the muscle spasm of stroke survivors and improving the lower limb function and gait. More evidence from Salom-Moreno's work showed that a single DN not only reduces the spasticity and extensive pressure sensitivity of patients with spasticity after stroke but also changes the plantar pressure by increasing the support surface and reducing the average pressure (16). Núñez-Cortés et al. (17) found that DN, either alone in combination with multimodal therapy, could effectively reduce stroke spasticity and improve passive range of motion in a short period. Echoing the above reports, Sánchez-Mila et al. (18) demonstrated that DN combined with Bobath therapy could effectively reduce spasticity, improve balance, range of motion, and maintain stable accuracy in stroke patients.

Although DN had a positive effect on lower limb spasticity of stroke patients, it had negative effects on upper limb spasticity. Mendigutia-Gómez et al. (12) revealed that DN, incorporated in the multimodal rehabilitation program, reduced the local pressure sensitivity and improved the range of motion of shoulder joint in stroke patients effectively; however, they reported no significant difference in muscle spasm relief. In another study, Cuenca Zaldívar et al. (19) found that addition of DN treatment to the standard physical therapy reduced the spasticity of the affected arm better but did not show additional effects in function, pain, and quality of life. More pieces of research by Ansari, Ghaffari, and Fakhari have shown that DN can reduce the upper limb spasm, improve the range of motion, and promote the recovery of joint function (20–22). In support of these findings, Lu et al. (23) demonstrated DN could immediately relieve finger flexor spasm, increase range of motion, and reduce motor unit action potential (MUAP), suggesting that there may be potential trigger points in spastic muscles of chronic stroke, which are related to spastic hypertension of flexor digitorum. These observations confirm our results that DN at the trigger point of the hand can effectively relieve hand spasticity after stroke. Additionally, Hernández-Ortiz et al. (24) found that the effect of DN on muscle tension (spasm) and upper limb function in stroke patients was not related to the intervention in and out of trigger points region. More research is warranted to further confirm or refute the effect of DN at the trigger point on muscle spasms.

Of note, the results presented here should be treated with caution because the majority of previous studies were scattered case reports or systematic reviews with low quality of data. In addition, the number of included cases was small and lacks the control group, and therefore were not eligible to prove the efficacy and safety of DN. It was not possible to explore the effect of DN alone because it was applied as a multimodal treatment. Contrary to previous studies, the present work used a larger sample size to conduct multicenter randomized controlled trials. The control group and sham acupuncture group were set up to exclude the effect of comfort treatment due to psychological factors, to better judge the curative effect of DN. Secondly, independent DN intervention and instant assessment of spasms were administered before routine rehabilitation training. This design is beneficial in the assessment of the effect of DN alone. In addition to the immediate effect, we also evaluated the cumulative effect and conducted a priori subgroup analysis (prior) to validate the internal consistency of clinical trial results and explore the most suitable beneficiary population. The results demonstrated that DN intervention at a single site myofascial trigger point could immediately relieve hand spasm after stroke. This approach is convenient and easy to promote.

Although the results of our multicenter randomized controlled trials are encouraging, potential limitations should be recognized. First, because we collected short-term results, whether the observed changes will last longer and whether the continuous stimulation given by the improvement of the needle can continuously relieve spasms remain elusive. A larger cohort and longer follow-up study are warranted in the future. Additionally, it would be imperative to fully clarify the mechanism of DN in alleviating muscle spasms.

CONCLUSION

Dry needling can relieve varying degrees of hand spasticity instantly in post-stroke patients.

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 human participants were reviewed and approved by the Medical Ethical Review Committee of the Seventh People's Hospital affiliated to Shanghai University of Traditional Chinese Medicine (2018-IRBQYYS). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WF, ZZ, KL, WW, and YS equally contributed to the design and implementation of the work. YZ, LJia, QL, and LJin were in charge of data collection. TZ was responsible for data analysis and interpretation. ZZ, KL, and TZ assisted in drafting the manuscript, which was critically revised by WF and finally approved by all the authors.

FUNDING

This work was supported by the Shanghai Science and Technology Commission (grant number 18401900300), the National Natural Science Foundation of China (grant number 81873328), and the Shanghai Characteristic Diagnosis and Treatment Technology Improvement Project of Traditional Chinese Medicine [grant number YZ (2018-2020)-ZYJS-04].

REFERENCES

1. Chen H, Shi L, Wang N, Han Y, Lin Y, Dai M, et al. Analysis on geographic variations in hospital deaths and endovascular therapy in ischaemic stroke patients: an observational cross-sectional study in China. *BMJ Open.* (2019) 9:e029079. doi: 10.1136/bmjopen-2019-029079
2. Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, et al. Prevalence, incidence, and mortality of stroke in china: results from a nationwide population-based survey of 480 687 adults. *Circulation.* (2017) 135:759–71. doi: 10.1161/CIRCULATIONAHA.116.025250
3. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: physiology, assessment and treatment. *Brain Injury.* (2013) 27:1093–105. doi: 10.3109/02699052.2013.804202
4. Wissel J, Manack A, Brainin M. Toward an epidemiology of poststroke spasticity. *Neurology*. (2013). 80(3 Suppl 2):S13–9. doi: 10.1212/WNL.0b013e3182762448
5. Ghai A, Garg N, Hooda S, Gupta T. Spasticity - pathogenesis, prevention and treatment strategies. *Saudi J Anaesth.* (2013) 7:453–60. doi: 10.4103/1658-354X.121087
6. Santamato A, Micello MF, Panza F, Fortunato F, Baricich A, Cisari C, et al. Can botulinum toxin type A injection technique influence the clinical outcome of patients with post-stroke upper limb spasticity? A randomized controlled trial comparing manual needle placement and ultrasound-guided injection techniques. *J Neurol Sci.* (2014) 347:39–43. doi: 10.1016/j.jns.2014.09.016
7. Sun LC, Chen R, Fu C, Chen Y, Wu Q, Chen R, et al. Efficacy and safety of botulinum toxin type a for limb spasticity after stroke: a meta-analysis of randomized controlled trials. *Biomed Res Int.* (2019) 2019:8329306. doi: 10.1155/2019/8329306
8. Zheng MX, Hua XY, Feng JT Li T, Lu YC, Shen YD, et al. Trial of contralateral seventh cervical nerve transfer for spastic arm paralysis. *N Engl J Med.* (2018) 378:22–34. doi: 10.1056/NEJMoa1615208
9. Kearns G, Fernández-De-Las-Peñas C, Brismée JM, Gan J, Doidge J. New perspectives on dry needling following a medical model: are we screening our patients sufficiently? *J Man Manip Ther.* (2019) 27:172–9. doi: 10.1080/10669817.2019.1567011
10. Tang L, Li Y, Huang QM, Yang Y. Dry needling at myofascial trigger points mitigates chronic post-stroke shoulder spasticity. *Neural Regen Res.* (2018) 13:673–6. doi: 10.4103/1673-5374.230293
11. Fernández-de-Las-Peñas C, Pérez-Bellmunt A, Llurda-Almuzara L, Plaza-Manzano G, De-la-Llave-Rincón AI, Navarro-Santana MJ. Is dry needling effective for the management of spasticity, pain, and motor function in post-stroke patients? A systematic review and meta-analysis. *Pain Med*. (2021). 22:131–41. doi: 10.1093/pm/pnaa392
12. Mendigutia-Gómez A, Martín-Hernández C, Salom-Moreno J. Fernández-de-Las-Peñas C. Effect of dry needling on spasticity, shoulder range of motion, and pressure pain sensitivity in patients with stroke: a crossover study. *J Manipul Physiol Therapeut.* (2016) 39:348–58. doi: 10.1016/j.jmpt.2016.04.006
13. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ.* (1980) 58:113–30.
14. Liu Z, Liu Y, Xu H, He L, Chen Y, Fu L, et al. Effect of electroacupuncture on urinary leakage among women with stress urinary incontinence: a randomized clinical trial. *Jama.* (2017) 317:2493–501. doi: 10.1001/jama.2017.7220
15. Ghannadi S, Shariat A, Ansari NN, Tavakol Z, Honarpishe R, Dommerholt J, et al. The effect of dry needling on lower limb dysfunction in poststroke survivors. *J Stroke Cerebrovasc Dis.* (2020) 29:104814. doi: 10.1016/j.jstrokecerebrovasdis.2020.104814
16. Salom-Moreno J, Sánchez-Mila Z, Ortega-Santiago R, Palacios-Ceña M, Truyol-Domínguez S. Fernández-de-las-Peñas C. Changes in spasticity, widespread pressure pain sensitivity, and baropodometry after the application of dry needling in patients who have had a stroke: a randomized controlled trial. *J Manipul Physiol Therapeut.* (2014) 37:569–79. doi: 10.1016/j.jmpt.2014.06.003
17. Núñez-Cortés R, Cruz-Montecinos C, Latorre-García R, Pérez-Alenda S, Torres-Castro R. Effectiveness of dry needling in the management of spasticity in patients post stroke. *J Stroke Cerebrovasc Dis.* (2020) 29:105236. doi: 10.1016/j.jstrokecerebrovasdis.2020.105236
18. Sánchez-Mila Z, Salom-Moreno J. Fernández-de-Las-Peñas C. Effects of dry needling on post-stroke spasticity, motor function and stability limits: a randomised clinical trial. *Acupunct Med.* (2018) 36:358–66. doi: 10.1136/acupmed-2017-011568
19. Cuenca Zaldívar JN, Calvo S, Bravo-Esteban E, Oliva Ruiz P, Santi-Cano MJ, Herrero P. Effectiveness of dry needling for upper extremity spasticity, quality of life and function in subacute phase stroke patients. *Acupunct Med.* (2021) 39:299–308. doi: 10.1177/0964528420947426
20. Ansari NN, Naghdi S, Fakhari Z, Radinmehr H, Hasson S. Dry needling for the treatment of poststroke muscle spasticity: a prospective case report. *NeuroRehabilitation.* (2015) 36:61–5. doi: 10.3233/NRE-141192
21. Ghaffari MS, Shariat A, Honarpishe R, Hakakzadeh A, Cleland JA, Haghighi S, et al. Concurrent effects of dry needling and electrical stimulation in the management of upper extremity hemiparesis. *J Acupunct Meridian Stud.* (2019) 12:90–4. doi: 10.1016/j.jams.2019.04.004
22. Fakhari Z, Ansari NN, Naghdi S, Mansouri K, Radinmehr H. A single group, pretest-posttest clinical trial for the effects of dry needling on wrist flexors spasticity after stroke. *NeuroRehabilitation.* (2017) 40:325–36. doi: 10.3233/NRE-161420
23. Lu Z, Briley A, Zhou P, Li S. Are there trigger points in the spastic muscles? Electromyographical evidence of dry needling effects on spastic finger flexors in chronic stroke. *Front Neurol.* (2020) 11:78. doi: 10.3389/fneur.2020.00078
24. Hernández-Ortíz AR, Ponce-Luceño R, Sáez-Sánchez C, García-Sánchez O. Fernández-de-Las-Peñas C, de-la-Llave-Rincón AI. Changes in muscle tone, function, and pain in the chronic hemiparetic shoulder after dry needling

within or outside trigger points in stroke patients: a crossover randomized clinical trial. *Pain Med.* (2020) 21:2939–47. doi: 10.1093/pm/pnaa132

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

MINI REVIEW
published: 18 November 2021
doi: 10.3389/fneur.2021.772199

Post-stroke Rehabilitation of Severe Upper Limb Paresis in Germany – Toward Long-Term Treatment With Brain-Computer Interfaces

Cornelius Angerhöfer[1], *Annalisa Colucci*[1], *Mareike Vermehren*[1], *Volker Hömberg*[2] *and Surjo R. Soekadar*[1]*

[1] *Clinical Neurotechnology Lab, Department of Psychiatry and Neurosciences, Charité–Universitätsmedizin Berlin, Berlin, Germany,* [2] *Department of Neurology, SRH Gesundheitszentrum Bad Wimpfen GmbH, Bad Wimpfen, Germany*

OPEN ACCESS

Edited by:
Giorgio Scivoletto, Santa Lucia Foundation (IRCCS), Italy

Reviewed by:
Floriana Pichiorri, Santa Lucia Foundation (IRCCS), Italy
Robert Guggenberger, University of Tübingen, Germany

***Correspondence:**
Surjo R. Soekadar
surjo.soekadar@charite.de

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *07 September 2021*
Accepted: *29 October 2021*
Published: *18 November 2021*

Citation:
Angerhöfer C, Colucci A, Vermehren M, Hömberg V and Soekadar SR (2021) Post-stroke Rehabilitation of Severe Upper Limb Paresis in Germany – Toward Long-Term Treatment With Brain-Computer Interfaces. Front. Neurol. 12:772199. doi: 10.3389/fneur.2021.772199

Severe upper limb paresis can represent an immense burden for stroke survivors. Given the rising prevalence of stroke, restoration of severe upper limb motor impairment remains a major challenge for rehabilitation medicine because effective treatment strategies are lacking. Commonly applied interventions in Germany, such as mirror therapy and impairment-oriented training, are limited in efficacy, demanding for new strategies to be found. By translating brain signals into control commands of external devices, brain-computer interfaces (BCIs) and brain-machine interfaces (BMIs) represent promising, neurotechnology-based alternatives for stroke patients with highly restricted arm and hand function. In this mini-review, we outline perspectives on how BCI-based therapy can be integrated into the different stages of neurorehabilitation in Germany to meet a long-term treatment approach: We found that it is most appropriate to start therapy with BCI-based neurofeedback immediately after early rehabilitation. BCI-driven functional electrical stimulation (FES) and BMI robotic therapy are well suited for subsequent post hospital curative treatment in the subacute stage. BCI-based hand exoskeleton training can be continued within outpatient occupational therapy to further improve hand function and address motivational issues in chronic stroke patients. Once the rehabilitation potential is exhausted, BCI technology can be used to drive assistive devices to compensate for impaired function. However, there are several challenges yet to overcome before such long-term treatment strategies can be implemented within broad clinical application: 1. developing reliable BCI systems with better usability; 2. conducting more research to improve BCI training paradigms and 3. establishing reliable methods to identify suitable patients.

Keywords: brain-computer interface, severe upper limb paresis, neurorehabilitation, long-term treatment, neurotechnology

INTRODUCTION

Stroke is a leading cause for long-term disability and often results in poor quality of life (1). In 2017, there were around 260,000 in-patient cases of stroke registered in German hospitals (2). While the incidence in Germany mostly remained constant (3), the probability to survive an acute stroke significantly improved over the last two decades (4). With a growing number of stroke survivors, the number of patients facing post-stroke impairments is increasing. Besides impairments in cognition, speech, mood regulation or sexual function, loss of motor function, especially in the upper extremity, is a severe burden after stroke.

Upper limb impairment occurs in approximately 80% of stroke survivors (5). Here, the initial severity of motor impairment often predicts chances for recovery (6). While there is a good chance for full recovery from mild paresis, this is less likely for severe upper limb paresis (7). In 30–50% of all stroke survivors, the affected arm is still severely impaired 6 months after stroke (8, 9). This group face immense difficulties in performing activities of daily living (ADLs) and must often rely on family support or caregivers (10). Given the rising burden of stroke, there is a pressing need for innovative tools that foster successful restoration of motor function.

REHABILITATION OF SEVERE UPPER LIMB PARESIS

Constraint-induced movement training (CIMT) represents an effective motor intervention in upper limb rehabilitation (11–13). However, as voluntary wrist and finger extension is a minimum requirement for CIMT, it is only applicable in a limited number of stroke patients, usually excluding those with severe upper limb paresis (14). The treatment repertoire for patients with severe motor impairment is small. Classical physiotherapy is often applied as standard therapy. Mirror therapy has shown to improve arm and hand function (13, 15, 16). In mirror therapy, the unimpaired hand is observed in a mirror projected onto the side of the impaired hand. Since such training does not require remaining motor function in the paretic limb, it is recommended as a complementary approach for stroke survivors with severe arm paralysis (17). Arm-BASIS-Training (ABT) is a method of impairment-oriented training that aims at restoring motoric innervation by selectively training specific arm movements (e.g., shoulder joint movements, elbow joint movements, wrist joint movements), exclusively designed for the rehabilitation of severe upper limb paresis (18). In a systematic review by Urton et al. (19), ABT was the only intervention that improved arm mobility in addition to standard physiotherapy, receiving recommendation grade A. The use of external devices (robotics) allows to train movements with high repetition rates which cannot be performed by the patient independently. It was shown that robotic-aided therapy can improve arm function, force and mobility in stroke patients with severe upper limb paresis (20, 21).

While there are well-evidenced motor interventions for mild paralysis, successful rehabilitation of severe upper limb paresis is still an unsolved problem: For classical physiotherapy, evidence of efficacy is not convincing (12, 22, 23). Impairment-oriented training was shown to improve selective arm mobility, but not arm function (18). Robotics-guided therapy is useful in the subacute stage, but there is still a controversy whether also chronic patients benefit from this therapy. Furthermore, it is not clear yet whether it can also improve ADL skills and thus reduce or prevent the necessity of long-term care (24, 25). The same has also not been conclusively clarified for mirror therapy (16, 26). With the lack of standardized and convincing treatment options, there is high demand to find new strategies to restore severe upper limp paresis in stroke survivors.

BRAIN-COMPUTER INTERFACE AND BRAIN-MACHINE INTERFACE

Brain computer interfaces (BCIs) use the modulation of neurometabolic or neuroelectric signals to control external devices (27). By analyzing changes in brain activity, BCI technology can convert the user's intention into control commands of digital devices or tools usually delivering some form of sensory feedback. A sub-form of BCI systems enabling volitional control of machines, e.g., exoskeletons or prostheses, are usually termed brain-machine interfaces (BMIs). The most established BCI paradigms are based on electroencephalography (EEG), due to its low cost and easy handling (28). In BCI and BMI applications for motor rehabilitation, EEG is typically used to record the sensorimotor rhythm (SMR), generated by neuronal cell populations of the sensorimotor cortex (29). During motor attempt or imagination, power of SMR decreases and this modulation, called event-related-desynchronization (ERD), can be translated into a control command for an external device. Since even stroke survivors with severe chronic motor deficits can modulate their SMR (30), and no actual physical movement is required to control BCI-based devices, they represent a promising rehabilitation strategy for stroke patients with severe upper limb paresis.

BCI technology addresses important physiological fundamentals of neurorehabilitation. Based on Hebbian learning principles, such systems can induce neuroplasticity by effectively coupling efferent brains signals to afferent input (e.g., caused by a closing exoskeleton) (31). This way, neural assemblies are activated in an associative manner, strengthening cortical connections, as evidenced by increased motor evoked potentials (MEP) in stroke survivors using a BCI (32). Linking central motor output to peripheral input in real-time closes the sensorimotor feedback loop, which can promote the integration of affected corticospinal connections (33) and foster voluntary motor control (34). Moreover, BCIs improve the ability to activate affected brain areas by visualizing changes in brain activity in real-time (a paradigm termed neurofeedback) (34). This was shown to result in greater involvement of the ipsilesional hemisphere compared to random feedback (35). Apart from influencing neurophysiological parameters reflecting neuroplasticity, BMI applications also showed to induce functional improvement (36–39).

Although BCI-based approaches appear to be promising for upper limb rehabilitation, sufficient evidence for broad clinical application is still lacking and more research is needed. However, conducting studies according to principles of evidence-based medicine (EBM) is often difficult due to the heterogeneity of stroke patients. Further, BCI-based motor therapy involves far more variables than just dose and timing, and double blinding is difficult to implement. Therefore, Coscia et al. (40) suggest investigating BCI applications in personalized longitudinal studies in contrast to randomized controlled trials (RCTs). In such a design, patients receive specific treatment until a functional plateau is reached, before continuing with another intervention. The primary aim of such approach is to improve the individual outcome in patient populations that usually have poor prospects for recovery and rarely show spontaneous remission (40). In this context, it is crucial to find long-term treatment strategies that can be well integrated throughout the different phases of neurorehabilitation. Beyond research, such strategies are of great importance for clinicians who apply BCI-based therapy as early-adopters to expand treatment options. Since BCI-based therapy addresses several aspects of motor learning (neurofeedback, training of repetitive tasks, active behavior in therapy), this provides good reason for early application (41) – especially as there are only few alternatives for restoring severe upper limb paresis in stroke patients.

BCI-BASED LONG-TERM TREATMENT STRATEGIES IN GERMANY

Thanks to its various applications, BCI-based therapy can be embedded in many stages of stroke rehabilitation. Here, based on a literature review, we derived the best strategies to facilitate and accelerate the integration of BCI-based therapy into the German process of neurorehabilitation. We include studies that assess the impact of BCI-based interventions on motor recovery of stroke patients with severe upper limb paresis, either in the subacute (<6 months) or chronic stage (>6 months). Study outcomes were either functional scores and/or neurophysiological parameters. Case studies and studies with small sample size (<10 participants) were not included. In Germany, the process of neurological rehabilitation is divided into 6 phases (A to F): Phase A represents the emergency care on a stroke unit, followed by phase B which is equivalent to early rehabilitation. In Phase C, patients can actively participate in rehabilitation interventions, however, there is still high demand for medical treatment. In Phase D, patients receive medical rehabilitation in specialized rehabilitation centers (Phase D), which corresponds to the concept of post hospital curative treatment. In Phase E, outpatient occupational reintegration is pursued and, in case long-time care is necessary, Phase F is initiated to support and maintain function (42).

In acute care and early rehabilitation (Phase A and B), BCI-based applications often cannot be applied due to patient's reduced vigilance and impaired cooperativity (43). However, as soon as active participation is possible (Phase C), BCI-based training can be started. At the beginning, it is advisable to familiarize patients with BCI technology by providing neurofeedback on SMR modulation related to motor imagery (MI). As shown by Pichiorri et al. (35) and Mihara et al. (44), BCI assisted neurofeedback on MI can contribute to functional recovery and enhance neural connectivity on the affected brain hemisphere in subacute stroke patients. Compared to visual feedback, somatosensory and/or proprioceptive feedback seems advantageous in rehabilitation (45). Furthermore, daily MI-based neurofeedback training has been shown to improve SMR control (46), facilitating the control of BMI motor interventions later on. Since patients do not have to be mobilized for neurofeedback training, this can be applied on bedside, increasing accessibility. In phase C, the patient's state of health is often still unstable, and exhaustion caused by intensive motor therapy could do more harm than good.

Although there are no RCTs comparing early vs. late onset, a general recommendation is that the earlier motor interventions start, the better (17). Thus, BCI therapy should advance once SMR control is well established, and the patient's clinical condition allows. In a next step, EEG-based BMI systems can be used to control robotic therapy devices to effectively link repetitive exercise training with cortical motor output. Ang et al. (36) showed that such a BMI system coupled with the MIT-Manus, a robotic arm that initiates and guides upper limb movements, enhances arm and hand function in stroke patients with severe upper limb paresis. It was reported that such therapy is well tolerated by patients and no adverse effects occur, making it an effective and safe method for upper limb rehabilitation. As BMI robotic training requires expensive equipment and specialized staff, it seems best to apply such therapy in specialized rehabilitation centers (Phase D). Here, subacute stroke patients come together in large numbers, guaranteeing maximum capacity utilization and effective use. Besides brain controlled robotic therapy, BCIs can be applied for exoskeleton control and FES. Exoskeletons are portable devices that support or completely imitate movement, while FES uses electrical pulses to stimulate muscle contractions, enabling the movement of paralyzed limbs. Biasiucci et al. (37) showed that BCI-driven FES can reduce severe upper limb impairment in subacute stroke patients. Most notably, functional improvement prevailed 6 months after therapy, making it a promising strategy for a curative treatment approach (Phase D).

There are good reasons to continue BCI therapy in chronic stroke patients that already showed some degree of motor recovery. In patients with initial hemiparesis but returning arm control, EEG-based hand exoskeletons can be used to restore hand function. It was shown that the application of a BCI-driven hand exoskeleton in chronic stroke patients reduces complete finger paralysis (39), improves grip function (47) and results in an increased use of the paralyzed hand in ADL tasks (48). A major advantage of BCI-based exoskeleton control is that it allows patients to perform grasping movements with their paralyzed hand and enables them to perform bimanual tasks in training sessions (e.g., eating with cutlery), counteracting the learned non-use of the paralyzed limb. The high relation of such exercises to everyday life situations promotes patient's motivation to continue therapy. This is especially important as depression and reduced drive are severe complications

following stroke (49). Considering the reduced effort needed in comparison to robotic-guided therapy, the applicability in chronic patients and the practicability in bimanual tasks, BMI hand exoskeleton training is well suited for outpatient occupational therapy (Phase E). This way, a continuous treatment is pursued even after medical rehabilitation (Phase D) is completed.

In case no sufficient improvement can be achieved, nursing or family care (Phase F) is often unavoidable for patients with remaining severe upper limb impairment. Although the rehabilitative potential might be exhausted in these cases, the BCI approach can be used to compensate for lost function by controlling assistive devices, e.g., exoskeletons or robotic prostheses (assistive BCIs). Bundy et al. (50) have demonstrated the feasibility of a BCI-based hand exoskeleton for home use in chronic stroke patients, using EEG signals of the unaffected hemisphere. Applied in a home-based setting, assistive BCIs allow patients to perform important ADLs such as eating and drinking independently (51). This way, patients become less reliant on family or caregiver support and can regain quality of life.

CURRENT CHALLENGES AND LIMITATIONS

Attaching and calibrating BCI systems currently requires the support of specially trained personnel and takes considerable amount of time (52). Since time is a scarce commodity in clinical practice, preparation for BCI-based therapy must become quick and easy, e.g., through intuitive graphical user interfaces and fast automatic calibration systems. For assistive BCIs applied in a home-based setting, the need of a supervisor contradicts the idea of giving back independency. Although improvements have been made to enhance practicability by implementing veto commands (53), establishing hybrid control paradigms (54) and developing user-friendly EEG systems (55, 56), assistive BCI systems that can be applied by the user without any external help are still missing. Another drawback of BCI-based interventions lies in the high acquisition costs of the technical devices. BCI-based therapy must yet prove its clear effectiveness to justify the high expenses, otherwise it will not find entrance in clinical practice. Consequently, efforts need to be made to drive technical development, lower cost of production and conduct studies that thoroughly investigate the benefit of BCI technology (33).

BCIs can fail to detect modulation of brain activity in up to 20% of individuals (57). While some speak of BCI-illiteracy, Vidaurre et al. (58) showed that machine learning approaches can considerably reduce the number of BCI "illiterates." This should encourage researchers to improve BCI classification and paradigms rather than to attribute the fault to the user (59). Current training approaches for brain modulation often seem inappropriate, e.g., lacking clear instructions, specific learning objectives and meaningful feedback. This affects BCI robustness and requires new training procedures (60). Stroke patients in particular may have difficulty modulating their cortical activity due to the brain lesion, potentially leading to frustration when trying to control BCI-based devices (61). In this context, it may be advantageous to individually adapt session time of BCI-based therapy since fatigue and lack of concentration can affect BCI control substantially (62, 63). While heart rate variability (HRV) (64) and task-related theta-band activity (65) have been proposed as possible biomarkers to monitor patient's mental capacity during BCI sessions, there is still much work needed to establish parameters that reliably anticipate mental workload and fatigue. Overall, more research assessing user experience with BCIs needs to be conducted, especially considering hedonic quality aspects such as motivation and frustration since they play an important role in stroke rehabilitation (66). Also, neuroplasticity mechanisms induced by BCI-based application need to be better understood, with regards to so far less studied aspects such as wide-spread neural networks and cortical excitability (67, 68).

For motor interventions to be most effective, it has been suggested to move from a "one-fits-all" approach toward customized rehabilitative interventions (69). In this context, identification of stroke patients that will benefit most from BCI therapy needs to be realized. So far, it has been shown that functional connectivity assessed by functional magnetic resonance imaging (fMRI) predicts motor recovery and outcome of sensorimotor function scores (70, 71). In this light, it may be reasonable to use fMRI to determine patient's potential for motor recovery and his/her eligibility to benefit from BCI therapy (33). Sannelli et al. (72) suggested to group BCI users according to their calibration and feedback performance to select subjects and allow customized training. Overall, however, it is not yet possible to precisely estimate how many stroke survivors can directly benefit from BCI-based therapy. Only largescale, longitudinal clinical studies will provide the necessary data to infer the underlying mechanisms of BCI-related recovery and to identify predictors of individual BCI-training response.

CONCLUSIONS

With its capability to advance motor recovery, BCI-based motor interventions provide a good argument to be implemented in stroke rehabilitation in Germany. BCI-based neurofeedback training is well suited to promote neural and functional recovery in early rehabilitation. BCI-based motor interventions showed efficiency in both subacute and chronic stroke patients, making them suitable for post hospital curative treatment and outpatient occupational therapy. Once a plateau in motor recovery is reached, assistive BCI-based devices can be applied in a home setting to improve quality of life. Put together, BCIs represent a promising approach for long-term treatment of severe upper limb paresis in stroke patients. Nevertheless, there are still some obstacles to overcome before BCI-based therapies can be applied in routine clinical practice.

AUTHOR CONTRIBUTIONS

CA and SRS conceived the topic. CA conceptualized the manuscript. CA took the lead in writing the manuscript and was supported by AC, MV, VH, and SRS. All authors provided critical feedback and helped shape the research idea and manuscript, reviewed the results, and approved the final version of the manuscript.

ACKNOWLEDGMENTS

This work was supported in part by the European Research Council (ERC) under the project NGBMI (759370), the Einstein Stiftung Berlin, the ERA-NET NEURON project HYBRIDMIND (BMBF, 01GP2121), and the Federal Ministry of Research and Education under the project SSMART (BMBF, 01DR21025A).

REFERENCES

1. Feigin V, Roth G, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of diseases, injuries and risk factors study 2013 and stroke experts writing group. global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the global burden of disease study 2013. *Lancet Neurol.* (2016) 15:913–24. doi: 10.1016/S1474-4422(16)30073-4
2. Eyding J, Bartig D, Weber R, Katsanos AH, Weimar C, Hacke W, et al. Inpatient TIA and stroke care in adult patients in Germany-retrospective analysis of nationwide administrative data sets of 2011 to 2017. *Neurol Res Pract.* (2019) 1:1–8. doi: 10.1186/s42466-019-0044-y
3. Icks A, Claessen H, Kvitkina T, Narres M, Weingärtner M, Schwab S, et al. Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: a community-based stroke register. *PLoS ONE.* (2017) 12:e0188306. doi: 10.1371/journal.pone.0188306
4. Rücker V, Wiedmann S, O'Flaherty M, Busch MA, Heuschmann PU. Decline in regional trends in mortality of stroke subtypes in Germany from 1998 to 2015. *Stroke.* (2018) 49:2577–83. doi: 10.1161/STROKEAHA.118.023193
5. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke.* (2001) 32:1279–84. doi: 10.1161/01.STR.32.6.1279
6. Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. *Clin Rehabil.* (2012) 26:291–313. doi: 10.1177/0269215511420305
7. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke.* (2003) 34:2181–6. doi: 10.1161/01.STR.0000087172.16305.CD
8. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry.* (1987) 50:714–9. doi: 10.1136/jnnp.50.6.714
9. Wade D, Langton-Hewer R, Wood VA, Skilbeck C, Ismail H. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry.* (1983) 46:521–4. doi: 10.1136/jnnp.46.6.521
10. Veerbeek JM, Kwakkel G, van Wegen EE, Ket JC, Heymans MW. Early prediction of outcome of activities of daily living after stroke: a systematic review. *Stroke.* (2011) 42:1482–8. doi: 10.1161/STROKEAHA.110.604090
11. Etoom M, Hawamdeh M, Hawamdeh Z, Alwardat M, Giordani L, Bacciu S, et al. Constraint-induced movement therapy as a rehabilitation intervention for upper extremity in stroke patients: systematic review and meta-analysis. *Int J Rehabil Res.* (2016) 39:197–210. doi: 10.1097/MRR.0000000000000169
12. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* (2009) 8:741–54. doi: 10.1016/S1474-4422(09)70150-4
13. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? a systematic review and meta-analysis. *PLoS ONE.* (2014) 9:e87987. doi: 10.1371/journal.pone.0087987
14. Wolf SL, Blanton S, Baer H, Breshears J, Butler AJ. Repetitive task practice: a critical review of constraint-induced movement therapy in stroke. *Neurologist.* (2002) 8:325. doi: 10.1097/00127893-200211000-00001
15. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev.* (2014) 2014:CD010820. doi: 10.1002/14651858.CD010820.pub2
16. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. *Stroke.* (2013) 44:e1–2. doi: 10.1161/STROKEAHA.112.673087
17. Platz T, Fheodoroff K, Mehrholz J. *S3 guideline "Rehabilitation therapy for Arm Paresis After Stroke" of the DGNR Long Version.* (2020). Available online at: https://www.awmf.org/uploads/tx_szleitlinien/080-001l_S3_Rehabilitative_Therapie_bei_Armparese_nach_Schlaganfall_2020-07.pdf
18. Platz T, Eickhof C, Van Kaick S, Engel U, Pinkowski C, Kalok S, et al. Impairment-oriented training or bobath therapy for severe arm paresis after stroke: a single-blind, multicentre randomized controlled trial. *Clin Rehabil.* (2005) 19:714–24. doi: 10.1191/0269215505cr904oa
19. Urton ML, Kohia M, Davis J, Neill MR. Systematic literature review of treatment interventions for upper extremity hemiparesis following stroke. *Occup Ther Int.* (2007) 14:11–27. doi: 10.1002/oti.220
20. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database Syst Rev.* (2018) 9:CD006876. doi: 10.1002/14651858.CD006876.pub5
21. Zhang C, Li-Tsang CW, Au RK. Robotic approaches for the rehabilitation of upper limb recovery after stroke: a systematic review and meta-analysis. *Int J Rehabil Res.* (2017) 40:19–28. doi: 10.1097/MRR.0000000000000204
22. Kollen BJ, Lennon S, Lyons B, Wheatley-Smith L, Scheper M, Buurke JH, et al. The effectiveness of the bobath concept in stroke rehabilitation: what is the evidence? *Stroke.* (2009) 40:e89–97. doi: 10.1161/STROKEAHA.108.533828
23. Winter J, Hunter S, Sim J, Crome P. Hands-on therapy interventions for upper limb motor dysfunction following stroke. *Cochrane Database Syst Rev.* (2011) 2011:CD006609. doi: 10.1002/14651858.CD006609.pub2
24. Hesse S, Mehrholz J, Werner C. Robot-assisted upper and lower limb rehabilitation after stroke: walking and arm/hand function. *Dtsch Ärztebl Int.* (2008) 105:330. doi: 10.3238/arztebl.2008.0330
25. Kwakkel G, Kollen BJ, Krebs HI. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. *Neurorehabil Neural Repair.* (2008) 22:111–21. doi: 10.1177/1545968307305457
26. Wu C-Y, Huang P-C, Chen Y-T, Lin K-C, Yang H-W. Effects of mirror therapy on motor and sensory recovery in chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil.* (2013) 94:1023–30. doi: 10.1016/j.apmr.2013.02.007
27. Birbaumer N, Cohen LG. Brain-computer interfaces: communication and restoration of movement in paralysis. *J Physiol.* (2007) 579:621–36. doi: 10.1113/jphysiol.2006.125633
28. Van Dokkum L, Ward T, Laffont I. Brain computer interfaces for neurorehabilitation–its current status as a rehabilitation strategy post-stroke. *Ann Phys Rehabil Med.* (2015) 58:3–8. doi: 10.1016/j.rehab.2014.09.016
29. Soekadar SR, Witkowski M, Mellinger J, Ramos A, Birbaumer N, Cohen LG. ERD-based online brain-machine interfaces (BMI) in the context of neurorehabilitation: optimizing BMI learning and performance. *IEEE Trans Neural Syst Rehabil Eng.* (2011) 19:542–9. doi: 10.1109/TNSRE.2011.2166809
30. Buch E, Weber C, Cohen LG, Braun C, Dimyan MA, Ard T, et al. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke.* (2008) 39:910–7. doi: 10.1161/STROKEAHA.107.505313
31. Soekadar SR, Birbaumer N, Slutzky MW, Cohen LG. Brain-machine interfaces in neurorehabilitation of stroke. *Neurobiol Dis.* (2015) 83:172–9. doi: 10.1016/j.nbd.2014.11.025

32. Mrachacz-Kersting N, Jiang N, Stevenson AJT, Niazi IK, Kostic V, Pavlovic A, et al. Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface. *J Neurophysiol.* (2016) 115:1410–21. doi: 10.1152/jn.00918.2015
33. Ushiba J, Soekadar SR. Brain-machine interfaces for rehabilitation of poststroke hemiplegia. *Prog Brain Res.* (2016) 228:163–83. doi: 10.1016/bs.pbr.2016.04.020
34. Laffont I, Bakhti K, Coroian F, Van Dokkum L, Mottet D, Schweighofer N, et al. Innovative technologies applied to sensorimotor rehabilitation after stroke. *Ann Phys Rehabil Med.* (2014) 57:543–51. doi: 10.1016/j.rehab.2014.08.007
35. Pichiorri F, Morone G, Petti M, Toppi J, Pisotta I, Molinari M, et al. Brain-computer interface boosts motor imagery practice during stroke recovery. *Ann Neurol.* (2015) 77:851–65. doi: 10.1002/ana.24390
36. Ang KK, Chua KSG, Phua KS, Wang C, Chin ZY, Kuah CWK, et al. A randomized controlled trial of EEG-based motor imagery brain-computer interface robotic rehabilitation for stroke. *Clin EEG Neurosci.* (2015) 46:310–20. doi: 10.1177/1550059414522229
37. Biasiucci A, Leeb R, Iturrate I, Perdikis S, Al-Khodairy A, Corbet T, et al. Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. *Nat Commun.* (2018) 9:1–13. doi: 10.1038/s41467-018-04673-z
38. Broetz D, Braun C, Weber C, Soekadar SR, Caria A, Birbaumer N. Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. *Neurorehabil Neural Repair.* (2010) 24:674–9. doi: 10.1177/1545968310368683
39. Ramos-Murguialday A, Broetz D, Rea M, Laer L, Yilmaz O, Brasil FL, et al. Brain-machine interface in chronic stroke rehabilitation: a controlled study. *Ann Neurol.* (2013) 74:100–8. doi: 10.1002/ana.23879
40. Coscia M, Wessel MJ, Chaudary U, Millán JdR, Micera S, Micera S, et al. Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke. *Brain.* (2019) 142:2182–97. doi: 10.1093/brain/awz181
41. Hömberg V. Neurorehabilitation approaches to facilitate motor recovery. *Handb Clin Neurol.* (2013) 110:161–73. doi: 10.1016/B978-0-444-52901-5.00014-9
42. Knecht S, Hesse S, Oster P. Rehabilitation after stroke. *Dtsch Ärztebl Int.* (2011) 108:600. doi: 10.3238/arztebl.2011.0600
43. Bertram M, Brandt T. Early neurological-neurosurgical rehabilitation. current state. *Nervenarzt.* (2007) 78:1160–74. doi: 10.1007/s00115-007-2269-1
44. Mihara M, Hattori N, Hatakenaka M, Yagura H, Kawano T, Hino T, et al. Near-infrared spectroscopy-mediated neurofeedback enhances efficacy of motor imagery-based training in poststroke victims: a pilot study. *Stroke.* (2013) 44:1091–8. doi: 10.1161/STROKEAHA.111.674507
45. Ono T, Shindo K, Kawashima K, Ota N, Ito M, Ota T, et al. Brain-computer interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke. *Front Neuroeng.* (2014) 7:19. doi: 10.3389/fneng.2014.00019
46. Ono T, Kimura A, Ushiba J. Daily training with realistic visual feedback improves reproducibility of event-related desynchronisation following hand motor imagery. *Clin Neurophysiol.* (2013) 124:1779–86. doi: 10.1016/j.clinph.2013.03.006
47. Frolov AA, Húsek Da, Biryukova EV, Bobrov PD, Mokienko OA, et al. Principles of motor recovery in post-stroke patients using hand exoskeleton controlled by the brain-computer interface based on motor imagery. *Neural Netw World.* (2017) 27:107. doi: 10.14311/NNW.2017.27.006
48. Nishimoto A, Kawakami M, Fujiwara T, Hiramoto M, Honaga K, Abe K, et al. Feasibility of task-specific brain-machine interface training for upper-extremity paralysis in patients with chronic hemiparetic stroke. *J Rehabil Med.* (2018) 50:52–8. doi: 10.2340/16501977-2275
49. Gaete JM, Bogousslavsky J. Post-stroke depression. *Expert Rev Neurother.* (2008) 8:75–92. doi: 10.1586/14737175.8.1.75
50. Bundy DT, Souders L, Baranyai K, Leonard L, Schalk G, Coker R, et al. Contralesional brain-computer interface control of a powered exoskeleton for motor recovery in chronic stroke survivors. *Stroke.* (2017) 48:1908–15. doi: 10.1161/STROKEAHA.116.016304
51. Soekadar SR, Nann M, Crea S, Trigili E, Gómez C, Opisso E, et al. Restoration of finger and arm movements using hybrid brain/neural assistive technology in everyday life environments. In: Christoph Guger NM-K, Allison BZ, Editors. *Brain-Computer Interface Research, A State-of-the-Art Summary*. Basel: Springer International Publishing (2019). p. 53–61. doi: 10.1007/978-3-030-05668-1_5
52. Serruya MD. Bottlenecks to clinical translation of direct brain-computer interfaces. *Front Syst Neurosci.* (2014) 8:226. doi: 10.3389/fnsys.2014.00226
53. Witkowski M, Cortese M, Cempini M, Mellinger J, Vitiello N, Soekadar SR. Enhancing brain-machine interface (BMI) control of a hand exoskeleton using electrooculography (EOG). *J Neuroeng Rehabil.* (2014) 11:165. doi: 10.1186/1743-0003-11-165
54. Colamarino E, de Seta V, Masciullo M, Cincotti F, Mattia D, Pichiorri F, et al. Corticomuscular and intermuscular coupling in simple hand movements to enable a hybrid brain–computer interface. *Int J Neural Syst.* (2021) 31:2150052. doi: 10.1142/S0129065721500520
55. Cavallo A, Roth V, Haslacher D, Nann M, Soekadar SR. Minimizing bio-signal recording sites for noninvasive hybrid brain/neural control. *IEEE Syst J.* (2020) 15:1540–6. doi: 10.1109/JSYST.2020.3021751
56. Kam JW, Griffin S, Shen A, Patel S, Hinrichs H, Heinze H-J, et al. Systematic comparison between a wireless EEG system with dry electrodes and a wired EEG system with wet electrodes. *Neuroimage.* (2019) 184:119–29. doi: 10.1016/j.neuroimage.2018.09.012
57. Blankertz B, Sannelli C, Halder S, Hammer EM, Kübler A, Müller K-R, et al. Neurophysiological predictor of SMR-based BCI performance. *Neuroimage.* (2010) 51:1303–9. doi: 10.1016/j.neuroimage.2010.03.022
58. Vidaurre C, Sannelli C, Müller K-R, Blankertz B. Co-adaptive calibration to improve BCI efficiency. *J Neural Eng.* (2011) 8:025009. doi: 10.1088/1741-2560/8/2/025009
59. Thompson MC. Critiquing the concept of BCI illiteracy. *Sci Eng Ethics.* (2019) 25:1217–33. doi: 10.1007/s11948-018-0061-1
60. Lotte F, Larrue F, Mühl C. Flaws in current human training protocols for spontaneous brain-computer interfaces: lessons learned from instructional design. *Front Hum Neurosci.* (2013) 7:568. doi: 10.3389/fnhum.2013.00568
61. Prasad G, Herman P, Coyle D, McDonough S, Crosbie J. Applying a brain-computer interface to support motor imagery practice in people with stroke for upper limb recovery: a feasibility study. *J Neuroeng Rehabil.* (2010) 7:60. doi: 10.1186/1743-0003-7-60
62. Hammer EM, Halder S, Blankertz B, Sannelli C, Dickhaus T, Kleih S, et al. Psychological predictors of SMR-BCI performance. *Biol psychol.* (2012) 89:80–6. doi: 10.1016/j.biopsycho.2011.09.006
63. Myrden A, Chau T. Effects of user mental state on EEG-BCI performance. *Front Hum Neurosci.* (2015) 9:308. doi: 10.3389/fnhum.2015.00308
64. Nann M, Haslacher D, Colucci A, Eskofier B, von Tscharner V, Soekadar SR. Heart rate variability predicts decline in sensorimotor rhythm control. *J Neural Eng.* (2021) 18:0460b5. doi: 10.1088/1741-2552/ac1177
65. Fels M, Bauer R, Gharabaghi A. Predicting workload profiles of brain–robot interface and electromygraphic neurofeedback with cortical resting-state networks: personal trait or task-specific challenge? *J Neural Eng.* (2015) 12:046029. doi: 10.1088/1741-2560/12/4/046029
66. Lorenz R, Pascual J, Blankertz B, Vidaurre C. Towards a holistic assessment of the user experience with hybrid BCIs. *J Neural Eng.* (2014) 11:035007. doi: 10.1088/1741-2560/11/3/035007
67. Guggisberg AG, Koch PJ, Hummel FC, Buetefisch CM. Brain networks and their relevance for stroke rehabilitation. *Clin Neurophysiol.* (2019) 130:1098–124. doi: 10.1016/j.clinph.2019.04.004
68. Ruddy K, Balsters J, Mantini D, Liu Q, Kassraian-Fard P, Enz N, et al. Neural activity related to volitional regulation of cortical excitability. *Elife.* (2018) 7:e40843. doi: 10.7554/eLife.40843.022
69. Raffin E, Hummel FC. restoring motor functions after stroke: multiple approaches and opportunities. *Neuroscientist.* (2017) 24:400–16. doi: 10.1177/1073858417737486
70. Van Meer MP, Van Der Marel K, Wang K, Otte WM, El Bouazati S, Roeling TA, et al. Recovery of sensorimotor function

after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. *J Neurosci.* (2010) 30:3964–72. doi: 10.1523/JNEUROSCI.5709-09.2010

71. Westlake KP, Hinkley LB, Bucci M, Guggisberg AG, Findlay AM, Henry RG, et al. Resting state alpha-band functional connectivity and recovery after stroke. *Exp Neurol.* (2012) 237:160–9. doi: 10.1016/j.expneurol.2012.06.020
72. Sannelli C, Vidaurre C, Muller KR, Blankertz B. A large scale screening study with a SMR-based BCI: categorization of BCI users and differences in their SMR activity. *PLoS ONE.* (2019) 14:e0207351. doi: 10.1371/journal.pone.0207351

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 December 2021
doi: 10.3389/fneur.2021.758536

Unmet Needs for Rehabilitative Management in Common Health-Related Problems Negatively Impact the Quality of Life of Community-Dwelling Stroke Survivors

Kyoung Tae Kim[1,2†], Won Kee Chang[1†], Yun-Sun Jung[1], Sungju Jee[3], Min Kyun Sohn[3], Sung-Hwa Ko[4], Yong-Il Shin[4], Ja-Ho Leigh[5,6], Won-Seok Kim[1] and Nam-Jong Paik[1*]*

[1] Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea, [2] Department of Rehabilitation Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, South Korea, [3] Department of Rehabilitation Medicine, Chungnam National University College of Medicine, Chugnam National University Hospital, Daejeon, South Korea, [4] Department of Rehabilitation Medicine, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea, [5] Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul, South Korea, [6] National Traffic Injury Rehabilitation Research Institute, National Traffic Injury Rehabilitation Hospital, Yangpyeong, South Korea

OPEN ACCESS

Edited by:
Stephanie Clarke,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

Reviewed by:
Mélanie Cogné,
University of Rennes 1, France
Sabahat Wasti,
Cleveland Clinic Abu Dhabi, United Arab Emirates

***Correspondence:**
Won-Seok Kim
wondol77@gmail.com
Nam-Jong Paik
njpaik@snu.ac.kr

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 14 August 2021
Accepted: 07 December 2021
Published: 23 December 2021

Citation:
Kim KT, Chang WK, Jung Y-S, Jee S, Sohn MK, Ko S-H, Shin Y-I, Leigh J-H, Kim W-S and Paik N-J (2021) Unmet Needs for Rehabilitative Management in Common Health-Related Problems Negatively Impact the Quality of Life of Community-Dwelling Stroke Survivors. Front. Neurol. 12:758536. doi: 10.3389/fneur.2021.758536

Purpose: Community-dwelling stroke survivors have various unmet needs for rehabilitative management, but there is a lack of in-depth investigations on common health problems after stroke. Moreover, the association between unmet needs and health-related quality of life (HRQoL) has not been thoroughly investigated. This study aimed to investigate the unmet needs for rehabilitative management in common problems after stroke and their associations with HRQoL among community-dwelling stroke survivors.

Methods: A face-to-face cross-sectional survey was conducted among community-dwelling stroke survivors visiting outpatient clinics of rehabilitation departments between June and October 2020 in three university-affiliated hospitals. Unmet needs for common problems after stroke were assessed across eight domains based on the post-stroke checklist: spasticity, dysphagia, communication, cognition, ambulation, pain/discomfort, anxiety/depression, and self-care. HRQoL was measured using the EuroQoL-5D three level (EQ-5D). The prevalence of unmet needs for rehabilitative management and their associations with the EQ-5D index were analyzed.

Results: Among the 239 participants who responded to the survey, 63% ($n = 150$) were men. The mean age was 63 ± 13 years, and the mean duration of stroke onset was 55.6 months. Overall, 49% reported at least one unmet need, and the most frequently reported unmet needs were anxiety/depression (20.9%), self-care (20.9%), and pain/discomfort (18.0%). The highest proportion of unmet needs was in the anxiety/depression, communication, and cognition domains. Patients with unmet needs for cognition and pain/discomfort showed a significantly lower EQ-5D index, even after

adjusting for age, sex, and modified Rankin scale scores. The total number of unmet needs was significantly correlated with a lower EQ-5D index (Pearson's $r = -0.329$, $p < 0.001$) in the multivariate linear regression model.

Conclusions: Unmet rehabilitative needs are prevalent among community-dwelling stroke survivors, and the proportion of unmet needs was high among non-physical domains such as anxiety/depression. The number of unmet needs is an independent negative predictor of HRQoL. Systematic approaches to identify unmet needs and provide appropriate rehabilitative management are required in long-term stroke survivors.

Keywords: stroke, unmet need, community-dwelling, rehabilitation, post-stroke checklist, quality of life, transitional care

INTRODUCTION

Stroke is one of the leading causes of mortality and long-term physical, psychological, and social disabilities (1, 2). Although the incidence of stroke is increasing, its mortality has been decreasing owing to improved acute stroke care. Consequently, the number of stroke survivors living with disabilities who need long-term care is also increasing (2–4) and its socioeconomic burden (5).

Stroke survivors have various long-term health problems, such as reduced physical functioning (6), spasticity (7), memory loss (8), urinary incontinence (9), communication (10), and mood (11), which can lead to increased socioeconomic burden, participation restriction, and worse health-related quality of life (HRQoL) (12). These long-term health problems in stroke survivors are often not properly managed and remain as unmet needs. A national survey of long-term needs of stroke survivors in the UK showed that over half of patients have unmet needs (13). Andrew et al. also demonstrated that 84% of stroke survivors reported having unmet needs at a median 2 years after stroke (14). Accordingly, various studies have investigated a wide range of multidimensional unmet needs after stroke (15–20). However, previous studies did not focus on the unmet need for care in specific health-related problems after stroke.

In this study, we developed a questionnaire based on a post-stroke checklist (PSC) to assess unmet needs for rehabilitation management in common health-related problems after stroke. The PSC is a set of questionnaires developed by the Global Stroke Community Advisory Panel to identify long-term problems in stroke survivors (21). It examines 11 domains of long-term problems, including, secondary prevention, activities of daily living, mobility, spasticity, pain, incontinence, communication, mood, cognition, life after stroke, and relationships with caregivers. It focuses on the areas where intervention can have a large impact on HRQoL and has been recognized as a standardized tool for assessing long-term unmet needs in clinical practice (22).

In addition, although there have been many reports on the prevalence of unmet needs among stroke survivors, only few studies have investigated their association with HRQoL. Im et al. reported that worsening of mobility and communication problems was significantly associated with worse HRQoL in stroke survivors at the 12-month follow-up (23). Andrew et al. (24) also reported that pain and activity limitation were related to long-term unmet needs at 90 and 180 days following stroke. Nonetheless, the prevalence of long-term unmet needs and their impact on HRQoL remains unclear among chronic community-dwelling stroke survivors. Additionally, identifying the prevalence of unmet needs and their relationship with HRQoL using a conveniently administrable questionnaire will help physicians quickly recognize unmet needs and provide proper management in clinical settings.

This study aimed to investigate the unmet needs for rehabilitation services in the domains of common health problems after stroke in community-dwelling stroke survivors and establish the relationship between unmet needs for rehabilitative management and HRQoL. To achieve this goal, we developed a questionnaire based on the PSC for unmet needs, specifically for the rehabilitative management of common health-related problems after stroke.

MATERIALS AND METHODS

Participants and Study Design

This study included 239 community-dwelling post-stroke patients aged over 18 years who visited the outpatient clinics of the Department of Rehabilitation Medicine at Seoul National University Bundang Hospital (Seongnam-si, Gyeonggi-do, Korea), Chungnam National University Hospital (Jung-gu, Daejeon, Korea), and Pusan National University Yangsan Hospital (Yangsan-si, Gyeongsangnam-do, Korea) between June and October 2020. The cross-sectional survey was conducted using structured questionnaires and face-to-face interviews of the patients or their proxies (e.g., parents, spouse, siblings, children, relatives, and other caregivers). The surveyors provided an oral presentation and obtained informed consent from the patient before the interview. If the patients could not participate due to severe cognitive or communication impairments, the oral presentation and written informed consent form were provided to the proxies. When proxies responded to the questionnaires, they were instructed to answer each question on behalf of the participant.

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1910/572-303). All participants provided written informed consent.

Measures

Unmet Needs for Rehabilitative Management

A survey questionnaire was developed to investigate the unmet needs for rehabilitation management of common post-stroke problems based on the PSC (21). Eight items (i.e., spasticity, dysphagia, communication, cognition, ambulation, pain/discomfort, mood [anxiety/depression], and self-care) were included in the survey. Through the questionnaire, the respondents were asked whether they have a need for rehabilitative management regarding each category. If the participants had a need for such, we asked whether sufficient treatment was received. Unmet needs were defined as a response of not receiving sufficient rehabilitative managements despite having the need for such. Meanwhile, met needs were defined as a participant response of not needing rehabilitative managements or receiving sufficient managements. The total number of unmet needs for each participant was then calculated.

Quality of Life

The HRQoL of participants was measured using the EuroQoL-5D three level (EQ-5D-3L). EQ-5D-3L consists of five domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression (25). Each domain is reported on a three-point Likert scale: no problem, moderate problem, and severe problem (25). The EQ-5D index was calculated using the Korean valuation set (26, 27).

Other Variables

Baseline demographics, including age, sex, marital status (married, widow/separated, single), living alone (yes/no), household income, type of health insurance (national health insurance [employed], and national health insurance [self-employed], medical aid) were obtained. The clinical data of participants, including time since the onset of stroke, type of stroke (ischemic or hemorrhagic), and modified Rankin Scale score (mRS) (0 to 2 / 3 to 6) assessed using a simplified mRS questionnaire (28), were investigated. The degree of disability was also surveyed and categorized as mild (grades 4–7), severe (grade 1–3), or not registered. The post-stroke grade of disability was determined based on the Korean version of the modified Barthel index score (29). We also asked the participants whether they experienced unexpected re-admission within 3 months after home discharge.

Statistical Analyses

The baseline characteristics are presented as numbers and percentages. The prevalence of needs and unmet needs for rehabilitative management in common problems after stroke and unexpected readmission within 3 months after home discharge were also presented as numbers and percentages. Analysis of covariance adjusting for age, sex, and mRS was performed to compare the EQ-5D index per problem between the met and unmet need groups.

To determine the final model for the EQ-5D index, univariate analyses were initially performed using a single linear regression. The EQ-5D index was set as a dependent variable, while baseline characteristics and the total number of unmet needs were set as independent variables. Then, significant variables in the univariate analyses (p-value < 0.05) were entered into a forward stepwise multiple linear regression model, with entry condition of p-value < 0.05 and removal condition of p-value > 0.10. Age was included as a continuous variable, while all other characteristics were included as categorical variables. All models were tested for collinearity, and a variance inflation factor <10 was considered acceptable. Pearson correlation analysis was performed to investigate the correlation between the number of unmet needs and the EQ-5D index. All analyses were conducted using SPSS v.21.0 (IBM Corp, Armonk, NY, USA), and a two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 239 stroke survivors completed the survey. Responses were provided directly by 147 patients (61.5%) and 92 proxies (38.5%). The baseline characteristics are presented in **Table 1**. The mean age was 63.0 $\pm$ 12.9 years, and 62.8% ($n = 150$) were men. Approximately 77.0% ($n = 184$) of the participants were in the chronic phase (i.e., more than 1 year after stroke onset), with a mean stroke onset duration of 55.7 $\pm$ 51.1 months. The mean mRS was 2.7 $\pm$ 1.7, and nearly half ($n = 107$) belonged to a low-income household (i.e., monthly incomes of $\leq$ 2 million won).

Unmet Needs for Rehabilitative Managements

In total, 118 (49.3%) participants reported at least one unmet need for rehabilitative management, with a mean of 2.6 $\pm$ 2.0 participants. The most prevalent need for rehabilitative management was for ambulation (50.2%), followed by self-care (44.8%), spasticity (43.5%), and pain/discomfort (42.1%). The most prevalent unmet needs were for anxiety/depression (20.9%), self-care (20.9%), and pain/discomfort (18.0%) (**Figure 1**). The proportion of unmet needs was the highest in the anxiety/depression domain (74.6%), followed by communication (61.9%) and cognition (59.7%).

Unmet Needs for Rehabilitative Managements and HRQoL

The unmet need group showed worse HRQoL than the met need group across all domains after adjusting for age and sex (**Figure 2**). Additionally, after adjusting for mRS, unmet needs for cognition and pain/discomfort were associated with worse HRQoL.

The increased number of unmet needs was associated with a lower EQ-5D index (Pearson's $r = -0.329$, $P < 0.001$). Five variables were fit in our final model ($R^2 = 0.602$, $F = 67.73$, $P < 0.001$). Among them, mRS, age, and the number of unmet needs showed significant negative correlations with the EQ-5D index, while disability grade and household income showed significant positive correlations with the EQ-5D index (**Table 2**).

TABLE 1 | Baseline patient characteristics ($n = 239$).

Characteristics	*n*	(%)
Age, years		
<40	11	(4.6)
40–59	79	(33.1)
60–69	70	(29.3)
≥70	79	(33.1)
Sex		
Male	150	(62.8)
Female	89	(37.2)
Time since stroke[a], years		
<1	53	(22.4)[a]
1 to <5	78	(32.6)[a]
5 to <10	81	(34.2)[a]
≥10	25	(10.5)[a]
Type of stroke[b]		
Ischemic	139	(58.9)[b]
Hemorrhagic	97	(41.1)[b]
Modified Rankin Scale score[c]		
0–2	112	(47.1)[c]
3–6	126	(53.9)[c]
Household income (KRW)/month)[d]		
<2000	107	(45.5)[d]
2000 to <3000	61	(26.)[d]
3000 to <5000	45	(19.1)[d]
5000 to <7000	12	(5.1)[d]
≥7000	10	(4.3)[d]
Health insurance[c]		
National health insurance (employed)	86	(36.1)[c]
National health insurance (self-employed)	125	(52.5)[c]
Medical aid	27	(11.3)[c]
Marital status[c]		
Married	158	(66.4)[c]
Widow or separated	51	(21.4)[c]
Single	29	(12.2)[c]
Living alone[a]		
Yes	36	(15.2)[a]
No	201	(84.8)[a]
Disability grade[a]		
Severe	83	(35.0)[a]
Mild	61	(25.7)[a]
Not registered	93	(39.2)[a]

[a]$n = 237$; [b]$n = 236$; [c]$n = 238$; [d]$n = 235$.

Unexpected Readmission Within 3 Months After Home Discharge

In total, 17.6% ($n = 42$) of the participants were readmitted within 3 months after home discharge. Among them, 23.8% ($n = 10$) were re-admitted due to stroke-related problems (e.g., stroke recurrence, decline in activities of daily living, pressure ulcers, and infections); 37.5% ($n = 15$), internal and surgical reasons; and another 37.5% ($n = 15$), other non-medical reasons such as difficulty in home care and transfer.

DISCUSSION

The association between unmet needs and HRQoL among community-dwelling stroke survivors remains unclear. In this study, 49.3% of the community-dwelling stroke survivors had at least one unmet need for rehabilitative management in common problems after stroke. Stroke survivors who had unmet needs, specifically for cognition and pain/discomfort showed worse HRQoL, even after adjusting for age, sex, and mRS. The total number of unmet needs was a significant predictor of worse HRQoL in the final multiple linear regression model.

The prevalence of unmet needs in our study was consistent with those of previous studies (13, 14); however, it was also significantly lower than those of other studies that reported >70% prevalence of unmet needs (15, 17, 19). A recent review article showed that the prevalence of unmet needs among stroke survivors varies widely from 19.8 to 91.7% (30). We assumed that this heterogeneity could be due to the differences in patient demographics, definition of unmet needs, and scope of the assessment tools used. In this study, we defined "unmet need" as a post-stroke problem that needs rehabilitative management but is not treated sufficiently. Meanwhile, other studies defined "unmet needs" to a wider extent, including no or insufficient help for difficulty or a problem that has not been addressed sufficiently (14, 19). Moreover, our study focused on identifying health-related unmet needs; thus, the unmet needs in other domains, such as leisure, work, and other socioeconomic domains were not included.

The mean age of the participants in our study was 63 years, which is younger than that of previously reported studies by Andrew et al. and Mckevitt et al. (13, 14). This may be related to possible selection bias. However, similar results have been reported in tertiary hospital outpatient clinics (31). Concerning the relationship between age and unmet needs, Kersten et al. (32) reported no difference in the number of unmet needs among age groups. Andrew et al. (14) have reported that age is negatively associated with unmet needs in the living, support, and financial categories, but not regarding health. Our study investigated health-related unmet needs and did not show a significant association between unmet needs and age.

Among the various health-related needs of stroke survivors, ambulation, self-care, and spasticity were the most frequently identified rehabilitative needs. These physical problems are associated with motor impairment, which is a common sequela of stroke (7, 33, 34). Moreover, these problems have been reported to be prominent in community-dwelling environments than in hospitals (23), resulting in a high prevalence of rehabilitative management needs among community-dwelling stroke survivors. In this study, the most frequently reported unmet rehabilitative need was for self-care, followed by anxiety/depression and pain/discomfort. Among participants who needed rehabilitative management, the highest proportion of unmet needs was for anxiety/depression (74.6%), followed by communication (61.9%) and cognition (59.7%). These results imply that non-physical needs were less likely to be met than physical needs, despite physical needs being more common. For example, in the domains of spasticity and ambulation, the rate

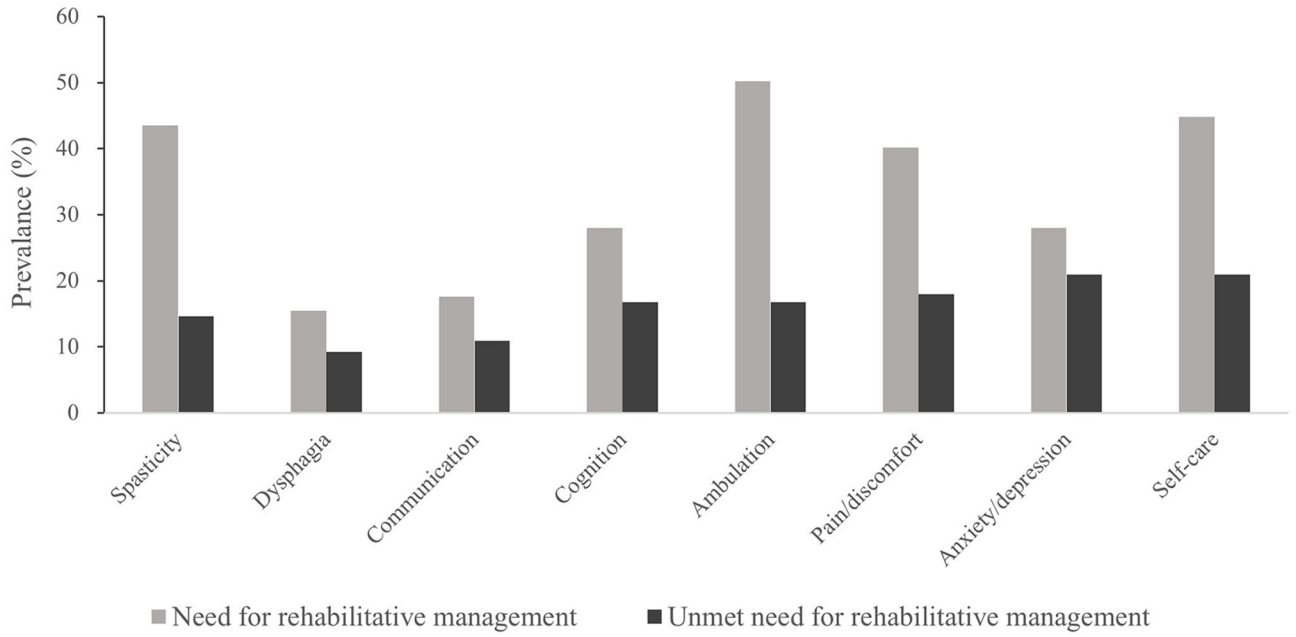


FIGURE 1 | Prevalence of met and unmet needs according to the common problems after stroke.

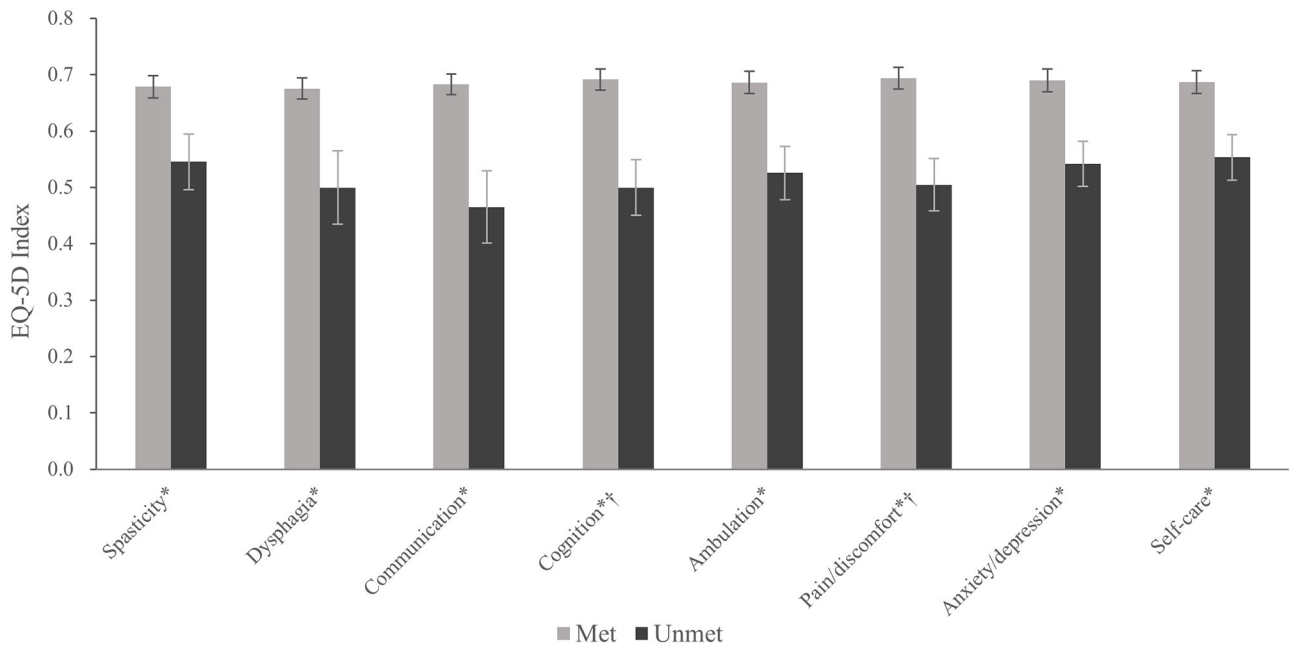


FIGURE 2 | EQ-5D index according to the presence of unmet need for each common problem after stroke. Values are presented as the mean and standard error. *$p < 0.05$, after adjusting for age and sex. †$p < 0.05$, after adjusting for age, sex, and modified Rankin Scale.

of met needs was high, while the rate of unmet needs was low. However, contradicting results were obtained in the domains of anxiety/depression, communication, and cognition.

Under-recognition of non-physical problems might be one explanation for the high proportion of unmet rehabilitative needs. More than 50% of patients experience emotional disturbances after stroke (35), and these are associated with worsened quality of life and increased burden on caregivers (36, 37). Despite its high prevalence, anxiety/depression problems have not been adequately addressed (14). A national audit of

TABLE 2 | Final multiple linear regression model for health-related quality of life.

Variables	β ± SE	95% CI	*p*-value
Modified Rankin Scale score	−0.099 ±0.009	−0.117, −0.082	<0.001
Disability grade[a]	0.072 ±0.017	0.038, −0.105	<0.001
Household income[b]	0.027 ±0.011	0.004, 0.049	0.020
Age	−0.002 ±0.001	-0.004, 0.000	0.035
Number of unmet needs	−0.015 ±0.007	−0.028, −0.001	0.037

$F = 67.73$ ($p < 0.001$), Adjusted R^2 for model = 0.602. [a]Disability grade is defined as an ordinal variable in the following order: severe/mild/not registered. [b]Household income is defined as an ordinal variable in the following order: ≤2000 KRW/2000-3000 KRW/3000-5000 KRW/5000-7000 KRW/≥7000 KRW.

inpatient rehabilitation in Australia reported that approximately only half of stroke patients received an assessment for mood (38). For communication problems, up to one-third of stroke survivors experience communication difficulties, such as aphasia (39). Communication problems in stroke survivors are highly related to their psychosocial well-being; (40) thus, understanding the full impact of communication disorders using a traditional approach based on specific impairments may be insufficient (41). Lastly, cognitive problems negatively impact self-esteem, confidence, and functional recovery, consequently increasing the long-term burden of stroke (42). Despite its importance, the underlying nature of cognitive problems is less understood than that of physical problems, including among clinicians and caregivers (43). Hence, these non-physical problems are often not recognized sufficiently and require more attention from clinicians.

The mean EQ-5D index was significantly lower in patients with unmet needs after adjusting for age and sex in all domains. However, only cognition and pain/discomfort showed a significantly lower EQ-5D index after additionally adjusting for mRS. Cognitive impairment negatively impacts the quality of life of stroke survivors (44–46). Pain is also known to be associated with HRQoL. Choi-Kwon et al. reported that musculoskeletal and central pain were closely associated with HRQoL at 1 year post-stroke, and the presence of central post-stroke pain was an important explanatory factor for overall QoL 3 years after stroke (47, 48). Notably, we found that these two domains were related to the EQ-5D index after adjusting for mRS, implying that unmet needs for cognition and pain/discomfort are associated with worse HRQoL independent of the respondents' overall functional status.

The number of unmet needs showed a significant negative correlation with the mean EQ-5D index. The Australian Stroke Clinical Registry reported a similar trend in which a negative exponential relationship was observed between the EQ-5D VAS scores and the number of unmet needs between 90 and 180 days after stroke (24). Our study results confirmed that this negative correlation is also applicable among long-term community-dwelling stroke survivors. Multivariate linear regression analysis showed that the number of unmet needs along with mRS, household income, degree of disability registration, and marital status were significant factors correlated with HRQoL. This result demonstrates the importance of recognizing the unmet needs of community-dwelling stroke survivors and providing proper intervention, as the number of unmet needs is negatively correlated with HRQoL.

Among the community-dwelling stroke survivors, 17.5% had unexpected re-admission within 3 months after home discharge; in total, 35 and 30% of these readmissions were due to internal or surgical medical causes and non-medical causes, respectively. Our study's unexpected re-admission rate was higher than those reported in the previous studies. Two reasons may contribute to this finding. First, in the study by the Kilkenny et al. (49) and Lin H-J et al. (50), readmission due to non-medical causes was excluded. In our case, non-medical cause such as difficulty of patient care accounted for 37.5% of total unexpected re-admissions. After excluding readmission due to non-medical causes, the unexpected re-admission rate is dropped to 11% (27 out of 239 participants). Additionally, considering the survey was performed in the outpatient setting of tertiary hospitals, our study participants may have greater disability severity than those of previous studies. Kilkenny et al. (49) have identified limited access to information, health, and community services as a risk factor for re-admission after home discharge in stroke patients. Moreover, caregiver burden is an important factor for re-admission, especially for those due to non-medical causes. Many caregivers of community-dwelling stroke survivors have increased burden, which negatively affects the patient's quality of life, leading to re-admission (51, 52). Providing adequate social support to lower the burden of caregivers and increasing accessibility to information and community services may be helpful in reducing unexpected readmissions.

Selection bias may have occurred in our study, as it was conducted at the outpatient clinics of tertiary hospitals. Thus, the survivors who required rehabilitative management but could not visit the clinic due to accessibility issues, including those with a severe disability who do not have a caregiver to bring the patient to the clinic, poor economic status, and long-term institutionalization, were likely to be excluded. However, in our study, the percentage of participants with mRS of 3–5 was 53.9%, which is higher than the results of a 3-month mRS from a multicenter study in Korea (53), signifying that our sample may represent the patients who could visit the rehabilitation outpatient clinic, regardless of their disability severity.

Moreover, the possibility of bias due to responder-type may also exist. Several studies have reported that proxy-responders report more disabilities and worse HRQoL than patients (54, 55). We have investigated whether there is a difference in the prevalence of unmet needs according to the responder type (participant vs. proxy-responder) and found none in terms of communication and cognition. The correlation between EQ-5D-3L and mRS, EQ-5D-3L with the number of unmet needs was also similar between the participant and surrogate responder groups, implying that the assessment of proxy-responders was comparable to that of the participants. Our study has a few other limitations. First, our survey did not cover the comprehensive scope of unmet needs, including social activities, finances, housing, community services, and employment. However, the in-depth investigation of unmet needs in a specific domain of rehabilitation management

overcame these limitations and provided additional information. Second, the definition of an unmet need in our study was based on the participant's self-reported questionnaire and did not include additional information regarding the actual dosage or quality of rehabilitation management received by the participants. Therefore, although we identified the patient's unmet needs subjectively, we were unable to differentiate between unmet and unresolved needs based on the questionnaire. Third, our study did not investigate the comorbidities of the participants. It has been reported that concurrent comorbidities are negatively associated with HRQoL (56). Our study examined the relationship between the number of unmet needs and HRQoL along with functional impairment, disability, age, and income, which have been reported as independent determinants of long-term HRQoL in stroke survivors (12). Finally, a causal relationship between unmet needs and HRQoL could not be established because of the limitations of the cross-sectional study design.

Nonetheless, the strength of our study is that we implemented an easily administrable self-reported questionnaire to identify long-term unmet needs in various categories, which may be improved with proper intervention. The results demonstrate a high prevalence of unmet needs in non-physical categories of long-term stroke survivors. Physicians can easily recognize these unmet needs using a questionnaire similar to that proposed in this study. Considering non-physical unmet needs are often underrecognized in clinical settings, our study emphasizes the demand to identify these unmet needs and plan for appropriative rehabilitation management in out-patient clinics. In conclusion, among community-dwelling stroke survivors, there is a high proportion of unmet needs in non-physical domains, such as anxiety/depression, communication, and cognition. Further, the number of unmet needs is an independent predictor of HRQoL. Systematic approaches to identify unmet needs and provide appropriate rehabilitative management are required in long-term stroke survivors.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Seoul National University Bundang Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KK, WC, SJ, MS, S-HK, Y-IS, J-HL, W-SK, and N-JP: conceptualization. KK, WC, Y-SJ, J-HL, MS, Y-IS, W-SK, and N-JP: methodology. KK, WC, Y-SJ, W-SK, and N-JP: validation/formal analysis. KK, WC, Y-SJ, SJ, MS, S-HK, Y-IS, W-SK, and N-JP: investigation. KK and WC: writing–original draft. KK, WC, Y-SJ, SJ, MS, S-HK, Y-IS, J-HL, W-SK, and N-JP: writing–review and editing. MS, Y-IS, W-SK, and N-JP: project administration. N-JP: funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Research Program funded by the Korea National Institute of Health (2020ER630601).

REFERENCES

1. Murray J, Young J, Forster A. Measuring outcomes in the longer term after a stroke. *Clin Rehabil.* (2009) 23:918–21. doi: 10.1177/0269215509341525
2. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res.* (2017) 120:439–48. doi: 10.1161/CIRCRESAHA.116.308413
3. Katan M, Luft A. Global burden of stroke. *Semin Neurol.* (2018) 38:208–11. doi: 10.1055/s-0038-1649503
4. Kim JS. Stroke in Asia: a global disaster. *Int J Stroke.* (2014) 9:856–7. doi: 10.1111/ijs.12317
5. Kim JS. Stroke becomes the 3rd important cause of death in Korea; is it a time to toast? *J Stroke.* (2014) 16:55. doi: 10.5853/jos.2014.16.2.55
6. Hartman-Maeir A, Soroker N, Ring H, Avni N, Katz N. Activities, participation and satisfaction one-year post stroke. *Disabil Rehabil.* (2007) 29:559–66. doi: 10.1080/09638280600924996
7. Urban PP, Wolf T, Uebele M, Marx JJ, Vogt T, Stoeter P, et al. Occurence and clinical predictors of spasticity after ischemic stroke. *Stroke.* (2010) 41:2016–20. doi: 10.1161/STROKEAHA.110.581991
8. Gamaldo A, Moghekar A, Kilada S, Resnick SM, Zonderman AB, O'Brien R. Effect of a clinical stroke on the risk of dementia in a prospective cohort. *Neurology.* (2006) 67:1363–9. doi: 10.1212/01.wnl.0000240285.89067.3f
9. Wissel J, Olver J, Sunnerhagen KS. Navigating the poststroke continuum of care. *J Stroke Cerebrovasc Dis.* (2013) 22:1–8. doi: 10.1016/j.jstrokecerebrovasdis.2011.05.021
10. Bertheir ML. Poststroke aphasia: epidemiology, pathophysiology and treatment. *Drugs Aging.* (2005) 22:163–82. doi: 10.2165/00002512-200522020-00006
11. Hackett ML, Anderson CS, House AO. Management of depression after stroke: a systematic review of pharmacological therapies. *Stroke.* (2005) 36:1092–7. doi: 10.1161/01.STR.0000162391.27991.9d
12. Sturm JW, Donnan GA, Dewey HM, Macdonell RAL, Gilligan AK, Srikanth V, et al. Quality of life after stroke: the north east melbourne stroke incidence study (NEMESIS). *Stroke.* (2004) 35:2340–5. doi: 10.1161/01.STR.0000141977.18520.3b
13. McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. *Stroke.* (2011) 42:1398–403. doi: 10.1161/STROKEAHA.110.598839
14. Andrew NE, Kilkenny M, Naylor R, Purvis T, Lalor E, Moloczij N, et al. Understanding long-term unmet needs in Australian survivors of stroke. *Int J Stroke.* (2014) 9:106–12. doi: 10.1111/ijs.12325
15. Forster A. Validation of the longer-term unmet needs after stroke (luns) monitoring tool: a multicentre study. *Clin Rehabil.* (2013) 27:1020–8. doi: 10.1177/0269215513487082
16. Groeneveld IF, Arwert HJ, Goossens PH, Vliet Vlieland TPM. The longer-term unmet needs after stroke questionnaire: cross-cultural adaptation, reliability, and concurrent validity in a dutch population. *J Stroke Cerebrovasc Dis.* (2018) 27:267–75. doi: 10.1016/j.jstrokecerebrovasdis.2017.08.043

17. Rothwell K, Boaden R, Bamford D, Tyrrell PJ. Feasibility of assessing the needs of stroke patients after six months using the GM-SAT. *Clin Rehabil.* (2013) 27:264–71. doi: 10.1177/0269215512457403
18. van de Port IGL, van den Bos GAM, Voorendt M, Kwakkel G, Lindeman E. Identification of risk factors related to perceived unmet demands in patients with chronic stroke. *Disabil Rehabil.* (2007) 29:1841–6. doi: 10.1080/09638280601129157
19. Olaiya MT, Cadilhac DA, Kim J, Nelson MR, Srikanth VK, Andrew NE, et al. Long-term unmet needs and associated factors in stroke or TIA survivors. *Neurology.* (2017) 89:68–75. doi: 10.1212/WNL.0000000000004063
20. Ullberg T, Zia E, Petersson J, Norrving B. Perceived unmet rehabilitation needs 1 year after stroke: an observational study from the swedish stroke register. *Stroke.* (2016) 47:539–41. doi: 10.1161/STROKEAHA.115.011670
21. Philp I, Brainin M, Walker MF, Ward AB, Gillard P, Shields AL, et al. Development of a poststroke checklist to standardize follow-up care for stroke survivors. *J Stroke Cerebrovasc Dis.* (2013) 22:e173–80. doi: 10.1016/j.jstrokecerebrovasdis.2012.10.016
22. Ward AB, Chen C, Norrving B, Gillard P, Walker MF, Blackburn S, et al. Evaluation of the post stroke checklist: a pilot study in the United Kingdom and Singapore. *Int J Stroke.* (2014) 9:76–84. doi: 10.1111/ijs.12291
23. Im HW, Kim WS, Kim SY, Paik NJ. Prevalence of worsening problems using post-stroke checklist and associations with quality of life in patients with stroke. *J Stroke Cerebrovasc Dis.* (2020) 29:1–8. doi: 10.1016/j.jstrokecerebrovasdis.2020.105406
24. Andrew NE, Kilkenny MF, Lannin NA, Cadilhac DA. Is health-related quality of life between 90 and 180 days following stroke associated with long-term unmet needs? *Qual Life Res.* (2016) 25:2053–62. doi: 10.1007/s11136-016-1234-5
25. Group TE. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy.* (1990) 16:199–208. doi: 10.1016/0168-8510(90)90421-9
26. Jo MW, Yun SC, Lee S-I. Estimating quality weights for EQ-5D health states with the time trade-off method in South Korea. *Value Health.* (2008) 11:1186–9. doi: 10.1111/j.1524-4733.2008.00348.x
27. Kim MH, Cho YS, Uhm WS, Kim S, Bae SC. Cross-cultural adaptation and validation of the Korean version of the EQ-5D in patients with rheumatic diseases. *Qual Life Res.* (2005) 14:1401–6. doi: 10.1007/s11136-004-5681-z
28. Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, et al. Simplified modified rankin scale questionnaire: Reproducibility over the telephone and validation with quality of life. *Stroke.* (2011) 42:2276–9. doi: 10.1161/STROKEAHA.111.613273
29. *Criteria For Evaluation Of Degree Of Disability Ministry Of Health And* Welfare (2017). Available online at: http://www.law.go.kr/LSW/admRulInfoP.do?admRulSeq=2100000083371. (2019)2019 (accessed October 6, 2019).
30. Chen T, Zhang B, Deng Y, Fan JC, Zhang L, Song F. Long-Term unmet needs after stroke: systematic review of evidence from survey studies. *BMJ Open.* (2019) 9:e028137 doi: 10.1136/bmjopen-2018-028137
31. H KK, Y YS, Tock Seng Hospital T, Tan Tock Seng J, Keng He Ang Mo Kio K. Health-related quality of life among chronic stroke survivors attending a rehabilitation clinic. *Singapore Med J.* (2006) 47:213–8.
32. Kersten P, Low JTS, Ashburn A, George SL, McLellan DL. The unmet needs of young people who have had a stroke: Results of a national UK survey. *Disabil Rehabil.* (2002) 24:860–6. doi: 10.1080/09638280210142167
33. Robinson CA, Shumway-Cook A, Matsuda PN, Ciol MA. Understanding physical factors associated with participation in community ambulation following stroke. *Disabil Rehabil.* (2011) 33:1033–42. doi: 10.3109/09638288.2010.520803
34. Fujita T, Iokawa K, Sone T, Yamane K, Yamamoto Y, Ohira Y, et al. Effects of the Interaction among Motor Functions on Self-care in Individuals with Stroke. *J Stroke Cerebrovasc Dis.* (2019) 28:104387. doi: 10.1016/j.jstrokecerebrovasdis.2019.104387
35. Ayerbe L, Ayis S, Crichton S, Wolfe CDA, Rudd AG. The natural history of depression up to 15 years after stroke: the South London stroke register. *Stroke.* (2013) 44:1105–10. doi: 10.1161/STROKEAHA.111.679340
36. Kim JS, Choi-Kwon S, Kwon SU, Lee HJ, Park K-A, Seo YS. Factors affecting the quality of life after ischemic stroke: young versus old patients. *J Clin Neurol.* (2005) 1:59. doi: 10.3988/jcn.2005.1.1.59
37. Choi-Kwon S, Kim HS, Kwon SU, Kim JS. Factors affecting the burden on caregivers of stroke survivors in South Korea. *Arch Phys Med Rehabil.* (2005) 86:1043–8. doi: 10.1016/j.apmr.2004.09.013
38. National Stroke Foundation *National Stroke Audit - Rehabilitation Services Report.* Melbourne. (2012). Available online at: https://informme.org.au/-/media/D6C49F8C3AB24F81AE3AB341C888CA61.ashx?la=en
39. Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke.* (2006) 37:1379–84. doi: 10.1161/01.STR.0000221815.64093.8c
40. Worrall L, Brown K, Cruice M, Davidson B, Hersh D, Howe T, et al. The evidence for a life-coaching approach to aphasia. *Aphasiology.* (2010) 24:497–514. doi: 10.1080/02687030802698152
41. Wray F, Clarke D. Longer-term needs of stroke survivors with communication difficulties living in the community: a systematic review and thematic synthesis of qualitative studies. *BMJ Open.* (2017) 7:1–18. doi: 10.1136/bmjopen-2017-017944
42. Barker-Collo S, Feigin VL, Parag V, Lawes CMM, Senior H. Auckland stroke outcomes study: part 2: cognition and functional outcomes 5 years poststroke. *Neurology.* (2010) 75:1608–16. doi: 10.1212/WNL.0b013e3181fb44c8
43. Patchick EL, Horne M, Woodward-Nutt K, Vail A, Bowen A. Development of a patient-centred, patient-reported outcome measure (PROM) for post-stroke cognitive rehabilitation: qualitative interviews with stroke survivors to inform design and content. *Health Expect.* (2015) 18:3213–24. doi: 10.1111/hex.12311
44. Cumming TB, Brodtmann A, Darby D, Bernhardt J. The importance of cognition to quality of life after stroke. *J Psychosom Res.* (2014) 77:374–9. doi: 10.1016/j.jpsychores.2014.08.009
45. Caro CC, Mendes PVB, Costa JD, Nock LJ, da Cruz DMC. Independence and cognition post-stroke and its relationship to burden and quality of life of family caregivers. *Top Stroke Rehabil.* (2017) 24:194–9. doi: 10.1080/10749357.2016.1234224
46. Pai HC, Tsai YC. The effect of cognitive appraisal on quality of life of providers of home care for patients with stroke. *J Neurosc Nurs.* (2016) 48:E2–11. doi: 10.1097/JNN.0000000000000175
47. Choi-Kwon S, Choi JM, Kwon SU, Kang D-W, Kim JS. Factors that affect the quality of life at 3 years post-stroke. *J Clin Neurol.* (2006) 2:34. doi: 10.3988/jcn.2006.2.1.34
48. Choi-Kwon S, Choi SH, Suh M, Choi S, Cho KH, Nah HW, et al. Musculoskeletal and central pain at 1 year post-stroke: associated factors and impact on quality of life. *Acta Neurol Scand.* (2017) 135:419–25. doi: 10.1111/ane.12617
49. Kilkenny MF, Dalli LL, Kim J, Sundararajan V, Andrew NE, Dewey HM, et al. Factors associated with 90-day readmission after stroke or transient ischemic attack: linked data from the Australian stroke clinical registry. *Stroke.* (2020) 51:571–8. doi: 10.1161/STROKEAHA.119.026133
50. Lin H-J, Chang W-L, Tseng M-C. Readmission after stroke in a hospital-based registry Risk, etiologies, and risk factors. *Neurology.* (2011) 76:438–43. doi: 10.1212/WNL.0b013e31820a0cd8
51. Pont W, Groeneveld I, Arwert H, Meesters J, Mishre RR, Vliet Vlieland T, et al. Caregiver burden after stroke: changes over time? *Disabil Rehabil.* (2020) 42:360–7. doi: 10.1080/09638288.2018.1499047
52. Caro CC, Costa JD, da Cruz DMC. Burden and quality of life of family caregivers of stroke patients. *Occup Ther Health Care.* (2018) 32:154–71. doi: 10.1080/07380577.2018.1449046
53. Kim SE, Lee H, Kim JY, Lee KJ, Kang J, Kim BJ, et al. Three-month modified Rankin Scale as a determinant of 5-year cumulative costs after ischemic stroke: an analysis of 11,136 patients in Korea. *Neurology.* (2020) 94:e978–91. doi: 10.1212/WNL.0000000000009034
54. Williams LS, Bakas T, Brizendine E, Plue L, Tu W, Hendrie H, et al. How valid are family proxy assessments of stroke patients' health-related quality of life? *Stroke.* (2006) 37:2081–5. doi: 10.1161/01.STR.0000230583.10311.9f
55. Carod-Artal FJ, Coral LF, Trizotto DS, Moreira CM. Self-and proxy-report agreement on the stroke impact scale. *Stroke.* (2009) 40:3308–14. doi: 10.1161/STROKEAHA.109.558031

56. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors' quality of life during subacute recovery. *Stroke.* (2005) 36:1480–4. doi: 10.1161/01.STR.0000170706.13595.4f

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

MINI REVIEW
published: 11 January 2022
doi: 10.3389/fneur.2021.711470

Transitional and Long-Term Care System in Japan and Current Challenges for Stroke Patient Rehabilitation

Shoji Kinoshita[1]*, *Masahiro Abo*[1], *Takatsugu Okamoto*[1,2] and *Kohei Miyamura*[1,3]

[1] Department of Rehabilitation Medicine, The Jikei University School of Medicine, Tokyo, Japan, [2] Department of Rehabilitation Medicine, Nishi-Hiroshima Rehabilitation Hospital, Hiroshima, Japan, [3] Department of Rehabilitation Medicine, Kawakita Rehabilitation Hospital, Tokyo, Japan

OPEN ACCESS

Edited by:
Fenella Jane Kirkham,
University College London,
United Kingdom

Reviewed by:
Yukio Mikami,
Wakayama Medical University, Japan
Yukihide Nishimura,
Iwate Medical University, Japan

***Correspondence:**
Shoji Kinoshita
kinoshita@jikei.ac.jp

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 18 May 2021
Accepted: 09 December 2021
Published: 11 January 2022

Citation:
Kinoshita S, Abo M, Okamoto T and Miyamura K (2022) Transitional and Long-Term Care System in Japan and Current Challenges for Stroke Patient Rehabilitation.
Front. Neurol. 12:711470.
doi: 10.3389/fneur.2021.711470

In Japan, the national medical insurance system and long-term care insurance (LTCI) system cover rehabilitation therapy for patients with acute, convalescent, and chronic stroke. Medical insurance covers early and multidisciplinary rehabilitation therapy during acute phase hospitalizations. Patients requiring assistance in their activities of daily living (ADL) after hospitalization are transferred to kaifukuki (convalescent) rehabilitation wards (KRW), which the medical insurance system has also covered. In these wards, patients can receive intensive and multidisciplinary rehabilitation therapy to improve their ADL and transition to a smooth home discharge. After discharge from these hospitals, elderly patients with stroke can receive outpatient (day-care) rehabilitation and home-based rehabilitation using the LTCI system. The Japanese government has proposed building a community-based integrated care system by 2025 to provide comprehensive medical services, long-term care, preventive care, housing, and livelihood support for patients. This policy aims to promote smooth coordination between medical insurance services and LTCI providers. Accordingly, the medical insurance system allows hospitals to receive additional fees by providing patient information to rehabilitation service providers in the LTCI system. A comprehensive database on acute, convalescent, and chronic phase stroke patients and seamless cooperation between the medical care system and LTCI system is expected to be established in the future. There are only 2,613 board-certified physiatrists in Japan, and many medical schools lack a department for rehabilitation medicine; establishing such a department at each school is encouraged to teach students efficient medical care procedures, to conduct research, and to facilitate the training of personnel in comprehensive stroke rehabilitation.

Keywords: cerebrovascular disease, rehabilitation, long-term care insurance, acute phase, convalescent phase, chronic phase

INTRODUCTION

Historically, stroke has been the number one cause of death among Japanese people, but has shifted to the fourth most common cause in recent years due to decreasing mortality rates, with cancer as the first, heart disease second, and senility third. These numbers reflect fewer deaths due to improved emergency medical services and advances in treatment methods, such as the use of recombinant tissue-type plasminogen activators (rt-PA) and mechanical thrombectomy. However, the overall number of patients with stroke remains high. In Japan, ∼220,000 people experience a new stroke and ∼290,000 people have recurring strokes annually (1). Endovascular treatment or neurosurgery is administered to 9.1% of patients, and 73% of patients receive rehabilitation. Another characteristic of stroke is that the number of patients affected increases with age. According to the 2019 surveys from the Ministry of Health, Labor, and Welfare, cerebrovascular disease accounted for 16.1% of primary causes, requiring long-term care (2). These diseases are serious problems for public life and health, despite being preventable, to a certain extent, through lifestyle improvements.

The clinical importance of rehabilitation therapy for patients with stroke is well-established. Rehabilitation must be provided in a timely and appropriate manner during acute, convalescent, and chronic phases. It is also important to transition seamlessly between the treatments for each phase to improve and maintain the function of patients with stroke. In Japan, the national medical insurance system and long-term care insurance (LTCI) system were established to provide rehabilitation services for patients with stroke (**Figure 1**). In fact, Japan's insurance system is unique. Furthermore, the length of hospital stay for patients with acute stroke in Japan is longer than in other countries, and medical costs are higher. It would be useful to introduce the transitional and long-term care system for rehabilitation of patients with stroke in Japan, where the population is aging to consider the adequate transitional and long-term care strategies after stroke in different health care systems.

The purpose of this mini-review is to outline the transitional and long-term care system in Japan and the current challenges for the rehabilitation of patients with stroke at each phase.

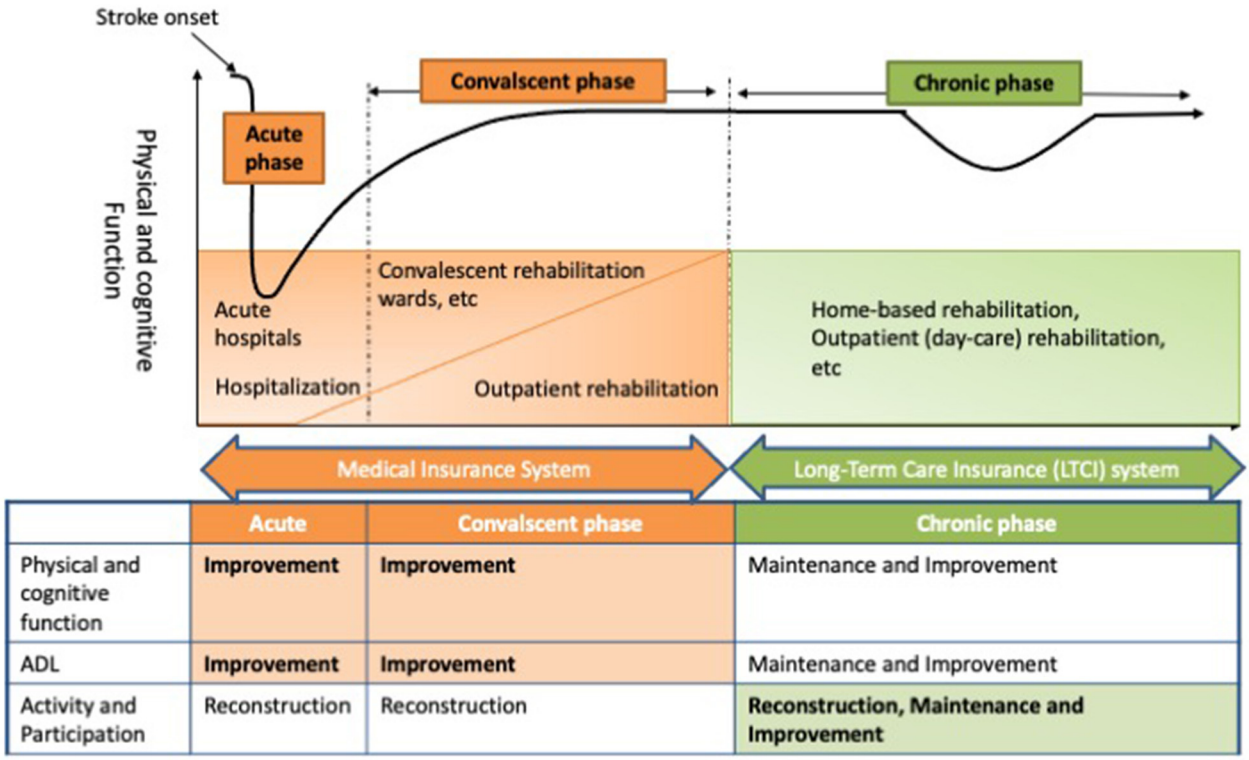
ACUTE PHASE

The main purpose of acute rehabilitation treatment for stroke is to prevent complications associated with immobility, to prevent systemic complications, and to promote functional reorganization of the brain. For this reason, mobilization, basic movement training, gait training, and activities of daily living (ADL) training are implemented as early rehabilitation. In Japan, in recent years, the importance of early rehabilitation for the treatment of acute stroke has been increasingly recognized, and its practice has become widespread. Evidence for these treatments is being collected, which leads to improved knowledge about early rehabilitation therapy (3). In observational studies from Japan (4, 5), very early mobilization was associated with functional recovery of patients with stroke. Initiating rehabilitative care within 24 h of stroke is safe and useful if provided by skilled therapists under physiatrist supervision. Using the Japanese Diagnosis Procedure Combination database, a cohort study analyzed 100,719 consecutive patients with ischemic stroke (6). Their results suggested that early and intensive rehabilitation improved patient ADL during hospitalization. Another study using the Diagnosis Procedure Combination database analyzed 4,266 patients with acute stroke who received intravenous thrombolysis using rt-PA (7). The results showed that a good prognosis at discharge was more likely in the group of patients who started rehabilitation treatment on the day of or after admission. In addition to timing (how early to start), the frequency (how often care is provided) is also important in early rehabilitation treatment (8). Using the Japan Rehabilitation Database, a cohort study of 8,033 patients with the acute cerebrovascular disease showed that high-frequency rehabilitation care (7 days a week for patients with early-onset acute stroke) was associated with better functional recovery (9). In fact, in most cases, rehabilitation was started the day after the onset of symptoms. The percentage of patients receiving rehabilitation 7 days a week was 35.%. The average length of rehabilitation provided per day was 76.7 min. In addition, the average length of stay in the hospital was 29.5 days (10). Based on these results, the medical insurance system can facilitate early rehabilitation therapy for patients with acute stroke in hospitals. Hospitals can charge an additional fee if they provide rehabilitation earlier in the course of the disease. The medical insurance system also assigns rehabilitation staff to intensive care units.

For acute rehabilitation, multidisciplinary cooperation is important for the functional recovery of patients with stroke. For example, early assessment of swallowing function after the stroke onset helps prevent aspiration pneumonia and to promote early oral intake (11). Aoki et al. (12) reported that the activities of a multidisciplinary swallowing team, consisting of nurses, speech therapists, occupational therapists, audiologists, dieticians, dental hygienists, and pharmacists, reduced the incidence of pneumonia in patients with acute cerebrovascular disease. Such a multidisciplinary team, facilitated by the medical insurance system, should be able to assess and manage swallowing function during the acute stroke phase.

CONVALESCENT PHASE

After acute hospitalization, patients who require ADL assistance are transferred to the kaifukuki (convalescent) rehabilitation wards (KRW), which have been covered by the medical insurance system since 2000 (13, 14). Patients with disabling conditions, including stroke, traumatic brain injury, and other neurological diseases, as well as orthopedic diseases, such as hip fractures, are eligible for KRW admission. Under the health insurance system in Japan, rehabilitation therapy (physical, occupational, and speech therapy) is limited to 3 h per day, and the maximum length of stay for patients with stroke in the KRW is limited to 150 days. When rehabilitation goals are met and home or institutional care services are available, the physiatrist can decide



	Acute	Convalscent phase	Chronic phase
Physical and cognitive function	**Improvement**	**Improvement**	Maintenance and Improvement
ADL	**Improvement**	**Improvement**	Maintenance and Improvement
Activity and Participation	Reconstruction	Reconstruction	**Reconstruction, Maintenance and Improvement**

FIGURE 1 | Transitional and long-term care system for rehabilitation of patients with stroke in Japan. In Japan, the medical insurance system covers rehabilitation services for stroke patients in acute and convalescent phases, while the long-term care insurance (LTCI) system covers chronic phase rehabilitation services. In the acute and convalescent phases, the main purpose of rehabilitation is to improve functional recovery and activities of daily living (ADL) of patients with stroke. In the chronic phase, the main aim of rehabilitation services is to maintain physical and cognitive functions and ADL, while improving the engagement of patients with stroke.

to discharge a patient from the KRW. The basic hospitalization fee for the KRW stay is based on the number of medical staff, the provision of rehabilitation on holidays, the percentage of seriously ill patients, the home discharge rate, and motor Functional Independence Measure (FIM) efficiency adjusted by the length of the hospital stay.

The KRW association annual survey reported almost 85,000 KRW beds in 1,500 hospitals in 2019 (15), with an average patient stay length of 67.5 days. The mean patient age was 76.6 years, and 57.8% of patients were female. Stroke was the cause of 36.9% of cases in the KRW. The average time from the stroke onset to the admission to the KRW was 24.2 days. An average of 137.4 min of rehabilitation therapy was provided per day. When the ADL gain of patients with stroke was analyzed in terms of the change in FIM between admission and discharge, the average FIM was determined to be 61.5 points at admission and 84.6 points at discharge, with an average FIM improvement of 23.1 points. Of these, 60.6% of patients were discharged to their homes.

A variety of cutting-edge rehabilitation therapies have been developed and practiced in the KRW. According to a cohort study analyzing 2,325 patients (16), intensive rehabilitation therapy, defined as rehabilitation therapy for more than 15 h per week,was provided for 862 patients (37.1%). Intensive rehabilitation therapy was significantly associated with increased functional gain in elderly patients with stroke in the KRW. Regarding the collaboration between acute care and convalescent rehabilitation, a shorter interval between the stroke onset and admission to the KRW contributes to improved outcomes in patients with ischemic stroke, including ADL, dysphagia, and home discharge rate (17). Prognostic predictions based on a large database have been developed to assess outcomes of patients with stroke (18, 19). Multidisciplinary collaboration from the International Classification of Functioning, Disability, and Health is also practiced according to patient assessment and information sharing (20, 21). Furthermore, innovative rehabilitation using advanced technology, such as robotics, is also becoming more widely developed and practiced (22). Therefore, IRT, collaborations between acute and chronic phase rehabilitation practices, and rehabilitation using innovative techniques are being developed and conducted in KRWs to improve the function of patients with stroke.

CHRONIC PHASE

Japan has an unprecedented aging population that affects health and long-term care systems. The LTCI system was introduced in Japan in 2000 to address the demands of older people with disabilities based on a user-oriented social insurance system supporting independence (23). Older people with certified LTCI service needs can utilize facility services, in-home services, and

community-based services. Following its implementation, the mean length of stay for patients with stroke in rehabilitation hospitals decreased (24). Furthermore, the Japanese government proposed establishing a community-based integrated care system by 2025 to comprehensively provide health care, nursing care, preventive care, housing, and livelihood support for patients (25). This national policy promotes the smooth coordination between medical insurance services and LTCI providers.

There are two main types of rehabilitation services in the LTCI system: home-based rehabilitation and outpatient (day-care) rehabilitation (26, 27). Home-based rehabilitation is provided by rehabilitation staff who visit patient homes. In 2019, there were ∼4,600 facilities and 115,000 recipients for home-based rehabilitation (28). Forty min a day, two times a week is a typical service provision for home-based rehabilitation. During outpatient (day-care) rehabilitation, nursing care services, such as meals and bathing, are provided along with hospital-based rehabilitation. In 2019, there were ∼8,000 facilities and 600,000 recipients for outpatient (day-care) rehabilitation (29). The outpatient (day-care) rehabilitation is generally provided one time or two times a week for 6–7 h each time. In outpatient (day-care) rehabilitation, rehabilitation to improve physical functions, such as muscle strength training and gait training, is often conducted.

To use LTCI services, a person must be certified as needing long-term care based on their physical and cognitive functions, as well as the status of their nursing care and medical treatment. For certified patients, the system requires that they use LTCI rehabilitation services instead of medical insurance, except when they are hospitalized or in the early stages of their illness. In addition, the medical insurance also covers the outpatient rehabilitation for younger patients with stroke and elderly patients who were not certified as needing long-term care in the chronic phase. Among rehabilitation services after returning home from the KRW, outpatient rehabilitation through medical insurance, outpatient (day-care) rehabilitation through LTCI, and home-based rehabilitation through LTCI each account for ∼10% of discharged patients (15).

In the LTCI system, using information and communication technology devices to collaborate with other professions is encouraged. If service providers provide information from medical insurance service centers to LTCI rehabilitation centers, they can charge an additional fee for linking the information using information and communication technology. Furthermore, holding conferences with other professionals within LTCI rehabilitation services is recommended, which also would allow the use of these technologies, such as video teleconferencing systems.

Scientific evidence is necessary to promote high-quality long-term care services. Therefore, the Japanese Ministry of Health, Labor, and Welfare launched a database for LTCI services, the Long-Term Care Information System for Evidence (LIFE), in April 2021. This database stores information on diseases, physical and cognitive functions, rehabilitation goals and interventions, ADL, instrumental ADL, and nutritional status. The purpose of this database is to provide feedback for users and facilities, as well as promote high-quality evidence-based services. Furthermore, by using the LIFE database, service providers can charge another additional fee within the LTCI system. Data from the LIFE database could allow the establishment of evidence for higher quality rehabilitation services for elderly patients, who also suffer from stroke. Although it is possible to link the National Database of medical claims data with the LIFE database in the LTCI system (30), there are no unified outcome measures for rehabilitation with medical insurance and LTCI. Moreover, since there are no standardized codes for individual rehabilitation interventions, it is difficult to clarify effective rehabilitation methods using a database. We hope comprehensive and standardized intervention methods and outcome measures are established for acute, convalescent, and chronic stroke phases.

FUTURE PERSPECTIVE

"The Cerebrovascular and Cardiovascular Disease Control Act" was enacted in December 2019 to control national cerebrovascular diseases. "The Japanese National Plan for Promotion of Cardiovascular Disease Control" based on this law set out three goals: prevention of cerebrovascular diseases and dissemination of correct knowledge; improvement of the service delivery system for health, medical care, and welfare; and promotion of research on cerebrovascular diseases (31, 32). By achieving these three goals, the basic plan thus aims to extend healthy life expectancy by 3 or more years and reduce the age-adjusted mortality rate for cerebrovascular diseases by 2040, which is when the elderly population in Japan will reach its peak. This law and basic plan state that coordination between the treatments for acute, convalescent, and chronic phases is important, and that appropriate services related to medical care, nursing care, and welfare should be provided. Since these require governments and prefectures to promote the control of cerebrovascular diseases, it is expected that the transitional and long-term care systems for stroke rehabilitation will be further developed.

Providing appropriate rehabilitation for patients with stroke requires active physiatrist participation. Physiatrists are usually involved in the clinical management of a multidisciplinary rehabilitation team that consists of nurses, physical therapists, occupational therapists, speech therapists, and medical social workers (33). The physiatrist is expected to implement the management of patients with stroke as a leader of the rehabilitation team. Board-certificated physiatrists with sufficient knowledge and experience about stroke rehabilitation are recommended to be the primary care providers for patients with stroke. A retrospective cohort study with the Japan Rehabilitation Database identified that the clinical management provided by board-certified physiatrists in the form of early rehabilitation for patients with acute and convalescent stroke is a significant predictor of a good functional prognosis (10, 34). In Japan, however, stroke rehabilitation is not always provided by a board-certified physiatrist. At some hospitals or facilities, physicians with other specialties lead the rehabilitation team. This is, in part, due to a shortage in the number of board-certified physiatrists. There were only 2,613 in 2021, and many medical schools

lack a department for rehabilitation medicine. Establishing such a department in each medical school would help teach students medicine and efficient medical care, enable research, and facilitate the training of personnel in comprehensive stroke rehabilitation.

Innovative neurorehabilitation techniques, such as non-invasive brain stimulation, are effective in functional recovery, primarily in patients with chronic stroke. Our group developed a combined protocol using repetitive transcranial magnetic stimulation (rTMS) and IRT that can effectively improve the function of patients with chronic stroke (35). This protocol is now being implemented in many facilities throughout Japan (36). Although the efficacy of non-invasive brain stimulation for patients with stroke in the acute and convalescent phases is controversial, it may be possible to perform it effectively according to brain condition, such as in the case of interhemispheric inhibition, by using functional brain imaging (37–39). We hope non-invasive brain stimulation and other neurorehabilitation techniques will become more widely implemented in the rehabilitation of patients with stroke for acute and convalescent phases.

AUTHOR CONTRIBUTIONS

SK designed concept, drafted the manuscript with important intellectual input from TO and KM, and takes responsibility for whole work from inception to published article. MA provided technical and administrative support and critically assessed the manuscript. All authors have read and approved the final version of the submitted paper.

ACKNOWLEDGMENTS

We express our deepest gratitude to the staff of the Department of Rehabilitation Medicine at the Jikei University School of Medicine. We would like to thank Uni-edit (https://uni-edit.net/) for editing and proofreading this manuscript.

REFERENCES

1. Takashima N, Arima H, Kita Y, Fujii T, Miyamatsu N, Komori M. et al. Incidence, management and short-term outcome of stroke in a general population of 14 million Japanese-Shiga Stroke Registry. *Circ J.* (2017) 81:1636–46. doi: 10.1253/circj.CJ-17-0177
2. Ministry of Health, Labour and Welfare. *National Survey on Basic Living Conditions in 2019.* (2019). Available online at: https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa19/index.html (accessed April 3, 2021).
3. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet.* (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0
4. Kinoshita T, Nishimura Y, Nakamura T, Hashizaki T, Kojima D, Kawanishi M, et al. Effects of physiatrist and registered therapist operating acute rehabilitation (PROr) in patients with stroke. *PLoS ONE.* (2017) 12:e0187099. doi: 10.1371/journal.pone.0187099
5. Kinoshita T, Yoshikawa T, Nishimura Y, Kamijo Y, Arakawa H, Nakamura T, et al. Mobilization within 24 hours of new-onset stroke enhances the rate of home discharge at 6-months follow-up: a prospective cohort study. *Int J Neurosci.* (2020) 22:1–10. doi: 10.1080/00207454.2020.1774578
6. Yagi M, Yasunaga H, Matsui H, Morita K, Fushimi K, Fujimoto M, et al. Impact of rehabilitation on outcomes in patients with ischemic stroke: a nationwide retrospective cohort study in Japan. *Stroke.* (2017) 48:740–6. doi: 10.1161/STROKEAHA.116.015147
7. Momosaki R, Yasunaga H, Kakuda W, Matsui H, Fushimi K, Abo M. Very early versus delayed rehabilitation for acute ischemic stroke patients with intravenous recombinant tissue plasminogen activator: a nationwide retrospective cohort study. *Cerebrovasc Dis.* (2016) 42:41–8. doi: 10.1159/000444720
8. Bernhardt J, Churilov L, Ellery F, Collier J, Chamberlain J, Langhorne P, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology.* (2016) 86:2138–45. doi: 10.1212/WNL.0000000000002459
9. Kinoshita S, Momosaki R, Kakuda W, Okamoto T, Abo M. Association between 7 days per week rehabilitation and functional recovery of patients with acute stroke: a retrospective cohort study based on the Japan Rehabilitation Database. *Arch Phys Med Rehabil.* (2017) 98:701–6. doi: 10.1016/j.apmr.2016.11.004
10. Kinoshita S, Kakuda W, Momosaki R, Yamada N, Sugawara H, Watanabe S, et al. Clinical management provided by board-certificated physiatrists in early rehabilitation is a significant determinant of functional improvement in acute stroke patients: a retrospective analysis of Japan rehabilitation database. *J Stroke Cerebrovasc Dis.* (2015) 24:1019–24. doi: 10.1016/j.jstrokecerebrovasdis.2014.12.026
11. Momosaki R, Abo M, Kakuda W, Kobayashi K. Applicability of the two-step thickened water test in patients with poststroke dysphagia: a novel assessment tool for paste food aspiration. *J Stroke Cerebrovasc Dis.* (2013) 22:817–21. doi: 10.1016/j.jstrokecerebrovasdis.2012.05.011
12. Aoki S, Hosomi N, Hirayama J, Nakamori M, Yoshikawa M, Nezu T, et al. The multidisciplinary swallowing team approach decreases pneumonia onset in acute stroke patients. *PLoS ONE.* (2016) 11:e0154608. doi: 10.1371/journal.pone.0154608
13. Miyai I, Sonoda S, Nagai S, Takayama Y, Inoue Y, Kakehi A, et al. Results of new policies for inpatient rehabilitation coverage in Japan. *Neurorehabil Neural Repair.* (2011) 25:540–7. doi: 10.1177/1545968311402696
14. Okamoto T, Ando S, Sonoda S, Miyai I, Ishikawa M. "Kaifukuki Rehabilitation Ward" in Japan. *Jpn J Rehabil Med.* (2014) 51:629–33. doi: 10.2490/jjrmc.51.629
15. Kaifukuki Rehabilitation Ward Association. *Annual Survey.* (2019). Available online at: http://www.rehabili.jp/publications/download.html (accessed April 14, 2021).
16. Kamo T, Momosaki R, Suzuki K, Asahi R, Azami M, Ogihara H, et al. Effectiveness of intensive rehabilitation therapy on functional outcomes after stroke: a propensity score analysis based on Japan Rehabilitation Database. *J Stroke Cerebrovasc Dis.* (2019) 28:2537–42. doi: 10.1016/j.jstrokecerebrovasdis.2019.06.007
17. Yoshimura Y, Wakabayashi H, Momosaki R, Nagano F, Shimazu S, Shiraishi A. Shorter interval between onset and admission to convalescent rehabilitation wards is associated with improved outcomes in ischemic stroke patients. *Tohoku J Exp Med.* (2020) 252:15–22. doi: 10.1620/tjem.252.15
18. Kinoshita S, Abo M, Okamoto T. Tanaka N. Utility of the revised version of the ability for basic movement scale in predicting ambulation during rehabilitation in poststroke patients. *J Stroke Cerebrovasc Dis.* (2017) 26:1663–9. doi: 10.1016/j.jstrokecerebrovasdis.2017.02.021
19. Yang G, Gu R, Sato S, Zheng F, Sano M, Yashima C, et al. The ability for basic movement scale ii can predict functional outcome and discharge destination in stroke patients. *J Stroke Cerebrovasc Dis.* (2020) 29:104484. doi: 10.1016/j.jstrokecerebrovasdis.2019.104484
20. Kinoshita S, Abo M, Okamoto T, Kakuda W, Miyamura K, Kimura I. Responsiveness of the functioning and disability parts of the International Classification of Functioning, Disability, and Health core sets in postacute stroke patients. *Int J Rehabil Res.* (2017) 40:246–53. doi: 10.1097/MRR.0000000000000235

21. Kinoshita S, Abo M, Okamoto T. Effectiveness of ICF-based multidisciplinary rehabilitation approach with serial assessment and discussion using the ICF rehabilitation set in a convalescent rehabilitation ward. *Int J Rehabil Res.* (2020) 43:255–60. doi: 10.1097/MRR.0000000000000421
22. Tanaka N, Matsushita S, Sonoda Y, Maruta Y, Fujitaka Y, Sato M, et al. Effect of stride management assist gait training for poststroke hemiplegia: a single center, open-label, randomized controlled trial. *J Stroke Cerebrovasc Dis.* (2019) 28:477–86. doi: 10.1016/j.jstrokecerebrovasdis.2018.10.025
23. Yamada M, Arai H. Long-term care system in Japan. *Ann Geriatr Med Res.* (2020) 24:174–80. doi: 10.4235/agmr.20.0037
24. Miyoshi Y, Teraoka JK, Date ES, Kim MJ, Nguyen RT, Miyoshi S. Changes in stroke rehabilitation outcomes after the implementation of Japan's long-term care insurance system: a hospital-based study. *Am J Phys Med Rehabil.* (2005) 84:613–9. doi: 10.1097/01.phm.0000171007.76831.01
25. Song P, Tang W. The community-based integrated care system in Japan: health care and nursing care challenges posed by super-aged society. *Biosci Trends.* (2019) 13:279–81. doi: 10.5582/bst.2019.01173
26. Maruta M, Tabira T, Makizako H, Sagari A, Miyata H, Yoshimitsu K, et al. Impact of outpatient rehabilitation service in preventing the deterioration of the care-needs level among Japanese older adults availing long-term care insurance: a propensity score matched retrospective study. *Int J Environ Res Public Health.* (2019) 16:1292. doi: 10.3390/ijerph16071292
27. Tsuchiya-Ito R, Ishizaki T, Mitsutake S, Hamada S, Yoshie S, Iijima K, et al. Association of household income with home-based rehabilitation and home help service utilization among long-term home care service users. *BMC Geriatr.* (2020) 20:314. doi: 10.1186/s12877-020-01704-7
28. Ministry of Health, Labour and Welfare. *182th Social Security Council, Long-Term Care Benefit Fee Divisional Meeting, Home-Based Rehabilitation.* (2020). Available online at: https://www.mhlw.go.jp/stf/newpage_13021.html (accessed April 13, 2021).
29. Ministry of Health, Labour and Welfare. *180th Social Security Council, Long-Term Care Benefit Fee Divisional Meeting, Outpatient (Day-Care) Rehabilitation.* (2020). Available online at: https://www.mhlw.go.jp/stf/newpage_12499.html (accessed April 13, 2021).
30. Mori T, Tamiya N, Jin X, Jeon B, Yoshie S, Iijima K, et al. Estimated expenditures for hip fractures using merged healthcare insurance data for individuals aged 75 years and long-term care insurance claims data in Japan. *Arch Osteoporos.* (2018) 13:37. doi: 10.1007/s11657-018-0448-2
31. Ministry of Health, Labour and Welfare. *The Basic Plan for Controlling Cerebrovascular Diseases.* (2020). Available online at: https://www.mhlw.go.jp/stf/newpage_14459.html (accessed May 17, 2021).
32. Kuwabara M, Mori M, Komoto S. Japanese National Plan for promotion of measures against cerebrovascular and cardiovascular disease. *Circulation.* (2021) 143:1929–31. doi: 10.1161/CIRCULATIONAHA.120.052737
33. Franceschini M, Caso V, Zampolini M, Negrini S, Giustini A. The role of the physiatrist in stroke rehabilitation: a European survey. *Am J Phys Med Rehabil.* (2009) 88:596–600. doi: 10.1097/PHM.0b013e3181aea225
34. Momosaki R, Kakuda W, Kinoshita S, Yamada N, Abo M. Clinical effectiveness of board-certificated physiatrists on functional recovery in elderly stroke patients during convalescence: a retrospective cohort study. *Int J Gerontol.* (2017) 1:7–11. doi: 10.1016/j.ijge.2016.05.005
35. Abo M, Kakuda W, Momosaki R, Harashima H, Kojima M, Watanabe S, et al. Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: the NEURO-VERIFY Study. *Int J Stroke.* (2014) 9:607–12. doi: 10.1111/ijs.12100
36. Kakuda W, Abo M, Sasanuma J, Shimizu M, Okamoto T, Kimura C, et al. Combination protocol of low-frequency rTMS and intensive occupational therapy for post-stroke upper limb hemiparesis: a 6-year experience of more than 1,700 Japanese patients. *Transl Stroke Res.* (2016) 7:172–9. doi: 10.1007/s12975-016-0456-8
37. Tamashiro H, Kinoshita S, Okamoto T, Urushidani N, Abo M. Effect of baseline brain activity on response to low-frequency rTMS/intensive occupational therapy in poststroke patients with upper limb hemiparesis: a near-infrared spectroscopy study. *Int J Neurosci.* (2019) 129:337–43. doi: 10.1080/00207454.2018.1536053
38. Urushidani N, Kinoshita S, Okamoto T, Tamashiro H, Abo M. Low-Frequency rTMS and intensive occupational therapy improve upper limb motor function and cortical reorganization assessed by functional near-infrared spectroscopy in a subacute stroke patient. *Case Rep Neurol.* (2018) 10:223–31. doi: 10.1159/000492381
39. Kinoshita S, Tamashiro H, Okamoto T, Urushidani N, Abo M. Association between imbalance of cortical brain activity and successful motor recovery in sub-acute stroke patients with upper limb hemiparesis: a functional near-infrared spectroscopy study. *Neuroreport.* (2019) 30:822–7. doi: 10.1097/WNR.0000000000001283

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 March 2022
doi: 10.3389/fneur.2022.744945

The Effect of Branched Chain Amino Acid Supplementation on Stroke-Related Sarcopenia

Min Kyu Park[1], *Sook Joung Lee*[2]*, *Eunseok Choi*[2], *Sangjee Lee*[2] and *JungSoo Lee*[2]

[1] Department of Clinical Pharmacology and Therapeutics, College of Medicine, Chungbuk National University Hospital, Cheongju-si, South Korea, [2] Department of Physical Medicine and Rehabilitation, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Background: Stroke-related sarcopenia is caused by various factors, such as brain damage, systemic catabolic state, skeletal muscle imbalance, and malnutrition. In the long-term care plan after stroke, appropriate rehabilitation strategies to achieve maximum functional improvement and prevent the development of sarcopenia are important. This study has investigated the effect of branched-chain amino acid (BCAA) supplementation on sarcopenia after stroke. We also evaluated the effect of BCAA on functional improvement during the intensive rehabilitation period.

Methods: Patients with subacute stroke with stroke-related disabilities were enrolled and given dietary supplement powder containing BCAAs for 1 month. These BCAAs were supplied through the nutrition team during feeding time. Patients whose age, sex, and stroke lesions were similar to those of the study group were enrolled in the control group through medical record review. Both groups received personalized intensive inpatient rehabilitation therapy in a single-unit rehabilitation center. All patients' target calories were calculated regularly by the nutritional support team in our institution. Sarcopenia status was evaluated using grip strength and the skeletal muscle index (SMI), which was assessed by dual-energy X-ray absorptiometry (DEXA). The functional status associated with stroke was evaluated every month, including activities of daily living, balance, gait, and swallowing.

Results: A total of 54 patients were enrolled, with 27 patients in each of the two groups. The study group showed significantly greater improvement in SMI after intervention than the control group. Both groups improved functionally over time, but the improvement in the study group was significantly greater than that in the control group. Univariate analysis revealed that patients with better functional status had a greater SMI with a combination of BCAA supplementation and intensive rehabilitation therapy.

Conclusion: Our results showed a positive effect of BCAA supplementation on sarcopenia after stroke. We also found that nutritional support helps functional improvement during neurological recovery. These results suggest that comprehensive rehabilitation intervention combined with BCAA supplementation could be a helpful option during the critical period of post-stroke neurological recovery.

Keywords: stroke, sarcopenia, rehabilitation, branched-chain amino acids, skeletal muscle index, function

OPEN ACCESS

Edited by:
Surjo R. Soekadar, Charité Universitätsmedizin Berlin, Germany

Reviewed by:
Torsten Rackoll, Charité Medical University of Berlin, Germany
Monika Błaszczyszyn, Opole University of Technology, Poland
Yongmin Choi, Keimyung University, South Korea

***Correspondence:**
Sook Joung Lee
lsj995414@hanmail.net

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *21 July 2021*
Accepted: *10 February 2022*
Published: *11 March 2022*

Citation:
Park MK, Lee SJ, Choi E, Lee S and Lee J (2022) The Effect of Branched Chain Amino Acid Supplementation on Stroke-Related Sarcopenia. Front. Neurol. 13:744945. doi: 10.3389/fneur.2022.744945

INTRODUCTION

Stroke-related sarcopenia occurs due to a variety of factors, such as brain damage, systemic catabolic state, skeletal muscle imbalance, and malnutrition (1). Rosenberg defined "sarcopenia" as an age-related decline in lean body mass (LBM), muscle mass, and function (2); similar changes are also seen after stroke. Brain lesions in patients with a stroke lead to complex systemic metabolic changes, characterized by weight loss and anabolic catabolic imbalance (3). According to current studies, it was estimated that the incidence of sarcopenia in patients with stroke has been reported to range from 14 to 54% (4).

Stroke-related sarcopenia can be distinguished from sarcopenia itself (1), and it is related to direct catabolic signals from stroke injury, a rapid decline in muscle mass, and structural muscle alterations. However, multiple factors related to stroke accelerate functional disabilities and decrease muscle mass that causes stroke-related sarcopenia.

In stroke, brain lesions cause various neurological deficits and functional impairments. The US National Longitudinal Health and Retirement Study confirmed the findings of previous studies that stroke is the most frequent cause of functional impairment (5). Approximately 50% of patients are disabled, and 30% of the remaining patients are unable to walk (1, 6). Swallowing difficulties are present in 30–50% of patients after stroke, leading to malnutrition (4, 7, 8).

Brain lesions also activate the systemic catabolic pathway. Muscle structural changes develop within hours after stroke, followed by a rapid reduction in muscle mass. As early as 3 weeks after stroke, a significant decrease in muscle mass can be observed (9). Within 1 year after stroke, up to 3% of the lean mass of the paretic limb is lost (10) and within 6–12 months after stroke, a decrease in the muscle volume of the paretic limb of up to 24% has been observed (11).

Furthermore, stroke-related sarcopenia may accelerate these disadvantages and the massive burden in all areas, such as delaying the poststroke rehabilitation period, worsening the patients' functional recovery (3), lengthening the hospital stay, and increasing economic burden (4, 12). Thus, strategies to prevent the development of sarcopenia after stroke are important.

To improve the functions of patients with stroke, various rehabilitation interventions have been implemented (13, 14). Previously recommended, management of stroke-related sarcopenia should include rehabilitation intervention and nutritional support. Recent review studies have emphasized the consumption of branched-chain amino acids (BCAAs) by sarcopenic patients (15). BCAAs are essential amino acids that induce a muscle protein anabolic response and stimulate muscle mass growth (16). It could also resolve malnutrition after stroke. However, few studies have investigated the BCAA supplementation and stroke-related sarcopenia.

As neurological recovery after stroke does not follow a linear but a logarithm pattern (13), early appropriate, multiple rehabilitation interventions are important for maximum functional improvement after stroke (14). We hypothesized that consuming BCAAs after stroke could prevent rapid muscle loss after stroke and lead to functional improvement during the important neurological recovery periods.

The aim of this study was to investigate the effect of BCAA supplementation on sarcopenia after stroke. We also evaluated the effect of BCAA on functional improvement during the intensive rehabilitation period after stroke.

MATERIALS AND METHODS

Participants

Patients with subacute stroke who had stroke-related disabilities and needed intensive rehabilitation intervention were registered. The following patients were included:

(1) Those with subacute stroke within 3 months after stroke.
(2) Those with stroke-related disabilities (> 3 mRS, which correlate moderate disability).
(3) Those with neurologically stable condition, without reattack and reinfarction-related stroke.
(4) Those who were medically stable and able to receive intensive rehabilitation therapy (>3 h/day).

The following patients were excluded:

(1) Those with chronic kidney disease (> CKD stage 2, which represent kidney damage with mild loss of kidney function).
(2) Those with elevated blood urea nitrogen (BUN) levels (over the normal range: 6–20 mg/dl).
(3) Those with elevated creatine (Cr) levels (over the normal range: 0.5–1.2 mg/dl).
(4) Those with uncontrolled infectious status, which needs antibiotic therapy and unstable vital sign (high temperature over 37.8°C, and lower or elevated heart rate, and pulse).

The study group was prospectively enrolled for ingesting BCAAs between January 2021 and June 2021; since the BCAAs were supplied through the nutrition support team during feeding time, this study could not be blinded with respect to the administration of the BCAAs. Patients whose age and stroke lesions were similar to those in the study group were enrolled in the control group through a retrospective medical record review between 2019 and 2020; those for whom dual-energy X-ray absorptiometry (DEXA) had not been performed were also excluded. This is a non-randomized, non-blinded as well as age, sex, and stroke lesion-matched comparative study. All patients were selected from the department of a rehabilitation unit in a single hospital and treated with the same intensive routine rehabilitation therapy for stroke. The study protocol was approved by the institutional review board of our hospital (DC21RISI0014).

Interventions

Patients in the study group were given 30 g of Seniup® (Enterogenomics Co., Daejeon, Korea) dietary supplement powder containing 6 g of BCAAs (2,976 mg of L-leucine, 1,512 mg of L-isoleucine, and 1,512 mg of L-valine) to be taken twice a day for 1 month. These BCAAs were provided by the nutrition team during feeding time. If the patient was fed through an enteral tube due to swallowing difficulty, the BCAAs were administered *via* the L-tube after being mixed with water. If the

patient was prescribed a therapeutic diet, such as a thickener with water, the BCAAs were administered by mixing them with water and the thickener. The patients' target calories were calculated regularly by the nutritional support team according to the patients' condition and feeding materials in our institution. Because patients were received intensive rehabilitation therapy, their required energy was calculated using the Harris-Benedict equation (HBE), which was equal to 110% of the estimated amount of basal energy expenditure (BEE). Thus, each patient was provided almost 30 kcal/kg per day.

All patients in the study group and the control group were treated with a personalized, routine intensive inpatient poststroke rehabilitation therapy (17, 18), which included physiotherapy, occupational therapy, swallowing therapy, speech therapy, and modality. The patients also received regular functional evaluations every month during the intensive rehabilitation treatment period.

Evaluations

Sarcopenia Evaluation

The sarcopenia status was assessed using handgrip strength and DEXA. Handgrip strength is a reliable and simple marker of muscle strength of the upper extremities (19). The highest test reliability for the unaffected side handgrip test was obtained when the mean of 3 measurements was used (20). DEXA is a standard tool for measuring muscle mass and is the most frequently used instrument for the assessment of body composition in patients with stroke (21). The skeletal muscle index (SMI) was defined as appendicular lean mass as assessed by DEXA divided by height in meters squared.

Unfortunately, the cutoff values for stroke-related sarcopenia have not yet been established; thus, we used the values of the definition of sarcopenia for Asian patients according to the Asian Working Group for Sarcopenia (15). Low muscle strength was defined as a handgrip strength <28 kg for men and <18 kg for women. The criteria for poor physical performance were a 6-m walk speed of <1.0 m/s and a height-adjusted muscle mass of <7.0 kg/m^2 in men and <5.4 kg/m^2 in women according to DEXA. Gait speed is an important diagnostic criterion for sarcopenia; however, the applicability of the assessment of gait speed is limited in patients with stroke. The short physical performance battery t(SPPBT) is another well-established scale for assessing physical performance and functions in sarcopenia (22). However, the SPPBT could not be administered in this study because most of the enrolled patients could not stand independently. Therefore, functional status was evaluated using various functional evaluation tools developed and verified for patients with stroke instead of the gait speed or SPPBT.

Functional Evaluation

We evaluated functional status related to stroke using the Korean version of modified Barthel index (K-MBI), Berg balance scale (BBS), functional ambulatory category (FAC), and manual function test (MFT), which have been well-established for patients with stroke. The K-MBI is used to assess performance in 10 basic activities related to self-care and mobility, with a score ranging from 0 to 100 and lower scores indicating greater dependency (23). The BBS is used to evaluate a patient's ability to safely balance during a series of predetermined tasks. The score ranges from 0 to 56; a score of 56 indicates functional balance and a score below 45 indicates that the individual may be at greater risk of falling (24). The FAC is a functional walking test that evaluates ambulation ability. This 6-point scale determines ambulation status by determining how much energy the patient requires when walking, regardless of whether or not they use an assistive device (25). The MFT measures gross and fine motor dexterities in the upper extremities on a scale of 0 to 32, and its reliability is considered excellent (26).

TABLE 1 | Demographic characteristics of patients in both groups.

Characteristic	Study group ($n = 27$)	Control group ($n = 27$)	*P*-value
Age (years)	76.52 ± 7.71	75.93 ± 8.53	0.790
Gender (male/female)	14/13	14/13	0.409
NIHSS (score)	13.7 ± 9.1	15.1 ± 7.3	0.285
Diabetes (n, %)	13 (48.15)	15 (55.56)	0.514
Hypertension (n, %)	16 (59.26)	17(62.96)	0.306
Stroke type Ischemic/hemorrhagic	15/12	15/12	0.903
Stroke lesion Cortical/subcortical/brainstem	11/8/8	10/9/8	0.534
Stroke side Right/left	15/12	14/13	0.627
Initial evaluations			
Days from stroke onset (Initial evaluation, days)	48.10 ± 21.68	51.34 ± 23.71	0.679
Cognition–MMSE	7.29 ± 6.91	9.05 ± 7.41	0.627
Swallowing function			
Non-oral feeding (n, %)	10 (37.04)	8 (29.63)	0.094
Limited diet (n, %)	13 (48.15)	16 (59.26)	0.328
Regular diet (n, %)	4 (14.81)	3 (11.11)	0.771
Albumin	3.54 ± 0.41	3.41 ± 0.42	0.258
BMI (kg/m^2)	19.51 ± 4.24	17.72 ±5.53	0.467
BMD	−2.71 ± 1.09	−2.38 ± 1.28	0.309
Handgrip strength (kg)	12.13 ±5.72	13.40 ± 12.43	0.174
DEXA			
SMI (kg/m^2)	4.70 ± 0.66	4.73 ± 0.70	0.902
Est. VAT area	107.9 ± 46.76	103.59 ± 34.98	0.703
LBM Affected upper extremity (g)	1,511.08 ±3 25.73	1,609.74 ± 335.84	0.278
Intact upper extremity (g)	1,595.53 ± 328.51	1,711.04 ± 330.64	0.204
Affected lower extremity (g)	4,432.34 ± 860.63	4,724.41 ± 975.46	0.249
Intact lower extremity (g)	4,494.71 ± 880.02	4,913.93 ± 983.88	0.105

Values are mean ± SD, or numbers. BMI, body mass index; BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; SMI, skeletal muscle index; LBM, lean body mass.

TABLE 2 | Sarcopenia and functional evaluations before and after treatment within the group.

Parameters	Study group			Control group		
Sarcopenic evaluations	**Pre-Tx**	**Post-Tx**	***P*-value**	**Pre-Tx**	**Post-Tx**	***P*-value**
Handgrip strength (kg)	12.13 ± 5.72	15.68 ± 6.22*	0.021	13.40 ± 12.43	15.19 ± 7.08	0.085
DEXA						
SMI (kg/m^2)	4.68 ± 0.66	4.79 ± 0.69*	0.023	4.73 ± 0.70	4.51 ± 0.74*	0.039
Est. VAT area	107.9 ± 46.76	108.41 ± 42.45	0.602	103.59 ± 34.98	104.85 ± 37.09	0.451
LBM						
Affected upper extremity (g)	1,511.08 ± 325.73	1,518.37 ± 138.50*	0.037	1,609.74 ± 335.84	1,604.37 ± 362.78	0.901
Intact upper extremity (g)	1,595.53 ± 328.51	1,602.93 ± 308.72*	0.040	1,711.04 ± 330.64	1,736.22 ± 341.48	0.128
Affected lower extremity (g)	4,432.34 ± 860.63	4,462.43 ± 904.04*	0.001	4,724.41 ± 975.46	4,467.48 ± 409.12*	<0.001
Intact lower extremity (g)	4,494.71 ± 880.02	4,559.30 ± 930.14	0.257	4,913.93 ± 983.88	4,607.52 ± 571.61*	0.004
Functional evaluations	**Pre-Tx**	**Post-Tx**	***P*-value**	**Pre-Tx**	**Post-Tx**	***P*-value**
Activities of daily living: K-MBI	27.19 ± 15.40	42.48 ± 20.42*	<0.001	24.07 ± 13.61	37.33 ±17.52*	<0.001
Balance and gait - BBS	9.45 ± 12.74	24.67 ± 16.67*	<0.001	6.48 ± 5.94	16.89 ± 15.26*	<0.001
Gait function- FAC	1.70 ± 0.91	3.26 ± 1.31*	0.021	1.48 ± 0.70	2.81 ± 1.30*	0.030
Upper ext. function - MFT	15.07 ± 7.21	20.85 ±6.31*	<0.001	15.22 ± 7.78	19.15 ± 7.57*	0.041
Swallowing function -FDS	35.63 ± 15.30	23.26 ± 11.47*	<0.001	39.85 ± 12.43	28.78 ± 14.35*	<0.001
Swallowing function - PAS	5.67 ± 2.45	3.89 ± 2.40*	0.034	6.44 ±1.78	4.89 ± 1.97*	0.048
Feeding materials - DOSS	4.04 ± 1.74	5.22 ± 1.48*	<0.001	3.04 ±1.65	4.63 ± 1.47*	<0.001

*Values are mean ± SD. DEXA, dual-energy X-ray absorptiometry; SMI, skeletal muscle index; LBM, lean body mass; K-MBI, Korean version of modified Barthel index; BBS, Berg balance scale; FAC, functional ambulatory category; MFT, manual function test; FDS, functional dysphagia scale; PAS, penetration aspiration scale; DOSS, dysphagia outcome and severity scale, *p < 0.05 according to paired t-test.*

Swallowing function was evaluated using the functional dysphagia scale (FDS) and penetration aspiration scale (PAS) (27) based on the results of the video fluoroscopic swallowing study (VFSS). The FDS (28) was developed to quantify the severity of dysphagia; it correlates well with the American Speech-Language-Hearing Association national outcome measurement system criteria. The higher the score, the more severe the dysphagia. The PAS evaluates airway invasions and has a maximum score of 8 points. Scores are determined based on the depth to which material passes into the airway and based on whether material passes below the vocal fold and any effort to make eject the material. The penetration category corresponds to level 3 to 5 on the scale, and levels 6 to 8 According to the results of the VFSS, the patients' feeding methods were decided as follows: non-oral feeding, limited diet, or normal regular diet. Feeding status was presented as a dysphagia outcome and severity scale (DOSS) (29). It consists of 7-point levels (1–7), with higher scores indicating a normal diet. Level 1 indicates severe dysphagia that patients could not be fed orally.

All evaluations, including sarcopenic and functional status, were part of routine evaluations in the rehabilitation unit, thus, they were measured in both the study and control groups every month. Patients in the study group were evaluated before and after 4 weeks of BCAA treatment. All assessments were done by blinded therapists who were unaware of the study protocol.

Statistical Analysis

SPSS 24.0 (IBM Co., Armonk, NY, USA) for Windows was used for statistical analysis. The Student's *t*-test and the chi-square test were used to compare the study and control groups. The paired *t*-test was used to compare the treatment effects measured before and 1 month after therapy in each group. Correlation analysis between sarcopenia and functional status was assessed using Pearson's correlation coefficients. Univariate and multivariate regression analyses were performed to determine which factors affected poststroke sarcopenia. A $p < 0.05$ was considered statistically significant. Since patients in the control group were enrolled *via* a retrospective chart review, the sample size could not be calculated before the study. Therefore, we have analyzed the power calculation for changes in the SMI and functional status between the two groups, and it showed a high effective sample size (>80%).

RESULTS

All enrolled patients aged above 65 years and had experienced a subacute stroke phase, within 3 months of the stroke onset. In total, 54 patients were enrolled, with 27 patients from each of the two groups. All patients were recruited from a single rehabilitation unit and received the same rehabilitation therapy except BCAA supplementation. **Table 1** shows the demographic characteristics of the patients in both groups. There was no significant difference between the two groups in the initial evaluations and demographic factors. According to the 2019 sarcopenia criteria, most of the enrolled patients already showed decreased SMI on DEXA and decreased handgrip strength in the baseline evaluation (15).

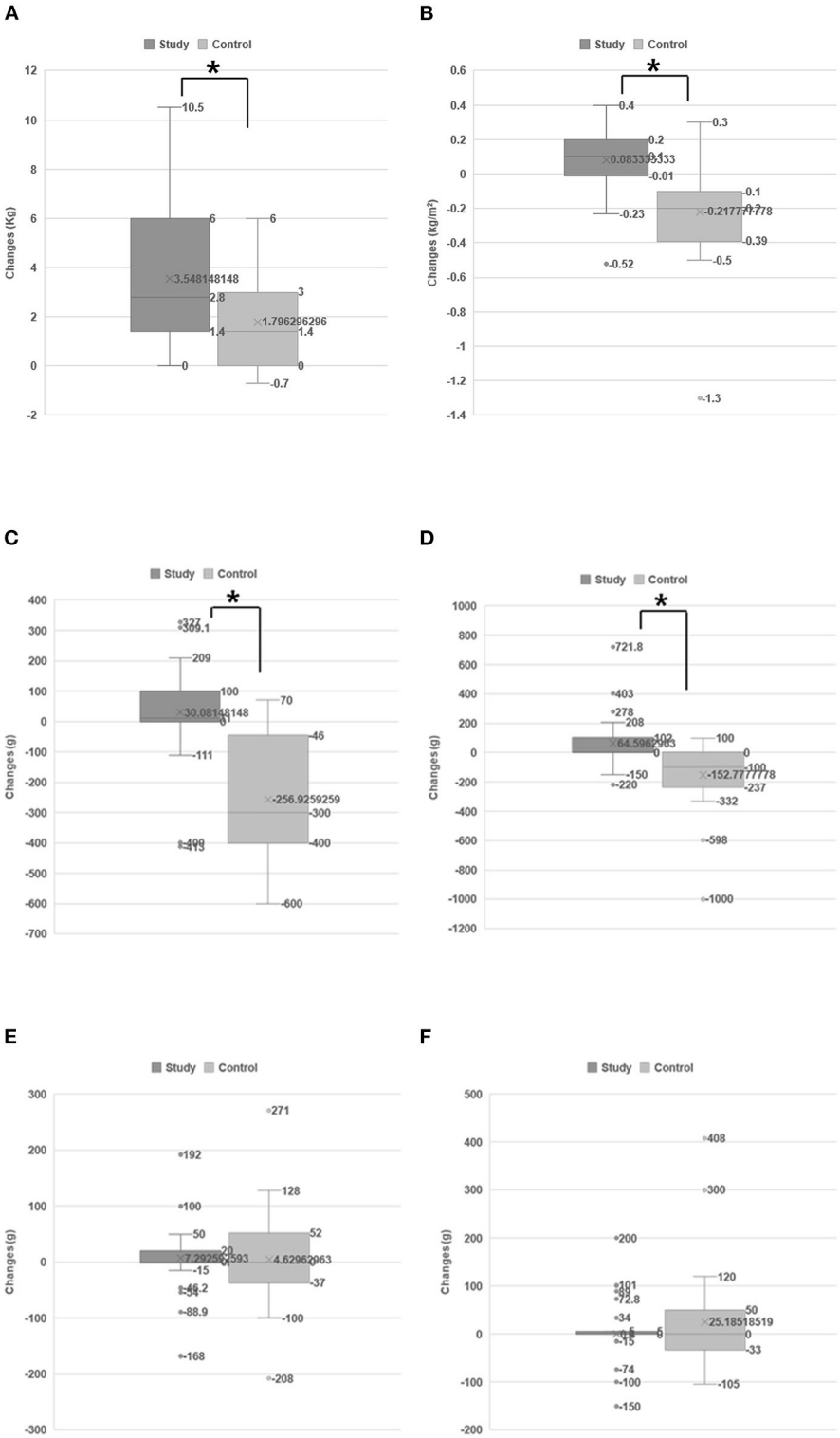


FIGURE 1 | Changes in sarcopenic status between two groups. The changes of handgrip strength **(A)** and SMI **(B)**. The study group improved significantly in terms of handgrip strength **(A)** and SMI **(B)** than the control group. The changes of LBM on each extremity: affected lower extremity **(C)**, intact lower extremity **(D)**, affected upper extremity **(E)**, and intact upper extremity **(F)**. The LBM of the affected lower extremities of the control group was markedly, significantly decreased after treatment **(C)**, and the intact lower extremities also showed a decreased LBM **(D)**. However, rather than decreasing, the LBM of the affected lower extremities of the study group patients was slightly, significantly increased **(C)**. *$p < 0.05$ according to independent *t*-test.

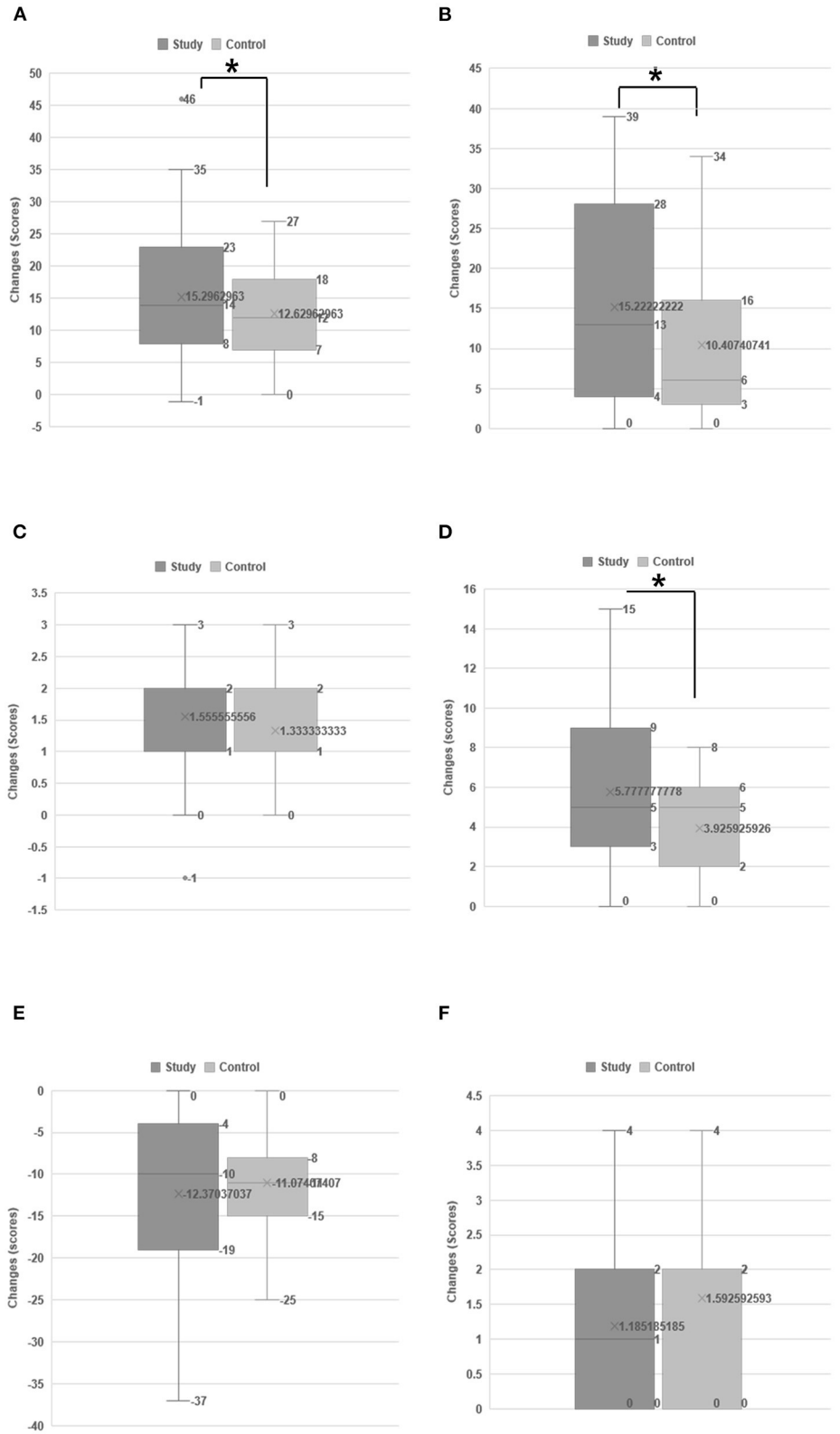


FIGURE 2 | Changes in the functional status between two groups. Changes in the functional status between two groups: Activities of daily living using MBI **(A)**, the Berg balance scale **(B)**, functional ambulation category **(C)**, upper extremity function using the manual function test **(D)**, swallowing function using the functional dysphagia scale **(E)**, and dysphagia outcome and severity scale **(F)**. Both groups showed functional improvement over time; however, the improvement in the study group was significantly greater than that in the control group. *$p < 0.05$ according to independent *t*-test.

TABLE 3 | Pairwise correlations between function and sarcopenia status.

Two test	Total		Study group		Control group	
	Pearson's correlation coefficient	*P*-value	Pearson's correlation coefficient	*P*-value	Pearson's correlation coefficient	*P*-value
Initial SMI - Δ K-MBI	0.1986	0.150	0.279	0.159	0.104	0.604
Initial SMI- Δ BBS	0.0299	0.830	0.100	0.617	0.04	0.412
Initial SMI- Δ FAC	0.1974	0.153	0.235	0.238	0.165	0.835
Initial SMI- Δ MFT	0.1624	0.241	0.290	0.143	0.013	0.949
Initial SMI- Δ Grip strength	0.181	0.191	0.348	0.074	−0.023	0.908
Initial SMI- Δ FDS	0.0525	0.707	0.194	0.334	−0.178	0.374
Initial SMI- Δ PAS	0.0561	0.687	−0.031	0.879	0.141	0.483
Initial SMI - Δ DOSS	0.0124	0.902	0.228	0.264	−0.175	0.383
ΔSMI - Δ K-MBI	0.293*	0.032	0.265	0.182	0.296	0.134
Δ SMI- Δ BBS	0.296*	0.030	0.461*	0.016	0.049	0.963
Δ SMI- Δ FAC	0.305*	0.025	0.543*	0.003	0.010	0.807
Δ SMI- Δ MFT	0.267	0.051	0.276	0.163	0.053	0.791
Δ SMI- Δ Grip strength	0.278*	0.042	0.445*	0.020	−0.118	0.559
Δ SMI- Δ FDS	−0.160	0.250	−0.137	0.496	−0.166	0.409
Δ SMI- Δ PAS	−0.130	0.347	−0.204	0.307	0.022	0.915
ΔSMI - Δ DOSS	−0.150	0.282	−0.093	0.641	−0.019	0.925

*Values are mean ± SD. K-MBI, Korean version of the modified Barthel index; BBS, Berg balance scale; FAC, functional ambulatory category; MFT, manual function test; FDS, functional dysphagia scale; PAS, penetration aspiration scale; DOSS, dysphagia outcome and severity scale; SMI, skeletal muscle index, *$p < 0.05$ by Pearson's correlation coefficient.*

Table 2 shows sarcopenia and functional evaluations before and after treatment in each group. The study group showed a slight increase in the handgrip strength and SMI after the intervention, but it was statistically significant. However, in the control group, SMI was slightly decreased. Both groups showed significant improvement in functional evaluations. **Figures 1**, **2** compared the changes in sarcopenia and functional evaluations between the two groups. After BCAA supplementation and intensive rehabilitation therapy, the study group showed significantly greater SMI than the control group, which showed significantly decreased SMI after therapy (**Table 2** and **Figure 1A**).

The DEXA system obtained the LBM from each of the four extremities (affected [hemiparetic side, weak] upper and lower extremities and intact upper and lower extremities). Among these, the affected (hemiparetic side) lower extremities in patients in the control group demonstrated markedly, significantly decreased LBM after conventional rehabilitation therapy. The intact lower extremities also showed significantly decreased LBM. In contrast, the LBM of the affected lower extremities of the study group patients increased slightly but significantly (**Table 2** and **Figure 1B**).

Both groups exhibited functional improvement over time, but the improvement in the study group was significantly greater than that in the control group (**Figure 2**). Based on the FAC, BBS, and K-MBI scores, 46% of patients in the study group and 37% of those in the control group were unable to walk due to stroke at the initial evaluation and were able to walk again with assistance after treatment (**Table 2**). Swallowing function also improved over time according to the DOSS, FDS, and PAS. After treatment, 59% of patients in the study group and 53% of those in the control group who were initially fed *via* Levin tube could feed orally (**Table 2**); however, this difference was not statistically significant between the two groups (**Figure 2**).

Table 3 shows a pairwise correlation analysis between sarcopenia and functional status. It shows a significant relationship between changes in the SMI and improvements in functional scores, especially ambulatory function, in the study group (BBS; Pearson's correlation coefficient: 0.461, $p = 0.016$, FAC; Pearson's correlation coefficient: 0.543, $p = 0.003$). The initial SMI was not related to functional changes in either group.

Univariate regression analysis (**Table 4**) revealed that patients in the study group with higher initial functional scores, higher grip strengths, and higher improvements in functional scores had significantly higher SMI after receiving both intensive rehabilitation therapy and BCAA supplementation. Among all enrolled patients between the study and control groups, an initial higher functional score and better functional improvement were also significantly related to SMI changes. Patients in the control group did not show significant results in univariate analysis.

Multivariate regression analysis (**Table 5**) was used for variables with a $p < 0.05$ in the univariate analysis, and the variables were entered into the model selection procedure using a backward stepwise process. According to the multivariate analysis, a high initial MBI score and increased handgrip strength were independent factors that predicted an increase in the SMI score in the study group. Among all enrolled patients, the initial BBS score and changes in the FAC score were independent factors predicting an increase in the SMI (**Table 5**).

TABLE 4 | Univariate linear regression analysis related factors for changes in SMI (dependent variable: Δ SMI).

Variables	Estimated	Total				Estimated	Study group			
		95% CI		R^2	*P*-value		95% CI		R^2	*P*-value
		Lower	Upper				Lower	Upper		
initial K-MBI	0.0056	0.003	0.010	0.080*	0.039	0.0110	0.004	0.018	0.274*	0.005
Initial BBS	0.0117	0.005	0.019	0.171*	0.002	0.0238	0.007	0.041	0.246*	0.009
Initial FAC	0.1233	0.031	0.216	0.122*	0.01	0.1994	0.053	0.346	0.240*	0.010
Initial MFT	0.0059	−0.005	0.017	0.023	0.274	0.0161	0.003	0.030	0.193*	0.022
Initial DOSS	0.0589	0.016	0.101	0.129*	0.008	0.0820	0.019	0.145	0.23*	0.012
Initial SMI	−0.0167	−0.136	0.102	0.002	0.779	−0.0172	−0.186	0.152	0.002	0.836
Initial grip strength	0.0083	−0.005	0.021	0.031	0.203	0.0174	0.008	0.034	0.158*	0.040
Δ K-MBI	0.0089	0.001	0.017	0.086*	0.032	0.0106	−0.005	0.026	0.070	0.182
Δ BBS	0.0080	0.001	0.015	0.088*	0.030	0.0133	0.003	0.024	0.213*	0.016
Δ FAC	0.0949	0.013	0.177	0.093*	0.025	0.1861	0.068	0.305	0.295*	0.003
Δ MFT	0.0230	−0.001	0.046	0.071	0.051	0.0326	−0.014	0.079	0.076	0.163
Δ FDS	−0.0057	−0.015	0.004	0.026	0.248	−0.0068	−0.027	0.014	0.019	0.496
Δ DOSS	−0.0376	−0.107	0.032	0.022	0.282	−0.0226	−0.121	0.076	0.009	0.641
Δ Grip strength	0.0301	0.001	0.059	0.077*	0.042	0.0694	0.012	0.127	0.198*	0.020

*Values are mean ± SD. K-MBI, Korean version of modified Barthel index; BBS, Berg balance scale; FAC, functional ambulatory category; MFT, manual function test; FDS, functional dysphagia scale; DOSS, dysphagia outcome and severity scale; SMI, skeletal muscle index; *p < 0.05 according to univariate linear regression analysis.*

There were few complications during BCAA supplementation and rehabilitation. A male patient who aged 65 years suffered from acute renal failure; his creatine level increased from 0.9 to 2.1, and the BUN level increased from 27 to 64. Another male patient who aged 79 years suffered from rhabdomyolysis; he also had several medical problems such as arterial fibrillation, diabetes, and anemia of chronic disease. The BCAA supplementation was stopped in these patients, and their conditions were restored. However, a direct relationship between these complications and BCAA ingestion could not be verified.

TABLE 5 | Multivariate linear regression analysis related factors for changes in SMI.

Outcome/independent predictors	95% CI		*P*-value	Adjusted R^2
	lower	Upper		
Δ SMI (Total patients)				
Initial BBS	0.004	0.018	0.002	0.245
Δ FAC	0.008	0.161	0.031	
Δ SMI (Study group)				
Initial K-MBI	0.002	0.017	0.01	0.396
Δ Grip strength	0.003	0.107	0.038	

Values are mean ± SD. SMI, skeletal muscle index; BBS, Berg balance scale; FAC, functional ambulatory category; K-MBI, Korean version of the modified Barthel index.

DISCUSSION

This study aimed to evaluate the effect of BCAA supplementation on stroke-related sarcopenia as well as the relationship between BCAA supplementation and functional recovery. Our results revealed that the study group improved significantly in terms of SMI and functional status after BCAA supplementation and intensive rehabilitation therapy than the control group. Recent stroke rehabilitation studies have suggested that stroke recovery does not follow a linear pattern; thus, maximal, multifactorial, comprehensive therapy should be used to treat patients with stroke during the critical recovery period (13, 14). We suggest that BCAA supplementation would be a helpful adjuvant therapy during the intensive stroke rehabilitation period for achieving good functional outcomes.

Stroke-Related Sarcopenia: Possible Mechanism and Prevention Strategies

After stroke, the brain lesion subsequently interrupts the corticospinal and corticobulbar tracts, resulting in weakness of the contralateral extremities and swallowing difficulty. Impairment of physical activities is accompanied by structural changes in skeletal muscle, resulting in disuse atrophy. Brain lesions also cause systemic activation of catabolic pathways, which are responsible for the apoptotic and proteolytic reactions in the muscles (1). These complex, systemic metabolic changes and the oxidative stress produced after stroke suppress protein synthesis, resulting in poststroke sarcopenia and impairment in brain recovery (8, 30). Additionally, the energy requirements of patients increase after stroke during the intensive rehabilitation period. Undernutrition and physical inactivity due to weakness in patients with stroke have been significantly associated with sarcopenia and poor clinical outcomes. In contrast, nutritional support has been shown to strongly enhance the functional outcomes of patients with stroke by preserving muscle and fat masses (8, 31, 32). Furthermore, better physical functions after stroke could shorten hospitalization stays and decrease the patients' economic burdens (12).

"Rehabilitation nutrition," presented by Wakabayashi (33), is a concept combining both rehabilitation and nutrition care management. This concept further improves outcomes in elderly patients with stroke with malnutrition and sarcopenia. A variety of nutritional supplements are available worldwide. Among them, BCAAs provide necessary amino acids that cannot be synthesized in the human body and are responsible for building muscle mass; thus, BCAA intake would be an essential ingredient for nutritional support. Furthermore, BCAAs could play an important role in providing anti-inflammatory and anabolic effects after stroke (32). Our results are consistent with previous results showing that protein supplementation is significantly associated with more favorable functional improvement and prevents decreased skeletal muscle mass in patients with stroke (32, 34). In addition, dysphagia after stroke causes malnutrition and is associated with a poor prognosis (8). The BCAA powder used in our study could be applied *via* a Levin tube if the patient could not feed orally. Thus, the early detection of sarcopenia after stroke and the combination of BCAA supplementation and intensive rehabilitation can promote the restoration of muscle mass and accelerate neurological recovery.

Effect of BCAA Supplementation on Sarcopenic Status After Stroke

Compared with the control group, the SMI of the study group significantly increased after BCAA supplementation and intensive rehabilitation therapy. After stroke, brain lesions activate the systemic catabolic pathway, and muscle structural changes lead to a rapid reduction in muscle mass. Furthermore, physical inactivity due to weakness and malnutrition caused by dysphagia accelerate this muscle loss. Previous studies have also demonstrated that muscle loss occurs over time after stroke. Only 3 weeks after stroke, a significant decrease in muscle mass was reported (10) and the lean mass of the paretic limb has been shown to decrease up to 24% within 6–12 months of stroke onset (11). Recently, it has been reported that up to 50% of older poststroke patients are diagnosed with sarcopenia as defined by the Asian Working Group for Sarcopenia (15, 32). Another study revealed that the ipsilateral leg, which was not affected by the brain lesion, also loses muscle mass (9). Our results are consistent with these findings; we enrolled patients within 3 months after stroke, and 89% of them already showed a decreased SMI based on initial evaluations. In addition, 32% of the study group and 60% of the control group had aggravated sarcopenia (decreased SMI scores) after stroke despite undergoing rehabilitation treatment.

In contrast to previous studies, we evaluated SMI and LBM for each of the four extremities (affected and intact upper and lower extremities). Among these, the affected lower extremities of the patients in the control group demonstrated a significantly decreased LBM despite undergoing rehabilitation treatment. The LBM decrease was more prominent in the weight-bearing affected lower extremity muscles than in the non-weight-bearing upper extremity muscles. In contrast, the LBM of the affected lower extremities of the study group patients significantly increased after the intervention. To our knowledge, this study is the first to show the effect of BCAAs on preventing a decrease in muscle mass in the affected lower extremities, particularly by analyzing each of the extremities individually. Thus, proactive management for preventing muscle mass loss, such as BCAA supplementation, neuromuscular electrical stimulation, or other intensive therapy, should be conducted after stroke.

BCAA Supplementation and Functional Improvement

We provided 12 g of BCAAs per day for 1 month, which is similar to the amount used in previous studies (35, 36). Previous studies have demonstrated the pharmacological effects of BCAAs, such as anti-inflammatory effects, improved liver cirrhosis, and reduced incidence of heart failure with hypoalbuminemia (32, 35, 37). This study was conducted on patients with stroke who were admitted to rehabilitation centers; thus, if the patients had abnormal laboratory findings, such as elevated C-reactive protein, white blood cell count, or liver enzymes, we managed them properly. Thus, we could not evaluate the effect of BCAAs on inflammation or liver enzymes. However, our results revealed that after controlling the inflammation and laboratory abnormalities, BCAA supplementation could have a positive effect on functional status in patients with stroke-related sarcopenia.

In this study, we divided patients' functions into various domains, such as ambulation, activities of daily living, and swallowing function. As mentioned earlier, both groups improved functionally over time; when compared with the control group, the study group improved significantly in ambulation and activities of daily living. Correlation analysis showed a significant correlation between improvement of functional status and increased SMI. For patients in the study group with higher initial functional scores, the univariate regression analysis revealed a positive effect on sarcopenia after stroke was achieved with BCAA supplementation. Our results support the potential benefit of BCAA supplementation in producing functional improvement through increasing SMI.

Study Limitations

This study has several limitations. We were unable to perform a randomized control trial since the BCAAs were administered during feeding time, and we did not use placebo drugs; thus, this study could not be blinded in regard to the use of BCAAs. Instead, we enrolled a control group whose age and stroke-lesions were similar to those of the study group *via* meticulous medical chart review, achieving a high effective sample size. All patients were selected from a single rehabilitation unit and received the same rehabilitation therapy. In addition, most (∼89%) of enrolled patients were sarcopenic, but we could not determine whether these patients had sarcopenia before stroke onset or whether it had developed after stroke. Thus, we could not evaluate the effect of sarcopenia on the stroke attack. Our intervention period was only 1 month; thus, the SMI scores did not dramatically change before and after treatment evaluation; however, we observed greater functional status changes than with the SMI. A randomized study with a longer intervention period is needed to further validate these results.

CONCLUSION

Our results showed a positive effect of BCAAs supplementation on stroke-related sarcopenia. The patients in the study group improved significantly in terms of SMI and functional status after BCAAs supplementation and intensive rehabilitation therapy than the control group. Stroke leads to complex systemic metabolic changes; thus, loss of muscle mass and malnutrition frequently occur after stroke. Besides, energy requirements are increased in patients with stroke during intensive rehabilitation period and malnutrition could affect neurological recovery. Thus, proper strategies involving rehabilitation interventions and nutritional support are important for maximum functional improvement after stroke. We suggest that BCAAs supplementation would be a helpful, adjuvant therapy at a critical period of poststroke neurological recovery during intensive stroke rehabilitation intervention.

DATA AVAILABILITY STATEMENT

Individualized data cannot be released due to personal data protection however the datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Daejeon St. Mary's Hospital, the Catholic University of Korea. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP and SoL contributed to the design and conception of the work and wrote the manuscript. EC and SaL performed the experiments and contributed materials. MP and JL analyzed the data. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Catholic Medical Center Research Foundation made in the program year of 2019.

ACKNOWLEDGMENTS

The authors wish to acknowledge the financial support of the Catholic Medical Center Research Foundation made in the program year of 2019.

REFERENCES

1. Scherbakov N, Sandek A, Doehner W. Stroke-related sarcopenia: specific characteristics. *J Am Med Dir Assoc.* (2015) 16:272–6. doi: 10.1016/j.jamda.2014.12.007
2. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr*. (1997) 127(5 Suppl):990s−1. doi: 10.1093/jn/127.5.990S
3. Scherbakov N, Dirnagl U, Doehner W. Body weight after stroke: lessons from the obesity paradox. *Stroke.* (2011) 42:3646–50. doi: 10.1161/STROKEAHA.111.619163
4. Mas MF, González J, Frontera WR. Stroke and sarcopenia. *Curr Phys Med Rehabil Rep.* (2020) 8:452–60. doi: 10.1007/s40141-020-00284-2
5. Hung WW, Ross JS, Boockvar KS, Siu AL. Association of chronic diseases and impairments with disability in older adults: a decade of change? *Med Care.* (2012) 50:501–7. doi: 10.1097/MLR.0b013e318245a0e0
6. Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis.* (2003) 12:119–26. doi: 10.1016/S1052-3057(03)00042-9
7. Crary MA, Humphrey JL, Carnaby-Mann G, Sambandam R, Miller L, Silliman S. Dysphagia, nutrition, and hydration in ischemic stroke patients at admission and discharge from acute care. *Dysphagia.* (2013) 28:69–76. doi: 10.1007/s00455-012-9414-0
8. Sabbouh T, Torbey MT. Malnutrition in stroke patients: risk factors, assessment, and management. *Neurocrit Care.* (2018) 29:374–84. doi: 10.1007/s12028-017-0436-1
9. Carin-Levy G, Greig C, Young A, Lewis S, Hannan J, Mead G. Longitudinal changes in muscle strength and mass after acute stroke. *Cerebrovas Dis.* (2006) 21:201–7. doi: 10.1159/000090792
10. Ryan AS, Dobrovolny CL, Smith GV, Silver KH, Macko RF. Hemiparetic muscle atrophy and increased intramuscular fat in stroke patients. *Arch Phys Med Rehabil.* (2002) 83:1703–7. doi: 10.1053/apmr.2002.36399
11. Ryan AS, Buscemi A, Forrester L, Hafer-Macko CE, Ivey FM. Atrophy and intramuscular fat in specific muscles of the thigh: associated weakness and hyperinsulinemia in stroke survivors. *Neurorehabil Neural Repair.* (2011) 25:865–72. doi: 10.1177/1545968311408920
12. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, et al. Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ.* (2019) 20:107–34. doi: 10.1007/s10198-018-0984-0
13. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet.* (2011) 377:1693–702. doi: 10.1016/S0140-6736(11)60325-5
14. Hatem SM, Saussez G, Della Faille M, Prist V, Zhang X, Dispa D, et al. Rehabilitation of Motor Function after Stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Front Hum Neurosci.* (2016) 10:442. doi: 10.3389/fnhum.2016.00442
15. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. (2020) 21:300–7.e2. doi: 10.1016/j.jamda.2019.12.012
16. Ko CH, Wu SJ, Wang ST, Chang YF, Chang CS, Kuan TS, et al. Effects of enriched branched-chain amino acid supplementation on sarcopenia. *Aging.* (2020) 12:15091–103. doi: 10.18632/aging.103576
17. foundation S. *Clinical Guidelines for Stroke Management 2017*. In: Foundation S, editor. Melbourne, VIC: Australian Government Department (2017).
18. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, Jong A, et al. Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. part one: rehabilitation and recovery following stroke; 6th edition update 2019. *Int J Strok*. (2020) 15:763–88. doi: 10.1177/1747493019897843
19. Bohannon RW. Test-retest reliability of hand-held dynamometry during a single session of strength assessment. *Phys Ther.* (1986) 66:206–9. doi: 10.1093/ptj/66.2.206
20. Knops M, Werner CG, Scherbakov N, Fiebach J, Dreier JP, Meisel A, et al. Investigation of changes in body composition, metabolic profile and skeletal muscle functional capacity in ischemic stroke patients: the rationale and design of the Body Size in Stroke Study (BoSSS). *J Cachexia Sarcopenia Muscle.* (2013) 4:199–207. doi: 10.1007/s13539-013-0103-0

21. English C, McLennan H, Thoirs K, Coates A, Bernhardt J. Loss of skeletal muscle mass after stroke: a systematic review. *Int J Stroke.* (2010) 5:395–402. doi: 10.1111/j.1747-4949.2010.00467.x
22. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* (1994) 49:M85–94. doi: 10.1093/geronj/49.2.M85
23. De Wit L, Putman K, Schuback B, Komárek A, Angst F, Baert I, et al. Motor and functional recovery after stroke: a comparison of 4 European rehabilitation centers. *Stroke*. (2007) 38:2101–7. doi: 10.1161/STROKEAHA.107.482869
24. Blum L, Korner-Bitensky N. Usefulness of the berg balance scale in stroke rehabilitation: a systematic review. *Phys Ther*. (2008) 88:559–66. doi: 10.2522/ptj.20070205
25. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessmen. *Phys Ther.* (1986) 66:1530–9. doi: 10.1093/ptj/66.10.1530
26. Nakamura R, Moriyama S, Yamada Y, Seki K. Recovery of impaired motor function of the upper extremity after stroke. *Tohoku J Exp Med*. (1992) 168:11–20. doi: 10.1620/tjem.168.11
27. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia.* (1996) 11:93–8. doi: 10.1007/BF00417897
28. Han TR, Paik NJ, Park JW. Quantifying swallowing function after stroke: a functional dysphagia scale based on videofluoroscopic studies. *Arch Phys Med Rehabil.* (2001) 82:677–82. doi: 10.1053/apmr.2001.21939
29. O'Neil KH, Purdy M, Falk J, Gallo L. The dysphagia outcome and severity scale. *Dysphagia.* (1999) 14:139–45. doi: 10.1007/PL00009595
30. Aquilani R, Sessarego P, Iadarola P, Barbieri A, Boschi F. Nutrition for brain recovery after ischemic stroke: an added value to rehabilitation. *Nutr Clin Pract.* (2011) 26:339–45. doi: 10.1177/0884533611405793
31. Nip WF, Perry L, McLaren S, Mackenzie A. Dietary intake, nutritional status and rehabilitation outcomes of stroke patients in hospital. *J Hum Nutr Diet*. (2011) 24:460–9. doi: 10.1111/j.1365-277X.2011.01173.x
32. Yoshimura Y, Bise T, Nagano F, Shimazu S, Shiraishi A, Yamaga M, et al. Systemic inflammation in the recovery stage of stroke: its association with sarcopenia and poor functional rehabilitation outcomes. *Prog Rehabil Med*. (2018) 3:20180011. doi: 10.2490/prm.20180011
33. Wakabayashi H, Sakuma K. Rehabilitation nutrition for sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle.* (2014) 5:269–77. doi: 10.1007/s13539-014-0162-x
34. Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Dir Assoc*. (2017) 18:553.e1–16. doi: 10.1016/j.jamda.2017.03.019
35. Uchino Y, Watanabe M, Takata M, Amiya E, Tsushima K, Adachi T, et al. Effect of oral branched-chain amino acids on serum albumin concentration in heart failure patients with hypoalbuminemia: results of a preliminary study. *Am J Cardiovasc Drugs.* (2018) 18:327–32. doi: 10.1007/s40256-018-0269-0
36. Mori T, Yoshioka K. Quick and effective improvement of leucine enriched dietary supplement on malnutrition in acute stroke patients receiving enteral tube feeding. *BMC Emerg Med.* (2020) 20:56. doi: 10.1186/s12873-020-00351-w
37. Tajiri K, Shimizu Y. Branched-chain amino acids in liver diseases. *Transl Gastroenterol Hepatol.* (2018) 3:47. doi: 10.21037/tgh.2018.07.06

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.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 15 March 2022
doi: 10.3389/fneur.2022.755316

Early Supported Discharge and Transitional Care Management After Stroke: A Systematic Review and Meta-Analysis

*Sungju Jee[1], Minah Jeong[1], Nam-Jong Paik[2], Won-Seok Kim[2], Yong-Il Shin[3], Sung-Hwa Ko[3], In Sun Kwon[4], Bo Mi Choi[5], Yunsun Jung[2], Wonkee Chang[2] and Min Kyun Sohn[1]**

[1] Department of Rehabilitation Medicine, Chungnam National University Hospital and Chungnam National University College of Medicine, Daejeon, South Korea, [2] Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea, [3] Department of Rehabilitation Medicine, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, Pusan, South Korea, [4] Clinical Trials Center, Chungnam National University Hospital, Daejeon, South Korea, [5] Department of Public Health and Medical Services, Chungnam National University Hospital, Daejeon, South Korea

Objective: To investigate the available evidence on early supported discharge (ESD) and transitional care (TC) delivery service in patients with cerebrovascular disease.

Methods: A systematic literature search was conducted to collect all available evidence on the use of ESD and TC services. We included cluster-randomized pragmatic trials or randomized controlled trials (RCTs) that recruited patients with stroke or transient ischemic attack to receive either conventional care or any care service intervention that included rehabilitation or support provided by professional medical personnel with the aim of accelerating and supporting home discharge. Relevant data were electronically searched through international databases (Cochrane Library, EMBASE, and PubMed) and incorporated into a summary grid to investigate research outcomes and provide a narrative synthesis. Furthermore, we compared the outcomes in terms of length of hospital stay, patient and caregiver outcomes, and mortality through meta-analysis.

Results: We identified and included a total of 20 publications of various original randomized studies. There were 18 studies conducted in western countries and 2 in eastern countries. The meta-analysis revealed a tendency that ESD or TC could decrease the length of hospital stay more than the usual care [standardized mean difference (SMD) −0.13; 95% confidence interval (CI) −0.31 to 0.04 days; $P = 0.14$]. Moreover, there was a tendency that ESD resulted in better activities of daily living (ADL) than usual care (SMD 0.29; 95% CI −0.04 to 0.61; $P = 0.08$). Patient outcome based on modified Rankin scale (mRS) score (SMD −0.11; 95% CI −0.38 to 0.17; $P = 0.45$] and mortality (odds ratio 0.80; 95% CI 0.56–1.17; $P = 0.25$) did not reveal any significant difference. The Caregiver Strain Index revealed no difference.

Conclusion: We did not find a large effect size for the use of TC and ESD. When implementing the TC and ESD model from western to Asian countries, services should be prepared and implemented in accordance with national medical rehabilitation pathways for cerebrovascular disease.

Keywords: cerebrovascular disease, continuity of patient care, transitional care, rehabilitation, early supported discharge (ESD)

OPEN ACCESS

Edited by:
Peter Langhorne, University of Glasgow, United Kingdom

Reviewed by:
Noreen Kamal, Dalhousie University, Canada
Lena Rafsten, University of Gothenburg, Sweden

***Correspondence:**
Min Kyun Sohn
mksohn@cnu.ac.kr

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *08 August 2021*
Accepted: *16 February 2022*
Published: *15 March 2022*

Citation:
Jee S, Jeong M, Paik N-J, Kim W-S, Shin Y-I, Ko S-H, Kwon IS, Choi BM, Jung Y, Chang W and Sohn MK (2022) Early Supported Discharge and Transitional Care Management After Stroke: A Systematic Review and Meta-Analysis. Front. Neurol. 13:755316. doi: 10.3389/fneur.2022.755316

INTRODUCTION

In national stroke guidelines of the USA (1), Canada (2), and Scotland (3), early supported discharge (ESD) is recommended as a rehabilitation strategy for post-acute care. In the UK, ESD is part of the stroke care system, and the target group, purpose, scope, and method of ESD are specified in the manuals (4, 5). Langhorne et al. reported that an ESD service comprising a multi-disciplinary team reduced long-term functional dependence and readmission in stroke patients and significantly shortened the length of hospital stay compared with the previous service (6). In particular, the total average length of hospital stay was reduced to 6 days, and the incidence of negative outcomes, such as death or readmission, was reduced by ∼5%. No significant differences were noted in the results reported in previous studies; however, the cost of the ESD program was 15–23% lower than that of conventional treatment (6).

In the USA, transitional care (TC) services are provided for various acute diseases (7). TC in the USA must satisfy the following three criteria: contact with the patient within 2 days of discharge, face-to-face follow-up interview/evaluation within 7 or 14 days of discharge depending on the severity of the disease, and non-face-to-face care service according to the patient's needs.

However, in a recent survey on TC including 40 hospitals in North Carolina, only 31.7% of the hospitals satisfied the above-mentioned three criteria of TC (8). Duncan et al. analyzed the effects of nationwide systematic TC in the USA; however, the effects were uncertain (9). The Cochrane review categorized several stages of ESD from full service with mobile rehab team to some minimal counseling before discharge (6). We thought that both ESD and TC could be in the same category of post-acute care (PAC) of stroke with a wide range of spectrum.

In Korea, as the number of cerebrovascular disease patients is increasing due to population aging, efforts are being made to provide standardized acute treatments by developing guidelines for stroke treatment, implementing quality evaluation control by the Health Insurance Review Assessment Service, and opening 14 regional cardio-cerebrovascular centers nationwide. As a result, the mortality rate of acute stroke is decreasing. However, unlike cardiovascular disease, stroke causes neurological disorder. Therefore, the number of stroke survivors who have disabilities after initial treatment and require care in hospitals, facilities, and communities has increased. Accordingly, the medical cost for rehabilitation and management after acute stroke treatment is also increasing. Therefore, there is a need for a continuous management model based on disability and patient characteristics after acute stroke treatment. Studies must focus on developing and standardizing continuous TC and a management model according to the triage for post-stroke care and analyze the effects and hindrance factors of the model in clinical settings.

Therefore, this aimed to investigate the effects of ESD and TC programs on mortality, readmission rate, length of hospital stay, and function through a systematic literature review and meta-analysis of existing and most recent data.

MATERIALS AND METHODS

Data Searches and Sources

A literature search was conducted using databases, including PubMed, EMBASE, and the Cochrane Library. For an extensive literature search, only the participants (P) and intervention (I) were considered, and searches were conducted using keywords, such as "stroke," "transient ischemic attack (TIA)," "early supported discharge," "transitional care," and "rehabilitation." The databases and search formulas used in each database are presented in **Table 1**.

Study Selection

The key question was selected according to a discussion about previous studies and expert opinion. The key question was "Can transitional care, including early supported discharge (ESD), have an impact on functional outcomes, readmission, mortality, and length of hospital stay after acute cerebrovascular accident?" **Table 2** describes the detailed strategies for study inclusion, including population, intervention/comparator, outcomes, time, setting, and design (PICOTS-SD). We included randomized pragmatic trials (RPTs) or randomized controlled trials (RCTs) that recruited patients with stroke or transient ischemic attack to receive either conventional care or any care service intervention, wherein rehabilitation or support was provided by professional medical personnel with the aim of accelerating and supporting home discharge. The RPT provides a real-world assessment of a new care model vs. the usual care. It did not include a control group but a usual care group was examined (9). The outcome parameters for effectiveness included functional status, readmission rate, mortality, and caregiver burden. We selected studies published after 1997, given that there were significant changes in the PAC of stroke patients, such as ESD implementation in London and UK.

Literature Screening Strategy

All the articles searched on each database were merged, and articles that were searched multiple times were removed. Thereafter, the title and abstract of the studies were reviewed to exclude irrelevant studies. If no decision could be made based on the title and abstract, the full text was systematically reviewed and analyzed. The literature review and analysis were conducted by the main researcher and another researcher with experience as an occupational therapist. Data were extracted by choosing necessary items from the list of available data in the selected articles. Two or more researchers independently extracted the data, and disagreements were settled through discussion. The main data that were extracted included study characteristics (study design, country, period, and patient inclusion criteria), patient characteristics (number of participants, disease classification, interventions for intervention and control groups, and location), and clinical outcomes. Each variable is described in the **Supplementary Table 1**. TC interventions were divided into two types: type I for interventions performed by medical staff, including doctors and nurses, excluding visiting rehabilitation; and type II for interventions that included visiting rehabilitation. This was a modified version

TABLE 1 | Search strategy according to the searching engine and queries.

	No	Search queries	Results (2020.7.7)
PubMed	#1	"Cerebrovascular Disorders"[Mesh:NoExp]	46,358
	#2	"Cerebrovascular Disorders"[TW] OR "Cerebrovascular Disorder"[TW] OR "Vascular Diseases, Intracranial"[TW] OR "Intracranial Vascular Disease"[TW] OR "Intracranial Vascular Diseases"[TW] OR "Vascular Disease, Intracranial"[TW] OR "Intracranial Vascular Disorders"[TW] OR "Intracranial Vascular Disorder"[TW] OR "Vascular Disorder, Intracranial"[TW] OR "Vascular Disorders, Intracranial"[TW] OR "Cerebrovascular Diseases"[TW] OR "Cerebrovascular Disease"[TW] OR "Disease, Cerebrovascular"[TW] OR "Diseases, Cerebrovascular"[TW] OR "Brain Vascular Disorders"[TW] OR "Brain Vascular Disorder"[TW] OR "Vascular Disorder, Brain"[TW] OR "Vascular Disorders, Brain"[TW] OR "Cerebrovascular Occlusion"[TW] OR "Cerebrovascular Occlusions"[TW] OR "Occlusion, Cerebrovascular"[TW] OR "Occlusions, Cerebrovascular"[TW] OR "Cerebrovascular Insufficiency"[TW] OR "Cerebrovascular Insufficiencies"[TW] OR "Insufficiencies, Cerebrovascular"[TW] OR "Insufficiency, Cerebrovascular"[TW]	63,453
	#3	"Basal Ganglia Cerebrovascular Disease"[MeSH]	558
	#4	"Basal Ganglia Cerebrovascular Disease"[TW] OR "Basal Ganglia Cerebrovascular Disease"[TW] OR "Vascular Diseases, Basal Ganglia"[TW] OR "Vascular Disease, Basal Ganglia"[TW] OR "Basal Ganglia Vascular Disease"[TW] OR "Cerebrovascular Disease, Basal Ganglia"[TW] OR "Lenticulostriate Vasculopathy"[TW] OR "Lenticulostriate Vasculopathies"[TW] OR "Vasculopathies, Lenticulostriate"[TW] OR "Vasculopathy, Lenticulostriate"[TW] OR "Lenticulostriate Vascular Diseases"[TW] OR "Lenticulostriate Vascular Disease"[TW] OR "Vascular Disease, Lenticulostriate"[TW] OR "Vascular Diseases, Lenticulostriate"[TW] OR "Lenticulostriate Diseases, Vascular"[TW] OR "Vascular Lenticulostriate Diseases"[TW]	272
	#5	"Brain Ischemia"[Mesh]	108,434
	#6	"Brain Ischemia"[TW] OR "Brain Ischemias"[TW] OR "Ischemia, Brain"[TW] OR "Ischemic encephalopathy"[TW] OR "Encephalopathy, Ischemic"[TW] OR "Ischemic Encephalopathies"[TW] OR "Cerebral Ischemia"[TW] OR "Cerebral Ischemias"[TW] OR "Ischemias, Cerebral"[TW] OR "Ischemia, Cerebral"[TW]	70,311
	#7	"Cerebral Small Vessel Diseases"[Mesh]	7,467
	#8	"Cerebral Small Vessel Diseases"[TW] OR "Cerebral Small Vessel Disease"[TW] OR "Cerebral Microangiopathies"[TW] OR "Cerebral Microangiopathy"[TW] OR "Microangiopathies, Cerebral"[TW] OR "Microangiopathy, Cerebral"[TW]	2,019
	#9	"Intracranial Arterial Diseases"[Mesh]	62,855
	#10	"Intracranial Arterial Diseases"[TW] OR "Arterial Disease, Intracranial"[TW] OR "Intracranial Arterial Disease"[TW] OR "Intracranial Arterial Disorders"[TW] OR "Arterial Disorder, Intracranial"[TW] OR "Arterial Disorders, Intracranial"[TW] OR "Intracranial Arterial Disorder"[TW] OR "Arterial Diseases, Intracranial"[TW] OR "Brain Diseases, Arterial"[TW] OR "Arterial Brain Disease"[TW] OR "Arterial Diseases, Brain"[TW] OR "Arterial Disease, Brain"[TW] OR "Brain Arterial Disease"[TW] OR "Brain Arterial Diseases"[TW] OR "Brain Disorders, Arterial"[TW] OR "Arterial Brain Disorder"[TW] OR "Arterial Brain Disorders"[TW] OR "Brain Disorder, Arterial"[TW] OR "Arterial Brain Diseases"[TW]	390
	#11	"Intracranial Embolism and Thrombosis"[Mesh]	21,176
	#12	"Intracranial Embolism and Thrombosis"[TW] OR "Cerebral Embolism and Thrombosis"[TW] OR "Brain Embolism and Thrombosis"[TW] OR "Embolism and Thrombosis, Brain"[TW]	8,697
	#13	"Intracranial Hemorrhages"[Mesh]	70,979
	#14	"Intracranial Hemorrhages"[TW] OR "Hemorrhages, Intracranial"[TW] OR "Intracranial Hemorrhage"[TW] OR "Hemorrhage, Intracranial"[TW] OR "Posterior Fossa Hemorrhage"[TW] OR "Hemorrhage, Posterior Fossa"[TW] OR "Hemorrhages, Posterior Fossa"[TW] OR "Posterior Fossa Hemorrhages"[TW] OR "Brain Hemorrhage"[TW] OR "Brain Hemorrhages"[TW] OR "Hemorrhage, Brain"[TW] OR "Hemorrhages, Brain"[TW]	16,875
	#15	"Stroke"[Mesh]	134,064
	#16	"Stroke"[TW] OR "Strokes"[TW] OR "Cerebrovascular Accident"[TW] OR "Cerebrovascular Accidents"[TW] OR "CVA"[TW] OR "CVAs"[TW] OR "Cerebrovascular Apoplexy"[TW] OR "Apoplexy, Cerebrovascular"[TW] OR "Vascular Accident, Brain"[TW] OR "Brain Vascular Accident"[TW] OR "Brain Vascular Accidents"[TW] OR "Vascular Accidents, Brain"[TW] OR "Cerebrovascular Stroke"[TW] OR "Cerebrovascular Strokes"[TW] OR "Stroke, Cerebrovascular"[TW] OR "Strokes, Cerebrovascular"[TW] OR "Apoplexy"[TW] OR "Cerebral Stroke"[TW] OR "Cerebral Strokes"[TW] OR "Stroke, Cerebral"[TW] OR "Strokes, Cerebral"[TW] OR "Stroke, Acute"[TW] OR "Acute Stroke"[TW] OR "Acute Strokes"[TW] OR "Strokes, Acute"[TW] OR "Cerebrovascular Accident, Acute"[TW] OR "Acute Cerebrovascular Accident"[TW] OR "Acute Cerebrovascular Accidents"[TW] OR "Cerebrovascular Accidents, Acute"[TW]	306,011
	#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	508,866
	#18	"Aftercare"[Mesh]	191,753
	#19	"Aftercare"[TW] OR "After Care"[TW] OR "After-Treatment"[TW] OR "After Treatment"[TW] OR "After-Treatments"[TW] OR "Follow-Up Care"[TW] OR "Care, Follow-Up"[TW] OR "Cares, Follow-Up"[TW] OR "Follow Up Care"[TW] OR "Follow-Up Cares"[TW] OR "Postabortion"[TW] OR "Postabortal Programs"[TW] OR "Postabortal Program"[TW] OR "Program, Postabortal"[TW] OR "Programs, Postabortal"[TW]	189,166
	#20	Ambulatory Care"[Mesh]	52,812

(Continued)

TABLE 1 | Continued

	No	Search queries	Results (2020.7.7)
	#21	Ambulatory Care"[TW] OR "Care, Ambulatory"[TW] OR "Outpatient Care"[TW] OR "Care, Outpatient"[TW] OR "Health Services, Outpatient"[TW] OR "Health Service, Outpatient"[TW] OR "Outpatient Health Service"[TW] OR "Service, Outpatient Health"[TW] OR "Outpatient Health Services"[TW] OR "Outpatient Services"[TW] OR "Outpatient Service"[TW] OR "Service, Outpatient"[TW] OR "Services, Outpatient"[TW] OR "Services, Outpatient Health"[TW] OR "Urgent Care"[TW] OR "Care, Urgent"[TW] OR "Cares, Urgent"[TW] OR "Urgent Cares"[TW] OR "Clinic Visits"[TW] OR "Clinic Visit"[TW] OR "Visit, Clinic"[TW] OR "Visits, Clinic"[TW]	84,040
	#22	Patient Discharge"[Mesh]	29,666
	#23	Patient Discharge"[TW] OR "Discharge, Patient"[TW] OR "Discharges, Patient"[TW] OR "Patient Discharges"[TW] OR "Discharge Planning"[TW] OR "Discharge Plannings"[TW] OR "Planning, Discharge"[TW] OR "Plannings, Discharge"[TW]	32,631
	#24	Transitional Care"[Mesh]	751
	#25	Transitional Care"[TW] OR "Care, Transitional"[TW] OR "Cares, Transitional"[TW] OR "Transitional Cares"[TW] OR "Transition Care"[TW] OR "Transition Cares"[TW]	2,108
	#26	Stroke Rehabilitation"[Mesh]	13,215
	#27	Stroke Rehabilitation"[TW] OR "Rehabilitation, Stroke"[TW]	14,786
	#28	Home Care Services"[Mesh]	47,203
	#29	Home Care Services"[TW] OR "Home Care Service"[TW] OR "Service, Home Care"[TW] OR "Care Services, Home"[TW] OR "Domiciliary Care"[TW] OR "Care, Domiciliary"[TW] OR "Services, Home Care"[TW] OR "Home Care"[TW] OR "Care, Home"[TW]	52,283
	#30	Progressive Patient Care"[Mesh]	1,202
	#31	Progressive Patient Care"[TW] OR "Care, Progressive Patient"[TW] OR "Cares, Progressive Patient"[TW] OR "Patient Care, Progressive"[TW] OR "Patient Cares, Progressive"[TW] OR "Progressive Patient Cares"[TW]	1,220
	#31	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	545,458
	#32	#17 AND #32	28,121
	#33	**#32 Filters: Pragmatic Clinical Trial, Randomized Controlled Trial, from 1997 - 2020**	**3,524**
Cochrane library	#1	MeSH descriptor: "Cerebrovascular Disorders" this term only	1,425
	#2	Cerebrovascular Disorders":ti, ab, kw OR "Cerebrovascular Disorder":ti, ab, kw OR "Vascular Diseases, Intracranial":ti ,ab, kw OR "Intracranial Vascular Disease":ti, ab, kw OR "Intracranial Vascular Diseases":ti, ab, kw OR "Vascular Disease, Intracranial":ti, ab, kw OR "Intracranial Vascular Disorders":ti, ab, kw OR "Intracranial Vascular Disorder":ti, ab, kw OR "Vascular Disorder, Intracranial":ti, ab, kw OR "Vascular Disorders, Intracranial":ti, ab, kw OR "Cerebrovascular Diseases":ti, ab, kw OR "Cerebrovascular Disease":ti, ab, kw OR "Disease, Cerebrovascular":ti, ab, kw OR "Diseases, Cerebrovascular":ti, ab, kw OR "Brain Vascular Disorders":ti, ab, kw OR "Brain Vascular Disorder":ti, ab, kw OR "Vascular Disorder, Brain":ti, ab, kw OR "Vascular Disorders, Brain":ti, ab, kw OR "Cerebrovascular Occlusion":ti, ab, kw OR "Cerebrovascular Occlusions":ti, ab, kw OR "Occlusion, Cerebrovascular":ti, ab, kw OR "Occlusions, Cerebrovascular":ti, ab, kw OR "Cerebrovascular Insufficiency":ti, ab, kw OR "Cerebrovascular Insufficiencies":ti, ab, kw OR "Insufficiencies, Cerebrovascular":ti, ab, kw OR "Insufficiency, Cerebrovascular":ti, ab, kw	4,373
	#3	[mh "Basal Ganglia Cerebrovascular Disease"]	28
	#4	Basal Ganglia Cerebrovascular Disease":ti, ab, kw OR "Basal Ganglia Cerebrovascular Disease":ti, ab, kw OR "Vascular Diseases, Basal Ganglia":ti, ab, kw OR "Vascular Disease, Basal Ganglia":ti, ab, kw OR "Basal Ganglia Vascular Disease":ti, ab, kw OR "Cerebrovascular Disease, Basal Ganglia":ti, ab, kw OR "Lenticulostriate Vasculopathy":ti, ab, kw OR "Lenticulostriate Vasculopathies":ti, ab, kw OR "Vasculopathies, Lenticulostriate":ti, ab, kw OR "Vasculopathy, Lenticulostriate":ti, ab, kw OR "Lenticulostriate Vascular Diseases":ti, ab, kw OR "Lenticulostriate Vascular Disease":ti, ab, kw OR "Vascular Disease, Lenticulostriate":ti, ab, kw OR "Vascular Diseases, Lenticulostriate":ti, ab, kw OR "Lenticulostriate Diseases, Vascular":ti, ab, kw OR "Vascular Lenticulostriate Diseases":ti, ab, kw	10
	#5	[mh "Brain Ischemia"]	3,534
	#6	Brain Ischemia":ti, ab, kw OR "Brain Ischemias":ti, ab, kw OR "Ischemia, Brain":ti, ab, kw OR "Ischemic encephalopathy":ti, ab, kw OR "Encephalopathy, Ischemic":ti, ab, kw OR "Ischemic Encephalopathies":ti, ab, kw OR "Cerebral Ischemia":ti, ab, kw OR "Cerebral Ischemias":ti, ab, kw OR "Ischemias, Cerebral":ti, ab, kw OR "Ischemia, Cerebral":ti, ab, kw	6,452
	#7	[mh "Cerebral Small Vessel Diseases"]	206
	#8	Cerebral Small Vessel Diseases":ti, ab, kw OR "Cerebral Small Vessel Disease":ti, ab, kw OR "Cerebral Microangiopathies":ti, ab, kw OR "Cerebral Microangiopathy":ti, ab, kw OR "Microangiopathies, Cerebral":ti, ab, kw OR "Microangiopathy, Cerebral":ti, ab, kw	141
	#9	[mh "Intracranial Arterial Diseases"]	1,140

(Continued)

TABLE 1 | Continued

No	Search queries	Results (2020.7.7)
#10	Intracranial Arterial Diseases":ti, ab, kw OR "Arterial Disease, Intracranial":ti, ab, kw OR "Intracranial Arterial Disease":ti, ab, kw OR "Intracranial Arterial Disorders":ti, ab, kw OR "Arterial Disorder, Intracranial":ti, ab, kw OR "Arterial Disorders, Intracranial":ti, ab, kw OR "Intracranial Arterial Disorder":ti, ab, kw OR "Arterial Diseases, Intracranial":ti, ab, kw OR "Brain Diseases, Arterial":ti, ab, kw OR "Arterial Brain Disease":ti, ab, kw OR "Arterial Diseases, Brain":ti, ab, kw OR "Arterial Disease, Brain":ti, ab, kw OR "Brain Arterial Disease":ti, ab, kw OR "Brain Arterial Diseases":ti, ab, kw OR "Brain Disorders, Arterial":ti, ab, kw OR "Arterial Brain Disorder":ti, ab, kw OR "Arterial Brain Disorders":ti, ab, kw OR "Brain Disorder, Arterial":ti, ab, kw OR "Arterial Brain Diseases":ti, ab, kw	13
#11	[mh "Intracranial Embolism and Thrombosis"]	308
#12	Intracranial Embolism and Thrombosis":ti, ab, kw OR "Cerebral Embolism and Thrombosis":ti, ab, kw OR "Brain Embolism and Thrombosis":ti, ab, kw OR "Embolism and Thrombosis, Brain":ti, ab, kw	88
#13	[mh "Intracranial Hemorrhages"]	1,926
#14	Intracranial Hemorrhages":ti, ab, kw OR "Hemorrhages, Intracranial":ti, ab, kw OR "Intracranial Hemorrhage":ti, ab, kw OR "Hemorrhage, Intracranial":ti, ab, kw OR "Posterior Fossa Hemorrhage":ti, ab, kw OR "Hemorrhage, Posterior Fossa":ti, ab, kw OR "Hemorrhages, Posterior Fossa":ti, ab, kw OR "Posterior Fossa Hemorrhages":ti, ab, kw OR "Brain Hemorrhage":ti, ab, kw OR "Brain Hemorrhages":ti, ab, kw OR "Hemorrhage, Brain":ti, ab, kw OR "Hemorrhages, Brain":ti, ab, kw	4,678
#15	[mh "Stroke"]	9,502
#16	Stroke":ti, ab, kw OR "Strokes":ti, ab, kw OR "Cerebrovascular Accident":ti, ab, kw OR "Cerebrovascular Accidents":ti, ab, kw OR "CVA":ti, ab, kw OR "CVAs":ti, ab, kw OR "Cerebrovascular Apoplexy":ti, ab, kw OR "Apoplexy, Cerebrovascular":ti, ab, kw OR "Vascular Accident, Brain":ti, ab, kw OR "Brain Vascular Accident":ti, ab, kw OR "Brain Vascular Accidents":ti, ab, kw OR "Vascular Accidents, Brain":ti, ab, kw OR "Cerebrovascular Stroke":ti, ab, kw OR "Cerebrovascular Strokes":ti, ab, kw OR "Stroke, Cerebrovascular":ti, ab, kw OR "Strokes, Cerebrovascular":ti, ab, kw OR "Apoplexy":ti, ab, kw OR "Cerebral Stroke":ti, ab, kw OR "Cerebral Strokes":ti, ab, kw OR "Stroke, Cerebral":ti, ab, kw OR "Strokes, Cerebral":ti, ab, kw OR "Stroke, Acute":ti, ab, kw OR "Acute Stroke":ti, ab, kw OR "Acute Strokes":ti, ab, kw OR "Strokes, Acute":ti, ab, kw OR "Cerebrovascular Accident, Acute":ti, ab, kw OR "Acute Cerebrovascular Accident":ti, ab, kw OR "Acute Cerebrovascular Accidents":ti, ab, kw OR "Cerebrovascular Accidents, Acute":ti, ab, kw	57,080
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	64,896
#18	[mh "Aftercare"]	22,451
#19	Aftercare":ti, ab, kw OR "After Care":ti, ab, kw OR "After-Treatment":ti, ab, kw OR "After Treatment":ti, ab, kw OR "After-Treatments":ti, ab, kw OR "Follow-Up Care":ti, ab, kw OR "Care, Follow-Up":ti, ab, kw OR "Cares, Follow-Up":ti, ab, kw OR "Follow Up Care":ti, ab, kw OR "Follow-Up Cares":ti, ab, kw OR "Postabortion":ti, ab, kw OR "Postabortal Programs":ti, ab, kw OR "Postabortal Program":ti, ab, kw OR "Program, Postabortal":ti, ab, kw OR "Programs, Postabortal":ti, ab, kw	44,805
#20	[mh "Ambulatory Care"]	3,605
#21	Ambulatory Care":ti, ab, kw OR "Care, Ambulatory":ti, ab, kw OR "Outpatient Care":ti, ab, kw OR "Care, Outpatient":ti, ab, kw OR "Health Services, Outpatient":ti, ab, kw OR "Health Service, Outpatient":ti, ab, kw OR "Outpatient Health Service":ti, ab, kw OR "Service, Outpatient Health":ti, ab, kw OR "Outpatient Health Services":ti, ab, kw OR "Outpatient Services":ti, ab, kw OR "Outpatient Service":ti, ab, kw OR "Service, Outpatient":ti, ab, kw OR "Services, Outpatient":ti, ab, kw OR "Services, Outpatient Health":ti, ab, kw OR "Urgent Care":ti, ab, kw OR "Care, Urgent":ti, ab, kw OR "Cares, Urgent":ti, ab, kw OR "Urgent Cares":ti, ab, kw OR "Clinic Visits":ti, ab, kw OR "Clinic Visit":ti, ab, kw OR "Visit, Clinic":ti, ab, kw OR "Visits, Clinic":ti, ab, kw	11,153
#22	[mh "Patient Discharge"]	1,444
#23	Patient Discharge":ti, ab, kw OR "Discharge, Patient":ti, ab, kw OR "Discharges, Patient":ti, ab, kw OR "Patient Discharges":ti, ab, kw OR "Discharge Planning":ti, ab, kw OR "Discharge Plannings":ti, ab, kw OR "Planning, Discharge":ti, ab, kw OR "Plannings, Discharge":ti, ab, kw	2,325
#24	[mh "Transitional Care"]	52
#25	Transitional Care":ti, ab, kw OR "Care, Transitional":ti, ab, kw OR "Cares, Transitional":ti, ab, kw OR "Transitional Cares":ti, ab, kw OR "Transition Care":ti, ab, kw OR "Transition Cares":ti, ab, kw	428
#26	[mh "Stroke Rehabilitation"]	2,378
#27	Stroke Rehabilitation":ti, ab, kw OR "Rehabilitation, Stroke":ti, ab, kw	3,807
#28	[mh "Home Care Services"]	2,395
#29	Home Care Services":ti, ab, kw OR "Home Care Service":ti, ab, kw OR "Service, Home Care":ti, ab, kw OR "Care Services, Home":ti, ab, kw OR "Domiciliary Care":ti, ab, kw OR "Care, Domiciliary":ti, ab, kw OR "Services, Home Care":ti, ab, kw OR "Home Care":ti, ab, kw OR "Care, Home":ti, ab, kw	5,461
#30	[mh "Progressive Patient Care"]	12
#31	Progressive Patient Care":ti, ab, kw OR "Care, Progressive Patient":ti, ab, kw OR "Cares, Progressive Patient":ti, ab, kw OR "Patient Care, Progressive":ti, ab, kw OR "Patient Cares, Progressive":ti, ab, w OR "Progressive Patient Cares":ti, ab, kw	16

(Continued)

TABLE 1 | Continued

	No	Search queries	Results (2020.7.7)
	#32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	84,278
	#33	#17 AND #32	6,937
	#34	**Filters: 1997 - 2020**	**6676**
EMBASE (Elsevier)	#1	cerebrovascular disease'/de	63,413
	#2	Cerebrovascular Disorders':ti, ab, kw,de OR 'Cerebrovascular Disorder':ti, ab, kw,de OR 'Vascular Diseases, Intracranial':ti, ab, kw,de OR 'Intracranial Vascular Disease':ti, ab, kw,de OR 'Intracranial Vascular Diseases':ti, ab, kw,de OR 'Vascular Disease, Intracranial':ti, ab, kw,de OR 'Intracranial Vascular Disorders':ti, ab, kw,de OR 'Intracranial Vascular Disorder':ti, ab, kw,de OR 'Vascular Disorder, Intracranial':ti, ab, kw,de OR 'Vascular Disorders, Intracranial':ti, ab, kw,de OR 'Cerebrovascular Diseases':ti, ab, kw,de OR 'Cerebrovascular Disease':ti, ab, kw,de OR 'Disease, Cerebrovascular':ti, ab, kw,de OR 'Diseases, Cerebrovascular':ti, ab, kw,de OR 'Brain Vascular Disorders':ti, ab, kw,de OR 'Brain Vascular Disorder':ti, ab, kw,de OR 'Vascular Disorder, Brain':ti, ab, kw,de OR 'Vascular Disorders, Brain':ti, ab, kw,de OR 'Cerebrovascular Occlusion':ti, ab, kw,de OR 'Cerebrovascular Occlusions':ti, ab, kw,de OR 'Occlusion, Cerebrovascular':ti, ab, kw,de OR 'Occlusions, Cerebrovascular':ti, ab, kw,de OR 'Cerebrovascular Insufficiency':ti, ab, kw,de OR 'Cerebrovascular Insufficiencies':ti, ab, kw,de OR 'Insufficiencies, Cerebrovascular':ti, ab, kw,de OR 'Insufficiency, Cerebrovascular':ti, ab, kw,de	89,473
	#3	basal ganglion hemorrhage'/exp	771
	#4	Basal Ganglia Cerebrovascular Disease':ti, ab, kw,de OR 'Basal Ganglia Cerebrovascular Disease':ti, ab, kw,de OR 'Vascular Diseases, Basal Ganglia':ti, ab, kw,de OR 'Vascular Disease, Basal Ganglia':ti, ab, kw,de OR 'Basal Ganglia Vascular Disease':ti, ab, kw,de OR 'Cerebrovascular Disease, Basal Ganglia':ti, ab, kw,de OR 'Lenticulostriate Vasculopathy':ti, ab, kw,de OR 'Lenticulostriate Vasculopathies':ti, ab, kw,de OR 'Vasculopathies, Lenticulostriate':ti, ab, kw,de OR 'Vasculopathy, Lenticulostriate':ti, ab, kw,de OR 'Lenticulostriate Vascular Diseases':ti, ab, kw,de OR 'Lenticulostriate Vascular Disease':ti, ab, kw,de OR 'Vascular Disease, Lenticulostriate':ti, ab, kw,de OR 'Vascular Diseases, Lenticulostriate':ti, ab, kw,de OR 'Lenticulostriate Diseases, Vascular':ti, ab, kw,de OR 'Vascular Lenticulostriate Diseases':ti, ab, kw,de	108
	#5	brain ischemia'/exp	186,618
	#6	'Brain Ischemia':ti, ab, kw,de OR 'Brain Ischemias':ti, ab, kw,de OR 'Ischemia, Brain':ti, ab, kw,de OR 'Ischemic Encephalopathy':ti, ab, kw,de OR 'Encephalopathy, Ischemic':ti, ab, kw,de OR 'Ischemic Encephalopathies':ti, ab, kw,de OR 'Cerebral Ischemia':ti, ab, kw,de OR 'Cerebral Ischemias':ti, ab, kw,de OR 'Ischemias, Cerebral':ti, ab, kw,de OR 'Ischemia, Cerebral':ti, ab, kw,de OR 'acute ischaemic stroke':ti, ab, kw,de OR 'brain ischemia':ti, ab, kw,de OR 'acute ischemic stroke':ti, ab, kw,de OR 'brain arterial insufficiency':ti, ab, kw,de OR 'brain circulation disorder':ti, ab, kw,de OR 'brain ischaemia':ti, ab, kw,de OR 'cerebral blood circulation disorder':ti, ab, kw,de OR 'cerebral blood flow disorder':ti, ab, kw,de OR 'cerebral circulation disorder':ti, ab, kw,de OR 'cerebral circulatory disorder':ti, ab, kw,de OR 'cerebral ischaemia':ti, ab, kw,de OR 'cerebral ischemia':ti, ab, kw,de OR 'cerebrovascular circulation disorder':ti, ab, kw,de OR 'cerebrovascular ischaemia':ti, ab, kw,de OR 'cerebrovascular ischemia':ti, ab, kw,de OR 'chronic ischaemic stroke':ti, ab, kw,de OR 'chronic ischemic stroke':ti, ab, kw,de OR 'ischaemia cerebri':ti, ab, kw,de OR 'ischaemic brain disease':ti, ab, kw,de OR 'ischaemic encephalopathy':ti, ab, kw,de OR 'ischaemic stroke':ti, ab, kw,de OR 'ischemia cerebri':ti, ab, kw,de OR 'ischemic brain disease':ti, ab, kw,de OR 'ischemic encephalopathy':ti, ab, kw,de OR 'ischemic stroke':ti, ab, kw,de OR 'neural ischaemia':ti, ab, kw,de OR 'neural ischemia':ti, ab, kw,de	183,481
	#7	cerebrovascular disease'/exp	733,323
	#8	Cerebral Small Vessel Diseases':ti, ab, kw,de OR 'Cerebral Small Vessel Disease':ti, ab, kw,de OR 'Cerebral Microangiopathies':ti, ab, kw,de OR 'Cerebral Microangiopathy':ti, ab, kw,de OR 'Microangiopathies, Cerebral':ti, ab, kw,de OR 'Microangiopathy, Cerebral':ti, ab, kw,de OR 'cerebrovascular disease':ti, ab, kw,de OR 'brain angiopathy':ti, ab, kw,de OR 'brain circulation failure':ti, ab, kw,de OR 'brain vascular disease':ti, ab, kw,de OR 'brain vasculopathy':ti, ab, kw,de OR 'cerebral small vessel disease':ti, ab, kw,de OR 'cerebral small vessel diseases':ti, ab, kw,de OR 'cerebral vascular disease':ti, ab, kw,de OR 'cerebral vascular disorder':ti, ab, kw,de OR 'cerebral vascular disturbance':ti, ab, kw,de OR 'cerebral vascular lesion':ti, ab, kw,de OR 'cerebral vasculopathy':ti, ab, kw,de OR 'cerebrovascular damage':ti, ab, kw,de OR 'cerebrovascular disorder':ti, ab, kw,de OR 'cerebrovascular disorders':ti, ab, kw,de OR 'cerebrovascular lesion':ti, ab, kw,de OR 'cerebrovascular pathology':ti, ab, kw,de OR 'cerebrovascular syndrome':ti, ab, kw,de	87,618
	#9	cerebral artery disease'/exp	5,201
	#10	Intracranial Arterial Diseases':ti, ab, kw,de OR 'Arterial Disease, Intracranial':ti, ab, kw,de OR 'Intracranial Arterial Disease':ti, ab, kw,de OR 'Intracranial Arterial Disorders':ti, ab, kw,de OR 'Arterial Disorder, Intracranial':ti, ab, kw,de OR 'Arterial Disorders, Intracranial':ti, ab, kw,de OR 'Intracranial Arterial Disorder':ti, ab, kw,de OR 'Arterial Diseases, Intracranial':ti, ab, kw,de OR 'Brain Diseases, Arterial':ti, ab, kw,de OR 'Arterial Brain Disease':ti, ab, kw,de OR 'Arterial Diseases, Brain':ti, ab, kw,de OR 'Arterial Disease, Brain':ti, ab, kw,de OR 'Brain Arterial Disease':ti, ab, kw,de OR 'Brain Arterial Diseases':ti, ab, kw,de OR 'Brain Disorders, Arterial':ti, ab, kw,de OR 'Arterial Brain Disorder':ti, ab, kw,de OR 'Arterial Brain Disorders':ti, ab, kw,de OR 'Brain Disorder, Arterial':ti, ab, kw,de OR 'Arterial Brain Diseases':ti, ab, kw,de	105
	#11	thromboembolism'/exp	513,919

(Continued)

TABLE 1 | Continued

No	Search queries	Results (2020.7.7)
#12	Intracranial Embolism and Thrombosis':ti, ab, kw,de OR 'Cerebral Embolism and Thrombosis':ti, ab, kw,de OR 'Brain Embolism and Thrombosis':ti, ab, kw,de OR 'Embolism and Thrombosis, Brain':ti, ab, kw,de	721
#13	brain hemorrhage'/exp	145,378
#14	Intracranial Hemorrhages':ti, ab, kw,de OR 'Hemorrhages, Intracranial':ti, ab, kw,de OR 'Intracranial Hemorrhage':ti, ab, kw,de OR 'Hemorrhage, Intracranial':ti, ab, kw,de OR 'Posterior Fossa Hemorrhage':ti, ab, kw,de OR 'Hemorrhage, Posterior Fossa':ti, ab, kw,de OR 'Hemorrhages, Posterior Fossa':ti, ab, kw,de OR 'Posterior Fossa Hemorrhages':ti, ab, kw,de OR 'Brain Hemorrhage':ti, ab, kw,de OR 'Brain Hemorrhages':ti, ab, kw,de OR 'Hemorrhage, Brain':ti, ab, kw,de OR 'Hemorrhages, Brain':ti, ab, kw,de	109,963
#15	cerebrovascular accident'/exp	327,527
#16	Stroke':ti, ab, kw,de OR 'Strokes':ti, ab, kw,de OR 'Cerebrovascular Accident':ti, ab, kw,de OR 'Cerebrovascular Accidents':ti, ab, kw,de OR 'CVA':ti, ab, kw,de OR 'CVAs':ti, ab, kw,de OR 'Cerebrovascular Apoplexy':ti, ab, kw,de OR 'Apoplexy, Cerebrovascular':ti, ab, kw,de OR 'Vascular Accident, Brain':ti, ab, kw,de OR 'Brain Vascular Accident':ti, ab, kw,de OR 'Brain Vascular Accidents':ti, ab, kw,de OR 'Vascular Accidents, Brain':ti, ab, kw,de OR 'Cerebrovascular Stroke':ti, ab, kw,de OR 'Cerebrovascular Strokes':ti, ab, kw,de OR 'Stroke, Cerebrovascular':ti, ab, kw,de OR 'Strokes, Cerebrovascular':ti, ab, kw,de OR 'Apoplexy':ti, ab, kw,de OR 'Cerebral Stroke':ti, ab, kw,de OR 'Cerebral Strokes':ti, ab, kw,de OR 'Stroke, Cerebral':ti, ab, kw,de OR 'Strokes, Cerebral':ti, ab, kw,de OR 'Stroke, Acute':ti, ab, kw,de OR 'Acute Stroke':ti, ab, kw,de OR 'Acute Strokes':ti, ab, kw,de OR 'Strokes, Acute':ti, ab, kw,de OR 'Cerebrovascular Accident, Acute':ti, ab, kw,de OR 'Acute Cerebrovascular Accident':ti, ab, kw,de OR 'Acute Cerebrovascular Accidents':ti, ab, kw,de OR 'Cerebrovascular Accidents, Acute':ti, ab, kw,de	513,283
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	1,267,908
#18	aftercare'/exp	1,569,098
#19	Aftercare':ti, ab, kw,de OR 'After Care':ti, ab, kw,de OR 'After-Treatment':ti, ab, kw,de OR 'After Treatment':ti, ab, kw,de OR 'After-Treatments':ti, ab, kw,de OR 'Follow-Up Care':ti, ab, kw,de OR 'Care, Follow-Up':ti, ab, kw,de OR 'Cares, Follow-Up':ti, ab, kw,de OR 'Follow Up Care':ti, ab, kw,de OR 'Follow-Up Cares':ti, ab, kw,de OR 'Postabortion':ti, ab, kw,de OR 'Postabortal Programs':ti, ab, kw,de OR 'Postabortal Program':ti, ab, kw,de OR 'Program, Postabortal':ti, ab, kw,de OR 'Programs, Postabortal':ti, ab, kw,de	261,420
#20	ambulatory care'/exp	50,314
#21	Ambulatory Care':ti, ab, kw,de OR 'Care, Ambulatory':ti, ab, kw,de OR 'Outpatient Care':ti, ab, kw,de OR 'Care, Outpatient':ti, ab, kw,de OR 'Health Services, Outpatient':ti, ab, kw,de OR 'Health Service, Outpatient':ti, ab, kw,de OR 'Outpatient Health Service':ti, ab, kw,de OR 'Service, Outpatient Health':ti, ab, kw,de OR 'Outpatient Health Services':ti, ab, kw,de OR 'Outpatient Services':ti, ab, kw,de OR 'Outpatient Service':ti, ab, kw,de OR 'Service, Outpatient':ti, ab, kw,de OR 'Services, Outpatient':ti, ab, kw,de OR 'Services, Outpatient Health':ti, ab, kw,de OR 'Urgent Care':ti, ab, kw,de OR 'Care, Urgent':ti, ab, kw,de OR 'Cares, Urgent':ti, ab, kw,de OR 'Urgent Cares':ti, ab, kw,de OR 'Clinic Visits':ti, ab, kw,de OR 'Clinic Visit':ti, ab, kw,de OR 'Visit, Clinic':ti, ab, kw,de OR 'Visits, Clinic':ti, ab, kw,de	105,250
#22	hospital discharge'/exp	124,630
#23	Patient Discharge':ti, ab, kw,de OR 'Discharge, Patient':ti, ab, kw,de OR 'Discharges, Patient':ti, ab, kw,de OR 'Patient Discharges':ti, ab, kw,de OR 'Discharge Planning':ti, ab, kw,de OR 'Discharge Plannings':ti, ab, kw,de OR 'Planning, Discharge':ti, ab, kw,de OR 'Plannings, Discharge':ti, ab, kw,de	8,399
#24	transitional care'/exp	2,855
#25	Transitional Care':ti, ab, kw,de OR 'Care, Transitional':ti, ab, kw,de OR 'Cares, Transitional':ti, ab, kw,de OR 'Transitional Cares':ti, ab, kw,de OR 'Transition Care':ti, ab, kw,de OR 'Transition Cares':ti, ab, kw,de	4,427
#26	stroke rehabilitation'/exp	3,448
#27	Stroke Rehabilitation':ti, ab, kw,de OR 'Rehabilitation, Stroke':ti, ab, kw,de	8,316
#28	home care'/exp	75,309
#29	Home Care Services':ti, ab, kw,de OR 'Home Care Service':ti, ab, kw,de OR 'Service, Home Care':ti, ab, kw,de OR 'Care Services, Home':ti, ab, kw,de OR 'Domiciliary Care':ti, ab, kw,de OR 'Care, Domiciliary':ti, ab, kw,de OR 'Services, Home Care':ti, ab, kw,de OR 'Home Care':ti, ab, kw,de OR 'Care, Home':ti, ab, kw,de	71,244
#30	progressive patient care'/exp	996
#31	Progressive Patient Care':ti, ab, kw,de OR 'Care, Progressive Patient':ti, ab, kw,de OR 'Cares, Progressive Patient':ti, ab, kw,de OR 'Patient Care, Progressive':ti, ab, kw,de OR 'Patient Cares, Progressive':ti, ab, kw,de OR 'Progressive Patient Cares':ti, ab, kw,de	1,079
#32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	2,059,138
#33	#17 AND #32	187,923
#34	#32 Filters: Randomized Controlled Trial, from 1997 - 2020	10,886

TABLE 2 | Strategy for study inclusion.

	Contents
Population	Stroke or transient ischemic attack (TIA)
Intervention/ comparator	Transitional care or early supported discharge program by hospital professionals/usual care
Outcomes	ADL, mRS, death, Quality of life, readmission rate, total length of hospital stay, care giver burden
Time	·Publication: after 1997 ·Duration of study and follow up: no limitation
Setting	–
Study design	·Randomized controlled clinical trial, RCT ·Randomized pragmatic controlled clinical trial, RPT

of the method used in the Cochrane review (6). The key search terms related to "early supported discharge for stroke patients" were used to search articles in international literature search databases such as PubMed, Embase, and the Cochrane Library. The total number of searched articles was 15,090, excluding those that were searched multiple times. The search formulas for each database are shown in the **Table 1**. In the 1st literature selection process, the title of the studies was reviewed to assess relevance. In the 2nd selection process, the abstract was reviewed to assess relevance to key questions, and a total of 44 studies were selected. Lastly, the main text of articles selected in the 2nd selection process was reviewed according to the selection and exclusion criteria. Finally, 20 articles (articles 1–20) were selected for systematic literature review. In the meta-analysis process, the subgroup study ($n = 1$) of other study and long-term (>5 years) follow-up studies ($n = 2$) were excluded to reduce bias. **Figure 1** illustrates a flowchart for selection of the articles included in this systematic literature review. Articles 5, 12, and 19 were excluded in the quantitative analysis process.

Quality Assessment of the Literature

The risk of bias (RoB) of the studies was assessed using the Cochrane risk-of-bias tool. Two researchers independently assessed the RoB of the selected studies, and disagreements were settled through discussion to reach a consensus. The detailed guidelines are described in **Supplementary Table 2**. RoB. If there was insufficient information about the relevant items, the RoB was evaluated as "uncertain (yellow)." If the RoB was small, it was evaluated as "low (green)." We measured RoB for only 17 RCTs excluding one RPT (article 9).

Statistical Analysis

Data were extracted in accordance with several categories, including study characteristics (design, country, duration, inclusion criteria), patient characteristics (numbers, disease categories, type of intervention, age, the composition of case and control group, place, duration of intervention, and frequency), and clinical outcomes. If a quantitative measurement was possible, we conducted a meta-analysis and confirmed heterogeneity, or we described the data qualitatively. We used the outcome value at the longest follow-up of each study. Dichotomous outcomes are presented as relative risks with 95% confidence intervals (CIs). Variance and heterogeneity among the included studies were explored using forest plots and I^2 statistics, respectively. Data from each study were pooled using a fixed-effects meta-analysis model for the analysis with $I^2 > 75\%$ as well as by the random-effects model. If statistical heterogeneity was identified, meta-regression was conducted to explore the covariance, which affects the random effects, and to confirm the reason for heterogeneity. All statistical analyses were performed using the Review Manager 5.3 software (RevMan 2014, The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Systematic Review

General Characteristics and Various Outcomes of Included Studies

This literature review finally examined 20 articles, of which 19 were RCTs and 1 was an RPT. Regarding international location, 85% of the studies were conducted in Europe [Norway (10–15): 6, Denmark (16–20): 5, Netherlands (21): 1, Sweden (22, 23): 2, UK (24, 25): 2, Portugal (26): 1], 10% were conducted in Asia [China (27): 1, Hong Kong (28): 1], and 5% were conducted in North America [USA (9): 1]. For the intervention types, seven studies provided type I intervention, whereas 13 studies provided type II intervention. The greatest number of studies (38%) followed up the participants for more than 12 months, whereas 33% and 28% of the studies followed up the participants for 3–6 months and <3 months, respectively. The publication year ranged from 1997 to June 2020. The greatest number of studies was published in 2004 (four studies). Two studies were published in each of 2002, 2019, and 2020, whereas one study was published each in 1997, 2000, 2001, 2003, 2005, 2009, 2011, 2014, 2015, 2016, and 2017. The list of the selected studies and the characteristics of each study are shown in **Supplementary Table 3**. The study design, study country, and publication year were described in a reverse order. The outcomes (measured values) of each study are summarized in **Supplementary Table 4**.

Meta-Analysis

Patient Outcomes

Length of Hospital Stay

The length of hospital stay was reported in six studies. A meta-analysis of the length of hospital stays using the fixed effect model revealed significant heterogeneity among the studies ($I^2 = 59\%$); thus, the fixed effect model could not be used. In contrast, analysis using a random-effects model revealed no significant heterogeneity [standardized mean difference (SMD) $= -0.13$; 95% CI, −0.31 to 0.04; $p = 0.14$] (**Figure 2**).

Activities of Daily Living

The ADL score was reported in 10 studies. The tool used to measure ADL (Barthel index, Modified Barthel index, Functional independent measure) was different in each of the studies; therefore, the scores were standardized and compared. First, a meta-analysis of ADL using the fixed effect model led to significant heterogeneity among studies ($I^2 = 90\%$; $p < 0.000001$). Thus, the fixed effect model could not be used. A

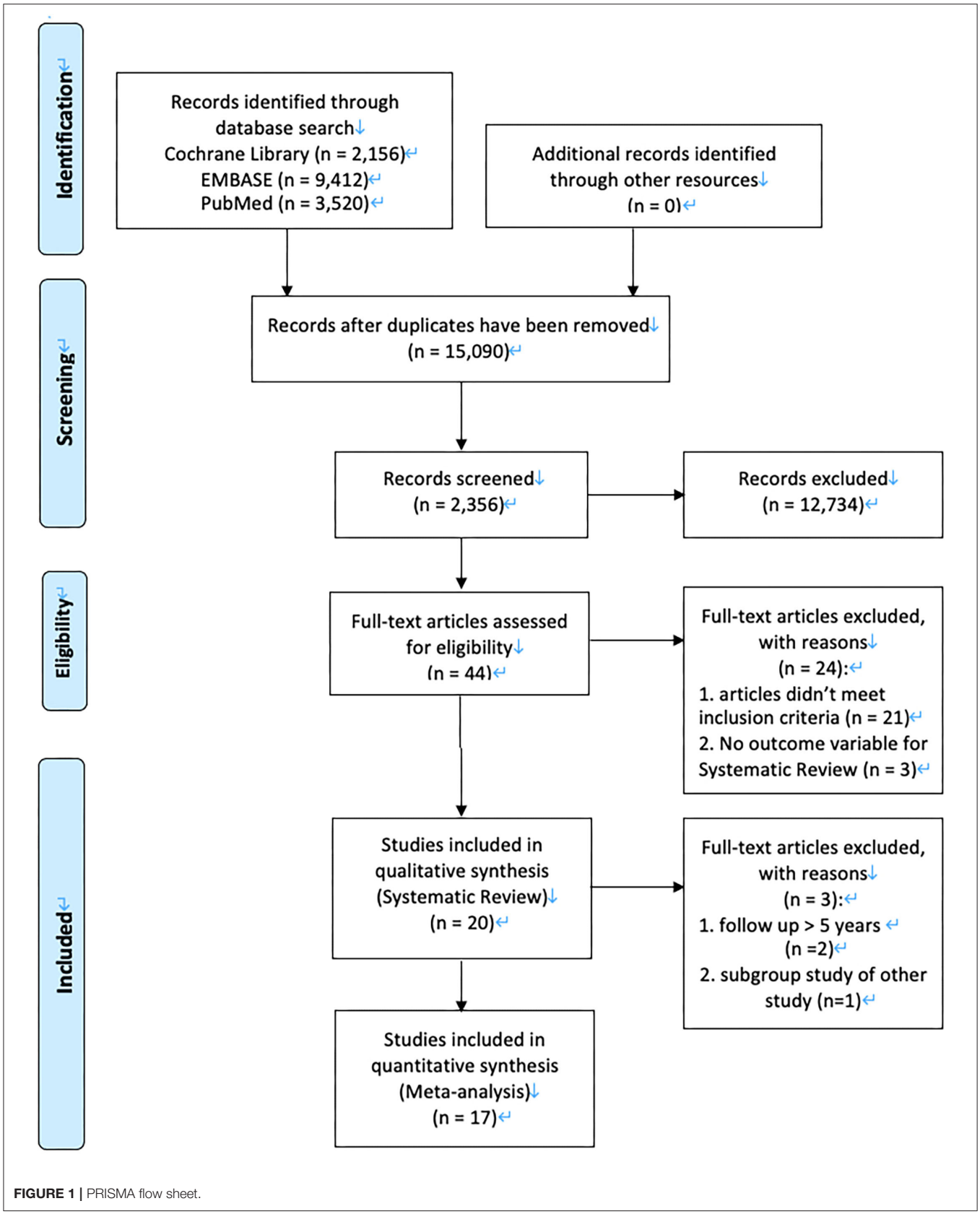


FIGURE 1 | PRISMA flow sheet.

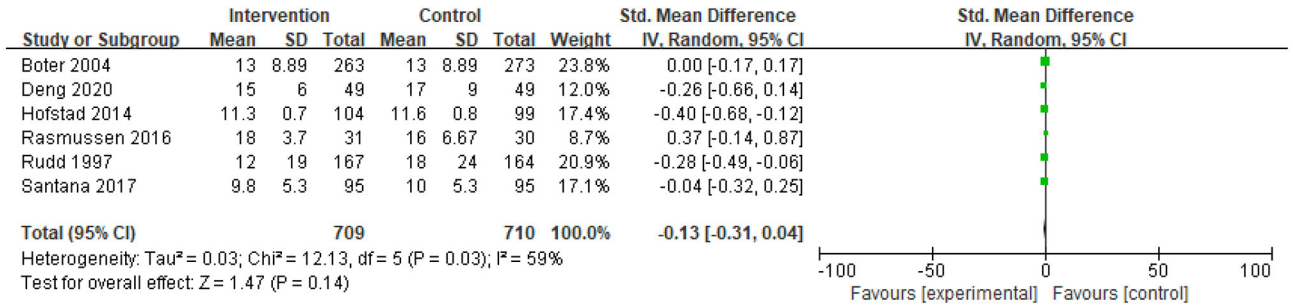


FIGURE 2 | Comparison ESD care vs. usual care; outcome I: length of hospital stay.

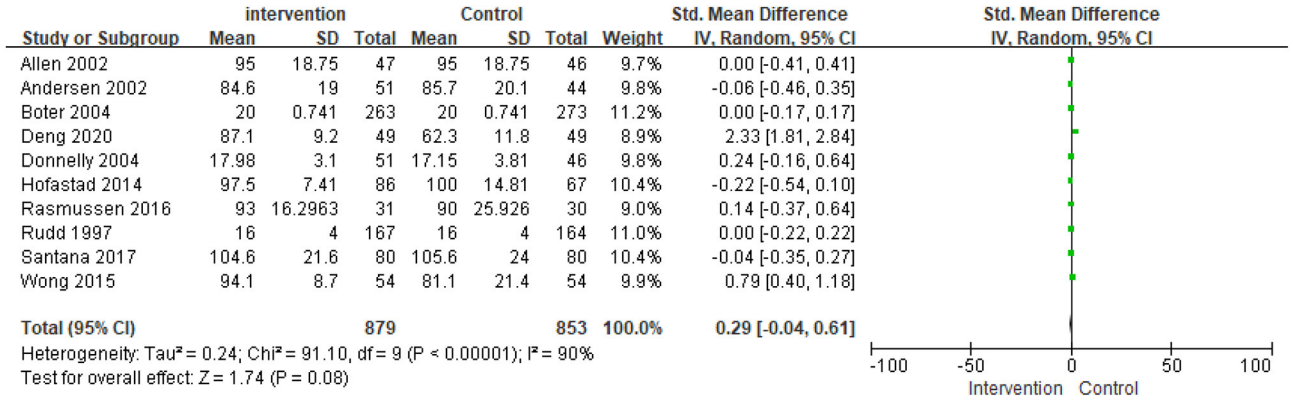


FIGURE 3 | Comparison ESD care vs. usual care; outcome II: activities of daily living (ADL).

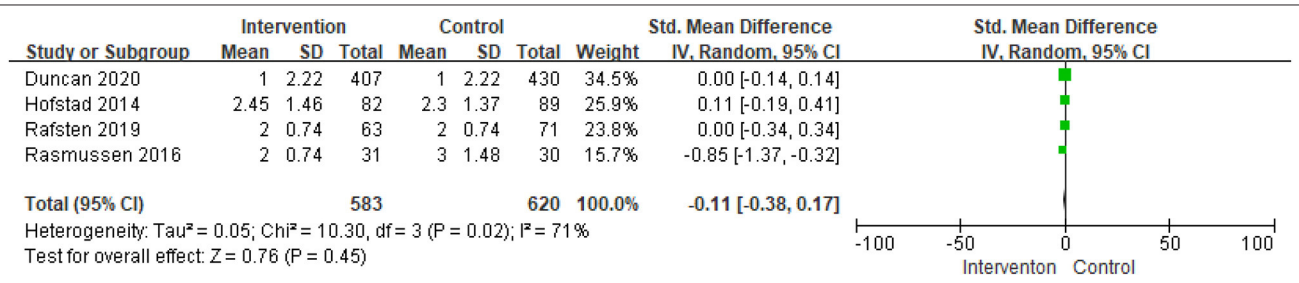


FIGURE 4 | Comparison ESD care vs. usual care; outcome III: modified Rankin scale (mRS).

meta-analysis of ADL using the random-effects model revealed no significant heterogeneity among studies (SMD = 0.29; 95% CI, −0.04 to −0.61; $p = 0.08$) (**Figure 3**).

mRS

The mRS score was reported in four studies. Analysis of the mRS scores using the fixed effect model led to significant heterogeneity among studies ($I^2 = 71\%$, $p = 0.02$). Thus, the fixed effect model could not be used. A meta-analysis of mRS scores using the random-effects model revealed no significant heterogeneity among studies (SMD = −0.11; 95% CI, −0.38 to 0.17; $p = 0.45$) (**Figure 4**).

Death

Death was reported in five studies. A meta-analysis of death using the fixed effect model revealed no significant heterogeneity among studies ($I^2 = 0\%$). Thus, the fixed effect model was used. However, the effect size was not significant [odds ratio (OR) = 0.80; 95% CI, 0.56–1.17; $p = 0.25$] (**Figure 5**).

Caregiver Strain Index

Care burden was reported in five studies. A meta-analysis of care burden using the fixed effect model led to significant heterogeneity among studies ($I^2 = 76\%$). Thus, the fixed effect model could not be used. A meta-analysis of care burden using the random-effects model revealed no significant heterogeneity

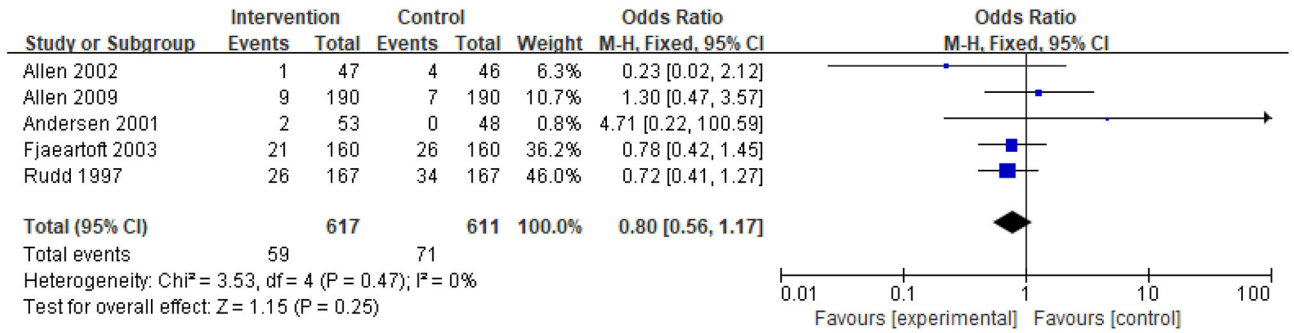


FIGURE 5 | Comparison ESD care vs. usual care; outcome IV: death.

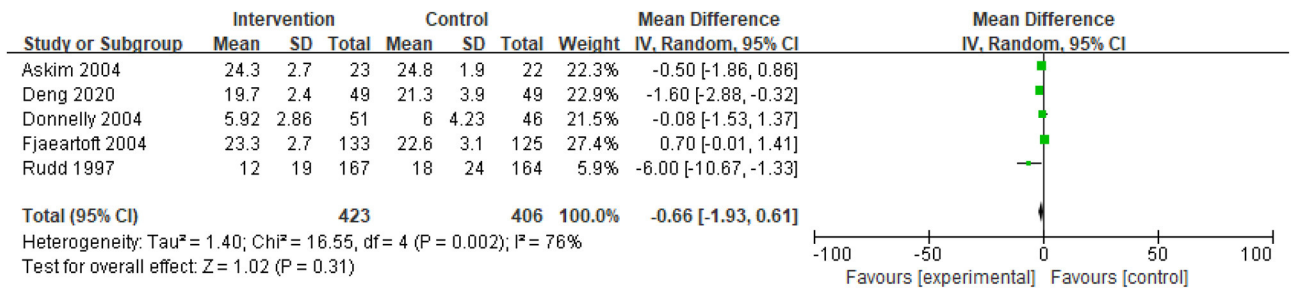


FIGURE 6 | Comparison ESD care vs. usual care; outcome 5: Caregiver Strain Index (CSI).

among studies (SMD = −0.66; 95% CI, −1.93 to 0.61; $p = 0.31$) (**Figure 6**).

RoB

There were some studies that revealed a high RoB in terms of performance bias, detection bias, and attrition bias. In contrast, the RoB was low for the selection bias and reporting bias. In particular, most studies revealed high or unclear RoB in performance bias (**Figure 7**).

Publication Bias

There was no evidence of funnel plot asymmetry for length of hospital stay (**Figure 8**), ADL (**Figure 9**), mRS (**Figure 10**), and death (**Figure 11**). For the CSI, it was impossible to examine small study bias due to the small number of studies reporting cardiac events.

DISCUSSION

In this study, we systematically reviewed articles on ESD to assess the effects of ESD or TC on ADL, residual symptoms, quality of life, mortality, length of hospital stay, and caregiver burden. A total of 15,118 related studies were searched on three databases. The titles and abstracts were analyzed, and studies that were searched multiple times were excluded. Finally, this systematic literature review examined 20 studies (19 RCTs and 1 RPT). Among these 20 studies, two studies that followed up the participants for more than 5 years and a subgroup study were excluded, and 17 studies were finally included in the meta-analysis. In terms of location, 85, 10, and 5% of the 20 studies were conducted in Europe, Asia, and North America, respectively, demonstrating that ESD is mainly limited to western countries. However, recent studies on ESD have been reported in China, suggesting that ESD programs are also being implemented in Asian countries.

Hempler et al. conducted a systematic literature review of studies on transition management in Germany. A total of 18 studies were included in the literature review; however, there were no high-quality studies on standardized transition management systems, and the literature review study suggested that standardized discharge management services, including ESD programs, are needed in Germany. This finding is consistent with the results of our study, wherein studies conducted in Germany were not included in the meta-analysis. However, countries other than Germany are attempting various types of services, and the services are also gradually being offered in Asian countries, suggesting the need for these services in Korea. Unlike the literature review study conducted in Germany (29), our study is meaningful because two researchers independently selected and evaluated the studies for meta-analysis.

In 2017, Langhorne et al. conducted a literature search similar to our study and performed a systematic literature review and meta-analysis of 17 RCTs that included 2,422 patients. In that study, ESD reduced the length of hospital stay by ∼6 days and might have reduced long-term functional dependence. In our study, there was a small number of cases in which

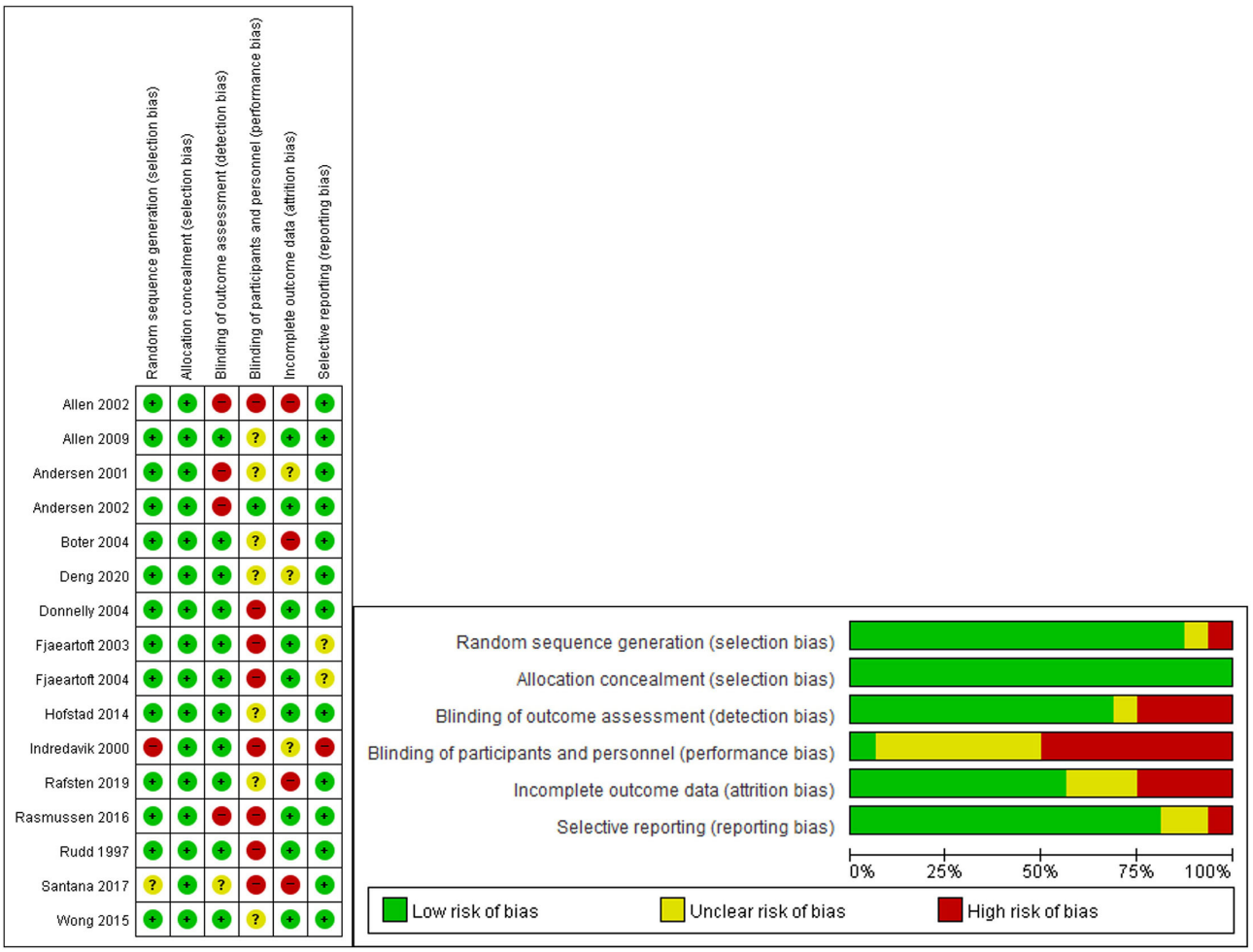


FIGURE 7 | "Risk of bias" graph: review authors' judgments about each risk of bias item presented as percentages across included studies. "Risk of bias" summary: review authors' judgments about each risk of bias item for each included study.

ESD led to significant differences in the outcomes. This may be attributed to the homogeneous standard of interventions, excluding patient-led, family-led, and tele-rehabilitation, unlike those used in Cochrane's study, which deliberately set a broad criteria for interventions. Such differences led to exclusion of various studies, which might have led to a reduced number of cases in which ESD significantly improved the study outcomes (6).

We observed no significant differences in ADL between the TC methods, including ESD and conventional treatment. However, several points must be considered in the interpretation of this finding. As shown in the previous meta-analysis (6), ESD was mainly provided to high-level performing stroke patients. Thus, the ADL index included in our analysis might not accurately reflect the ADL functional status of patients due to the ceiling effects. Therefore, future studies must evaluate ADL using indicators that can evaluate high-level functions.

This systematic literature review and meta-analysis is meaningful because the most recent study (9) on TC has been included, and the types of services provided included ESD and TC in the literature search and selection.

However, this study also has several limitations. First, the definition of the interventions was unclear in each study. Thus, the type, duration, and period of intervention, and ESD team members were not completely identical. Second, most studies included in the meta-analysis were blinded to the assessor; however, the study participants could not be blinded. Thus, double-blinded studies could not be included. Third, pragmatic trials reflect realistic medical settings and could be as scientifically essential as an RCT, but it still needs a control group to be able to demonstrate an effect of the intervention. Lastly, we chose a particular set of trials relevant to the Republic of Korea. Therefore, caution is needed when interpreting the results of this study. We considered that TC programs should be a part of the ESD service in our country.

This study systematically investigated the effects of ESD and TC on medical use, function, mortality, and caregiver burden in stroke patients. We did not find a large effect size for the use

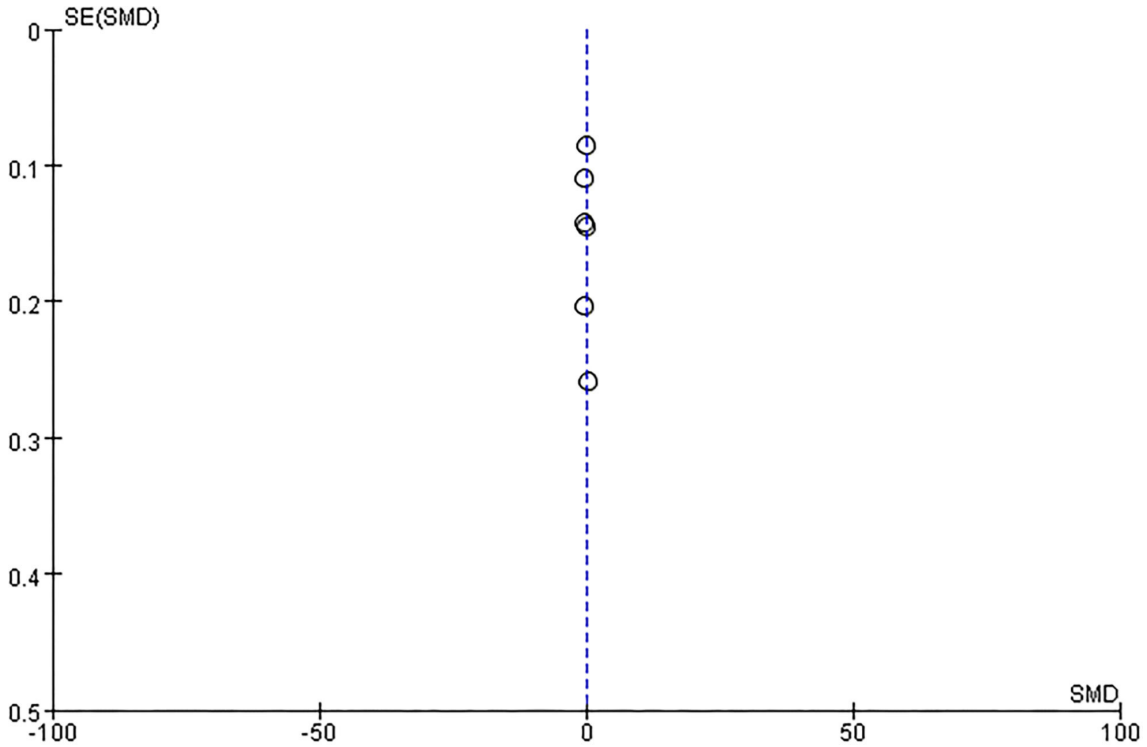


FIGURE 8 | Funnel plot of comparison: ESD care vs. usual care, outcome: length of hospital stay.

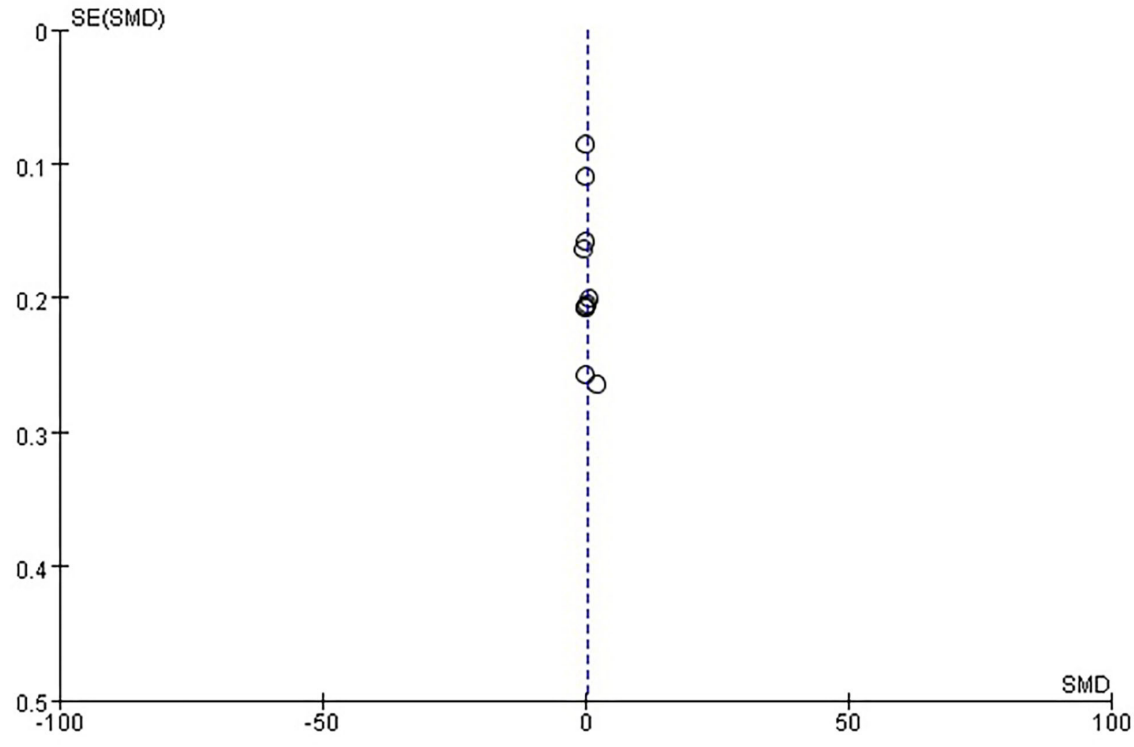


FIGURE 9 | Funnel plot of comparison: ESD care vs. usual care, outcome: activities of daily living (ADL).

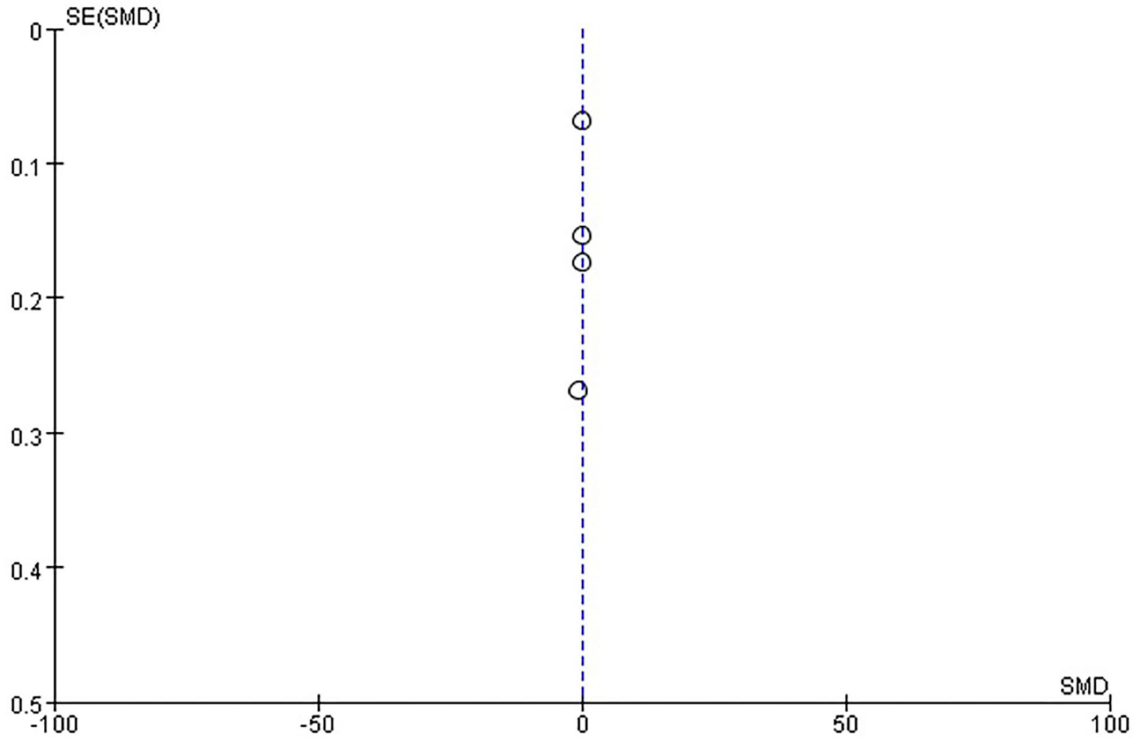


FIGURE 10 | Funnel plot of comparison: ESD care vs. usual care, outcome: modified Rankin scale (mRS).

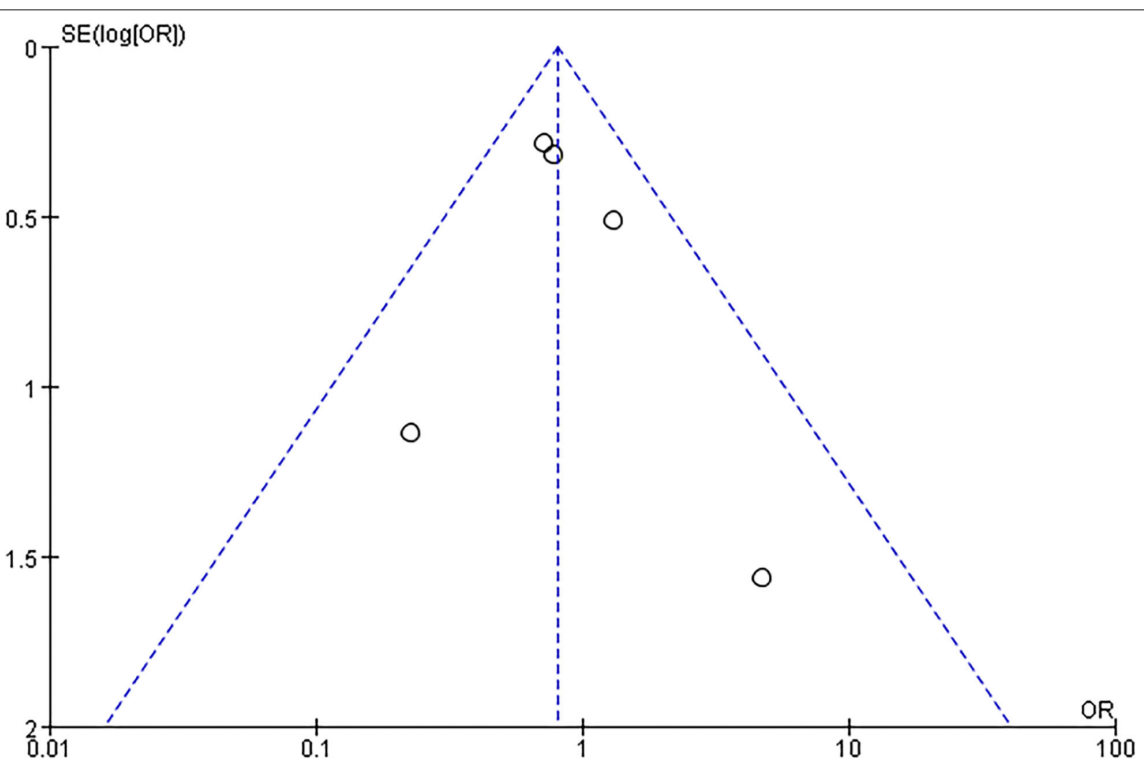


FIGURE 11 | Funnel plot of comparison: ESD care vs. usual care, outcome: death.

of TC and ESD. When implementing the TC and ESD model from western to Asian countries, services should be prepared and implemented in accordance with national medical rehabilitation pathways for cerebrovascular disease.

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/s.

AUTHOR CONTRIBUTIONS

SJ and MS contributed to the conception or design of the work. MJ, WK, Y-IS, and S-HK contributed to the data acquisition. IK, BC, YJ, and WC especially did statistical analysis and interpreted result of data for the work. All authors participated in drafting the work or revising it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This work was supported by the Research Program funded by the Korea National Institute of Health (Grant Number: 2020ER630601).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.755316/full#supplementary-material

REFERENCES

1. Sall J, Eapen BC, Tran JE, Bowles AO, Bursaw A, Rodgers ME. The management of stroke rehabilitation: a synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline. *Ann Inter Med.* (2019) 171:916–24. doi: 10.7326/M19-1695
2. Mountain A, Patrice Lindsay M, Teasell R, Salbach NM, de Jong A, Foley N, et al. Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. Part two: transitions and community participation following stroke. *Int J Stroke.* (2020) 15:789–806. doi: 10.1177/1747493019897847
3. Smith LN, James R, Barber M, Ramsay S, Gillespie D, Chung C. Rehabilitation of patients with stroke: summary of sign guidance. *BMJ.* (2010) 340:c2845–c. doi: 10.1136/bmj.c2845
4. Langhorne P, Holmqvist LW, Early Supported Discharge T. Early supported discharge after stroke. *J Rehabil Med.* (2007) 39:103–8. doi: 10.2340/16501977-0042
5. Langhorne P, Taylor G, Murray G, Dennis M, Anderson C, Bautz-Holter E, et al. Early supported discharge services for stroke patients: a meta-analysis of individual patients' data. *Lancet.* (2005) 365:501–6. doi: 10.1016/S0140-6736(05)17868-4
6. Langhorne P, Baylan S, Early Supported Discharge T. Early supported discharge services for people with acute stroke. *Cochrane Database Syst Rev.* (2017) 7:CD000443. doi: 10.1002/14651858.CD000443.pub4
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
8. Bettger JP, Jones SB, Kucharska-Newton AM, Freburger JK, Coleman SW, Mettam LH, et al. Meeting medicare requirements for transitional care: do stroke care and policy align? *Neurology.* (2019) 92:427–34. doi: 10.1212/WNL.0000000000006921
9. Duncan PW, Bushnell CD, Jones SB, Psioda MA, Gesell SB, D'Agostino RB, et al. Randomized pragmatic trial of stroke transitional care: the compass study. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e006285. doi: 10.1161/CIRCOUTCOMES.119.006285
10. Askim T, Rohweder G, Lydersen S, Indredavik B. Evaluation of an extended stroke unit service with early supported discharge for patients living in a rural community. A randomized controlled trial. *Clin Rehabil.* (2004) 18:238–48. doi: 10.1191/0269215504cr752oa
11. Fjæartoft H, Indredavik B, Johnsen R, Lydersen S. Acute stroke unit care combined with early supported discharge. Long-term effects on quality of life. A randomized controlled trial. *Clin Rehabil.* (2004) 18:580–6. doi: 10.1191/0269215504cr773oa
12. Fjaertoft H, Indredavik B, Lydersen S. Stroke unit care combined with early supported discharge: long-term follow-up of a randomized controlled trial. *Stroke.* (2003) 34:2687–91. doi: 10.1161/01.STR.0000095189.21659.4F
13. Fjærtoft H, Rohweder G, Indredavik B. Stroke unit care combined with early supported discharge improves 5-year outcome: a randomized controlled trial. *Stroke.* (2011) 42:1707–11. doi: 10.1161/STROKEAHA.110.601153
14. Hofstad H, Gjelsvik BE, Næss H, Eide GE, Skouen JS. Early supported discharge after stroke in Bergen (ESD stroke Bergen): three and six months results of a randomised controlled trial comparing two early supported discharge schemes with treatment as usual. *BMC Neurol.* (2014) 14:239. doi: 10.1186/s12883-014-0239-3
15. Indredavik B, Fjaertoft H, Ekeberg G, Løge AD, Mørch B. Benefit of an extended stroke unit service with early supported discharge: a randomized, controlled trial. *Stroke.* (2000) 31:2989–94. doi: 10.1161/01.STR.31.12.2989
16. Allen K, Hazelett S, Jarjoura D, Hua K, Wright K, Weinhardt J, et al. A randomized trial testing the superiority of a postdischarge care management model for stroke survivors. *J Stroke Cerebrovasc Dis.* (2009) 18:443–52. doi: 10.1016/j.jstrokecerebrovasdis.2009.02.002
17. Allen KR, Hazelett S, Jarjoura D, Wickstrom GC, Hua K, Weinhardt J, et al. Effectiveness of a postdischarge care management model for stroke and transient ischemic attack: a randomized trial. *J Stroke Cerebrovasc Dis.* (2002) 11:88–98. doi: 10.1053/jscd.2002.127106
18. Andersen HE, Eriksen K, Brown A, Schultz-Larsen K, Forchhammer BH. Follow-up services for stroke survivors after hospital discharge–a randomized control study. *Clin Rehabil.* (2002) 16:593–603. doi: 10.1191/0269215502cr528oa
19. Andersen HE, Jurgensen K-L, Kreiner S, Forchhammer BH, Eriksen K, Brown A. Can readmission after stroke be prevented? Results of a randomised clinical study: a postdischarge follow-up service for stroke survivors. *Stroke.* (2000) 163:6421-7. doi: 10.1161/01.STR.31.5.1038
20. Rasmussen RS, Østergaard A, Kjær P, Skerris A, Skou C, Christoffersen J, et al. Stroke rehabilitation at home before and after discharge reduced disability and improved quality of life: a randomised controlled trial. *Clin Rehabil.* (2016) 30:225–36. doi: 10.1177/0269215515575165
21. Boter H. Multicenter randomized controlled trial of an outreach nursing support program for recently discharged stroke patients. *Stroke.* (2004) 35:2867–72. doi: 10.1161/01.STR.0000147717.57531.e5
22. Rafsten L, Danielsson A, Nordin A, Björkdahl A, Lundgren-Nilsson A, Larsson MEH, et al. Gothenburg very early supported discharge study (Gotved): a randomised controlled trial investigating anxiety and overall disability in the first year after stroke. *BMC Neurol.* (2019) 19:277. doi: 10.1186/s12883-019-1503-3

23. Thorsén AM, Holmqvist LW, de Pedro-Cuesta J, von Koch L. A randomized controlled trial of early supported discharge and continued rehabilitation at home after stroke: five-year follow-up of patient outcome. *Stroke.* (2005) 36:297–303. doi: 10.1161/01.STR.0000152288.42701.a6
24. Donnelly M, Power M, Russell M, Fullerton K. Randomized controlled trial of an early discharge rehabilitation service: the belfast community stroke trial. *Stroke.* (2004) 35:127–33. doi: 10.1161/01.STR.0000106911.96026.8F
25. Rudd AG, Wolfe CDA, Tilling K, Beech R. Randomised controlled trial to evaluate early discharge scheme for patients with stroke. *Br Med J.* (1997) 315:1039–44. doi: 10.1136/bmj.315.7115.1039
26. Santana S, Rente J, Neves C, Redondo P, Szczygiel N, Larsen T, et al. Early home-supported discharge for patients with stroke in portugal: a randomised controlled trial. *Clin Rehabil.* (2017) 31:197–206. doi: 10.1177/0269215515627282
27. Deng A, Yang S, Xiong R. Effects of an integrated transitional care program for stroke survivors living in a rural community: a randomized controlled trial. *Clin Rehabil.* (2020) 34:524–32. doi: 10.1177/0269215520905041
28. Wong FK, Yeung SM. Effects of a 4-week transitional care programme for discharged stroke survivors in hong kong: a randomised controlled trial. *Health Soc Care Commun.* (2015) 23:619–31. doi: 10.1111/hsc.12177
29. Hempler I, Woitha K, Thielhorn U, Farin E. Post-stroke care after medical rehabilitation in Germany: a systematic literature review of the current provision of stroke patients. *BMC Health Serv Res.* (2018) 18:468. doi: 10.1186/s12913-018-3235-2

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 17 March 2022
doi: 10.3389/fneur.2022.834240

The Relationship Between Dysphagia and Pneumonia in Acute Stroke Patients: A Systematic Review and Meta-Analysis

Min Cheol Chang[1], *Yoo Jin Choo*[1], *Kyung Cheon Seo*[2] *and Seoyon Yang*[3]*

[1] Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, South Korea, [2] Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Ulsan, South Korea, [3] Department of Rehabilitation Medicine, Ewha Womans University Seoul Hospital, School of Medicine, Ewha Womans University, Seoul, South Korea

OPEN ACCESS

Edited by:
Surjo R. Soekadar,
Charité Universitätsmedizin
Berlin, Germany

Reviewed by:
Seong Hoon Lim,
Catholic University of Korea,
South Korea
Shi-Bing Liang,
Beijing University of Chinese
Medicine, China
Sang Seok Yeo,
Dankook University, South Korea

***Correspondence:**
Seoyon Yang
seoyonyang@gmail.com

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 13 December 2021
Accepted: 21 February 2022
Published: 17 March 2022

Citation:
Chang MC, Choo YJ, Seo KC and Yang S (2022) The Relationship Between Dysphagia and Pneumonia in Acute Stroke Patients: A Systematic Review and Meta-Analysis. Front. Neurol. 13:834240. doi: 10.3389/fneur.2022.834240

Background: Dysphagia is a common complication after stroke and is associated with the development of pneumonia. This study aimed to summarize the relationship between dysphagia and pneumonia in post-stroke patients.

Materials and Methods: Articles published up to November 2021 were searched in the PubMed, Embase, Cochrane library, and Scopus databases. Studies that investigated the development of pneumonia in acute stroke patients with and without dysphagia were included. The methodological quality of individual studies was evaluated using the Risk Of Bias In Non-randomized Studies-of Interventions tool, and publication bias was evaluated using a funnel plot and Egger's test.

Results: Of 5,314 studies, five studies were included in the meta-analysis. The results revealed that the incidence of pneumonia was significantly higher in the dysphagia group than in the non-dysphagia group (OR 9.60; 95% CI 5.75–16.04; $p < 0.0001$; $I^2 = 78\%$). There was no significant difference in the mortality rate between the two groups (OR 5.64; 95% CI 0.83–38.18; $p = 0.08$; $I^2 = 99\%$).

Conclusion: Dysphagia is a significant risk factor for pneumonia after stroke. The early diagnosis and treatment of dysphagia in stroke patients are important to prevent stroke-associated pneumonia.

Keywords: pneumonia, stroke, mortality, meta-analysis, dysphagia

INTRODUCTION

Stroke is one of the leading causes of disability and mortality worldwide (1, 2). The number of stroke patients is gradually increasing around the world, leading to increases in healthcare costs (3). Patients with stroke have various clinical conditions, including hemiparesis, loss of dexterity, functional limitations, gait disturbance, cognitive impairment, dysarthria, spasticity, neglect, and dysphagia (4).

Dysphagia is a symptom characterized by difficulties in the passage of food or liquid from the mouth through the pharynx, esophagus, and stomach (5). The difficulty in swallowing can occur in any of the four phases (i.e., oral preparatory, oral, pharyngeal, and esophageal phases) (6). Dysphagia occurs in ∼3% of the general population, frequently affecting the elderly and patients with cerebrovascular accidents (7). The prevalence of dysphagia after stroke has been reported to be around 30–65% (2, 8). Post-stroke dysphagia may show improvements during the first week after stroke; however, it may also persist as a chronic condition with many complications. The presence of dysphagia in stroke patients may cause poor dietary intake, dehydration, malnutrition, and pulmonary complications, which can lead to poor prognosis (9).

Stroke-associated pneumonia is one of the most common post-stroke infections with a prevalence of 14.3% (10). It affects clinical outcomes and is associated with an increased risk of prolonged hospital stay and poor recovery (11). Pneumonia is the leading cause of death during the acute phase of stroke, with a 30-day mortality rate of 30% (12). Dysphagia is one of the most significant risk factors in the development of pneumonia (2). Aspiration pneumonia is defined as pneumonia with preexisting risk factors accompanying demonstrated or suspected aspiration (13). The presence of oropharyngeal aspiration is associated with various clinical symptoms, including choking, coughing, or a wet-sounding voice during or after eating (14). In addition, it may occur without cough or airway protective responses, making diagnosis more difficult (14). Patients with dysphagia have a higher risk of aspiration, leading to an increased risk of acquiring pneumonia. Previous animal models and human clinical studies have shown that the primary cause of aspiration pneumonia is silent aspiration (15). It has been reported that stroke patients with dysphagia have a 3- to 11-fold increased risk of acquiring pneumonia, and the prevalence of pneumonia is higher among patients with dysphagia compared with those without dysphagia (8).

Considering that both dysphagia and aspiration are highly prevalent in stroke patients, clarifying the relationship between dysphagia and pneumonia can contribute to the early detection and better management of dysphagia in stroke patients. Investigating the risk factors of pneumonia can help reduce post-stroke infections and associated complications. The objective of this systematic review and meta-analysis was to investigate and summarize the effect of dysphagia on pneumonia and mortality in patients with stroke.

METHODS

A systematic review of studies related to post-stroke dysphagia and complications (pneumonia and mortality) in patients with stroke was conducted.

Search Strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). The protocol of this meta-analysis was registered on INPALSY (International Platform of Registered Systematic Review and Meta-analysis Protocols) with a registration number of INPALSY2021110108. Relevant articles were systematically searched using the PubMed, Embase, Cochrane library, and Scopus databases up to November 2021. The following keywords were used in the search: "deglutition disorders," "deglutition," "dysphagia," "swallowing," "deglutition pneumonia," and "aspiration pneumonia." Used search terms and strategies are presented in **Supplementary Appendix 1**.

Study Selection

The eligibility criteria for this meta-analysis were based on the Population. Intervention, Comparison, and Outcome (PICO) framework (17). Using the PICO strategy, patients with acute stroke were classified as the population, and patients with and without dysphagia were classified as the intervention and comparison groups, respectively. The main outcomes of interest were the incidence of pneumonia and number of deaths attributed to post-stroke dysphagia. The following inclusion criteria were used for the selection of articles: (1) acute stroke patients were recruited; (2) dysphagia was diagnosed in the intervention group (dysphagia group) and not diagnosed in the comparison group (control group); (3) development of pneumonia or number of deaths were evaluated in both groups. The exclusion criteria were as follows: (1) studies not related to dysphagia, pneumonia, or mortality; (2) reviews, case reports, commentaries, letters, and animal studies; (3) study outcomes that were not reported or insufficient. Two independent reviewers excluded articles after reading the titles and abstracts (KCS and SYY), and full-text assessments were conducted to reject those not fulfilling the inclusion criteria. The reviewers attempted to resolve any disagreement by consensus. If necessary, the opinion of a third reviewer was taken into consideration to resolve the disagreement.

Data Extraction

All data were extracted independently by two reviewers (SYY and MCC) using a standard data collection form. Discrepancies were resolved through consensus and discussion with another reviewer (YJC) if necessary. The following data were recorded using a table for each eligible article: (1) name of the first author; (2) year of publication; (3) number of patients; (4) number of diagnoses of dysphagia; (5) incidence of pneumonia and number of deaths.

Quality Assessment

The methodological quality was assessed using the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool for the included studies. The specific domains of ROBINS-I are as follows: bias from confounding, bias from the process of participant selection, bias due to classification of interventions, bias due to deviations from intended interventions, bias from missing data, bias from measurement of outcomes, and bias from selection of the reported results. Judgments of bias were expressed as "low risk," "high risk," or "unclear risk." Two reviewers (SYY and MCC) independently assessed the risk of bias

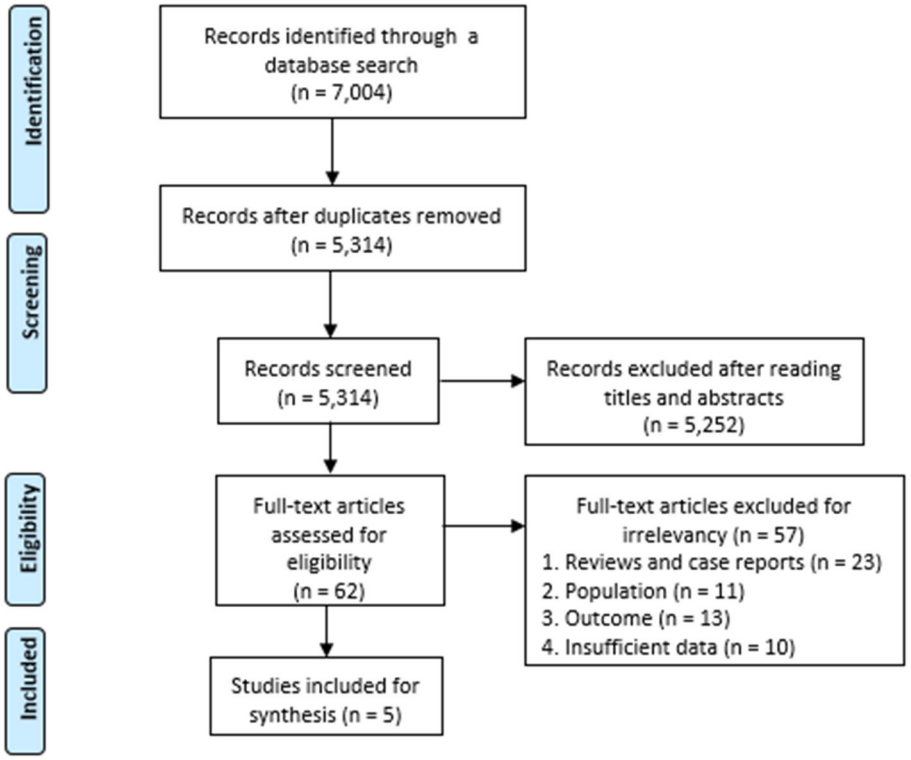


FIGURE 1 | PRISMA flow diagram.

in each domain. If there is any disagreement between the two reviewers, discussion was continued until consensus was achieved.

Statistical Analysis

All statistical analyses of the pooled data were performed using RevMan 5.3 software (http://tech.cochrane.org/revman). I^2 statistics were used to assess heterogeneity between studies, which measures the extent of inconsistency among the results. I^2 percentages of around 25, 50, 75% represent low, medium, and high heterogeneity, respectively. Significant heterogeneity was considered to be present if $I^2 \geq 50\%$, and the random-effects model was used for data analysis. The pooled data were considered to be homogenous if $I^2 < 50\%$, and the fixed effects model was used. The odds ratio (OR) was analyzed to evaluate differences in outcome measures (development of pneumonia and number of deaths) among patients with and without dysphagia. The 95% confidence interval (CI) was used in the analysis, and $p < 0.05$ was considered statistically significant. A funnel plot and Egger's test were also used to assess publication bias with R version 4.1.2. The funnel plot was used to determine the publication bias of individual studies based on the pooled estimate. Egger's test was used to determine whether the funnel plot was symmetrical $p < 0.05$ indicated the possibility of publication bias.

RESULTS

A total of 7,004 articles were identified using the search terms, and 1,690 duplicates were removed. After reading the titles and abstracts, 5,252 of the initially identified 5,314 articles that did not meet the inclusion criteria were excluded. The remaining 62 articles were assessed for eligibility, and 56 articles were excluded due to following reasons: 22 studies were reviews and case reports, 11 studies did not involve stroke patients, 13 studies did not report the prevalence of pneumonia for stroke patients with dysphagia, and 10 studies had insufficient data. Finally, five observational studies were included in this meta-analysis (**Figure 1**). The incidence of pneumonia and mortality rate of patients with dysphagia (intervention group) were compared with those of patients without dysphagia (control group). The characteristics of the included studies are summarized in **Table 1**.

Study Characteristics

In 2006, Kwon et al. (21) demonstrated that dysphagia was associated with the development of pneumonia (OR 15.56; CI 3.8–63.1; $p < 0.001$), suggesting that patients with dysphagia who aspirate were likely to have an increased risk of pneumonia. Additionally, they reported that the incidence of pneumonia was higher among patients with a higher National Institute of Health Stroke Scale (NIHSS) score (OR 3.44; CI 1.2–9.8; $p = 0.02$), possibly due to decreased consciousness or gastroesophageal reflux in the supine or recumbent position.

TABLE 1 | Characteristics of included studies.

No.	References	Number of patients (dysphagia vs. non-dysphagia)	Type of stroke	Diagnosis of dysphagia	Diagnosis of pneumonia	Outcomes
1	Feng et al. (8)	660 vs. 610	Stroke patients according to ICD-9 code (ischemic or hemorrhagic)	Dysphagia was diagnosed using ICD-9 787.2.	Pneumonia was diagnosed using ICD-9-CM 507 (pneumonitis due to solids and liquids).	Diagnosis of pneumonia, risk of aspiration pneumonia of stroke patients in the dysphagia and non-dysphagia groups after 1, 3, 5 years, and morality risk after 1, 3, 5 years
2	Al-Khaled et al. (18)	3,083 vs. 9,193	Clinical presentation and brain imaging (cranial CT and MRI)	Dysphagia was determined in cases of deglutition, drooling, absent swallow reflex, cough or voice change after swallowing, reduced water control, decreased oral clearance, or involuntary cough.	A combination of clinical presentations, radiologic signs detected on chest x-ray, and blood test results (C-reactive protein and leukocytes).	Pneumonia rate and mortality during hospitalization and disability defined as mRS $\geq$ 2 at discharge and 3 months after discharge
3	Brogan et al. (19)	312 vs. 224	Retrospective medical record review with a primary diagnosis of "Stroke" or "CVA"	Standard practice for diagnosing a patient with dysphagia was used, including clinical bedside evaluation of swallowing. Specific criteria for diagnosis were not specified.	Not specified.	Presence or absence of respiratory infection, mobility, incontinence, and dysphagia at admission
4	Walter et al. (20)	69 vs. 167	Brain imaging (cranial CT and MRI)	Clinical examination and a water swallowing test with pulse oximetry were performed. Severity of dysphagia was scored from 0 to 3.	Pneumonia was diagnosed according to the Center for Disease Control and Prevention criteria based on clinical, microbiological, and chest x-ray findings.	Presence and severity of dysphagia, pneumonia rate, and NIHSS score
5	Kwon et al. (21)	96 vs. 190	Stroke occurred within 4 days of admission; others not specified	Dysphagia was diagnosed if positive clinical signs were accompanied by pathologic findings from additional water swallowing or pharyngeal sensation tests.	Pneumonia was diagnosed if a patient had at least one of the following: (1) auscultatory respiratory crackles and fever ($\geq$37.7°C in the axillary area); (2) radiographic evidence; (3) new purulent sputum, as mentioned in the previous report.	Pneumonia rate, hospital stay, mRS at discharge, dysphagia, and NIHSS score at admission

AIS, acute ischemic stroke; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

In 2007, Walter et al. (20) conducted a study on patients with acute ischemic stroke to investigate various risk factors that contribute to the development of stroke-associated pneumonia. In the study, they reported that dysphagia was an independent risk factor for stroke-associated pneumonia (OR 15.7; CI 5.6–43.7; $p < 0.001$). A high NIHSS score ($\geq$10) was also associated with an increased risk of pneumonia in stroke patients (OR 2.9; CI 1.0–8.2; $p = 0.046$).

A study in 2014 by Brogan et al. (19) showed that 17% of stroke patients who had dysphagia were diagnosed with a respiratory infection. Interestingly, the study reported that dysphagia was not a significant independent predictor of respiratory infection in multivariate analysis and suggested that full assistance with mobility and incontinence were associated with respiratory infection. Respiratory infection was observed frequently in immobile and incontinent patients with an associated risk ratio of 6.5 and 3.2, respectively. The study concluded that the occurrence of aspiration pneumonia was multifactorial.

In 2016, Al-Khaled et al. (18) showed that dysphagia was independently associated with an increased risk of pneumonia

(OR 3.4; 95% CI 2.8–4.2; $p < 0.001$) and case fatality (OR 2.8; 95% CI 2.1–3.7; $p < 0.001$) during hospitalization. Dysphagia was also associated with disability at discharge (OR 2.0; 95% CI 1.6–2.3; $p < 0.001$). These effects continued for 3 months after discharge; the mortality rate at 3 months after discharge was higher among patients with dysphagia compared with those without dysphagia (OR 3.2; 95% CI 2.4–4.2; $p < 0.001$), and there was a higher likelihood of disability (OR 2.3; 95% CI 1.8–3.0; $p < 0.001$).

A study by Feng et al. (8) included 1,220 patients with acute stroke (610 patients in the dysphagia group and 610 patients in the non-dysphagia group). Patients in the dysphagia group were followed for an average of 2.96 years, and patients in the non-dysphagia group were followed for an average of 3.73 years. The risk of aspiration pneumonia was significantly different between the two groups within the first year (adjusted hazard ratio (aHR) 4.69, 95% CI 2.83–7.77, $p < 0.001$), 3 years (aHR 3.49, 95% CI 2.43–5.01, $p < 0.001$), and 5 years (aHR 2.93, 95% CI 2.15–3.99, $p < 0.001$) after the stroke episode. In addition, the mortality risk was significantly different between the two groups within the first year (aHR 1.90, 95% CI 1.45–2.49, $p < 0.001$), 3 years (aHR 1.93, 95% CI 1.60–2.32, $p < 0.001$), and 5 years (aHR 1.84, 95% CI 1.57–2.16, $p < 0.001$) after the stroke episode. The study demonstrated the longitudinally relative risk of aspiration pneumonia after stroke by comparing patients with and without dysphagia.

Risk of Bias

The risk of bias was assessed using the ROBINS-I tool for the included studies by two reviewers (SYY and MCC). All studies had a low risk of bias in the domains of confounding, participant selection, measurement of outcomes, and selection of the reported results. In the domain of classification of interventions, three studies had a low risk of bias, and two studies had a high risk of bias. In the domain of deviations from intended interventions, three studies had a low risk of bias, and two studies had an unclear risk of bias. In the domain of missing data, four studies had a low risk of bias, and one study had an unclear risk of bias (**Figure 2**).

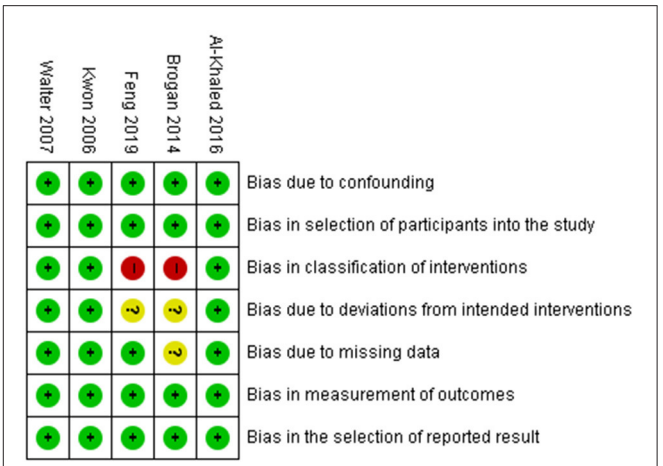


FIGURE 2 | Risk of bias summary.

Results of Meta-Analysis

For the pooled analysis for incidence of pneumonia and mortality rate, the random-effect model was used because the I^2 values were $I^2 \geq 50\%$. The results of the meta-analysis revealed that stroke patients in the dysphagia group had a significantly higher incidence of pneumonia compared with that of patients in the non-dysphagia group (OR 9.60; 95% CI 5.75–16.04; $p < 0.0001$; $I^2 = 78\%$). There was no significant difference in the mortality rate between the two groups (OR 5.64; 95% CI 0.83–38.18; $p = 0.08$; $I^2 = 99\%$) (**Figure 3**).

Publication Bias

Two reviewers (SKC and MCC) evaluated publication bias using two different methods. A funnel plot and Egger's test were used to assess publication bias for studies related to pneumonia and dysphagia. As there were only two studies on mortality associated with dysphagia, the assessment of publication bias was not applicable. The funnel plot appeared to be symmetrical on visual examination, and the results of Egger's test did not reveal significant publication bias (pneumonia, $p = 0.314$) (**Figure 4**).

DISCUSSION

This meta-analysis demonstrated the close relationship between dysphagia and pneumonia, providing evidence for the increased risk of pneumonia in patients who developed dysphagia after stroke. Previous studies have reported that post-stroke dysphagia results in poor nutritional status and aspiration pneumonia, leading to prolonged hospital stay, poor functional capacity, poor prognosis, and increased mortality (8, 22). This is the first meta-analysis to demonstrate that dysphagia is significantly associated with the development of pneumonia after stroke. The results showed that the incidence of pneumonia was higher among patients with dysphagia compared with those without dysphagia. The mortality rate of patients with dysphagia was not significantly higher compared with that of patients without dysphagia after stroke.

The common signs and symptoms of dysphagia include choking on food, coughing during and after eating, drooling, effortful eating, and difficulties when swallowing (23). Post-stroke dysphagia is associated with pharyngeal muscular dysfunction and incoordination, second to central nervous system loss of control. The development of dysphagia is caused by a loss of neurological connectivity within the neural swallowing network (24). The ability to swallow may be impaired because of weakness or dysfunction of the oropharyngeal, laryngeal, and esophageal musculatures (25). Impairment in the pharyngeal phase of the swallowing process is usually associated with a risk of aspiration, leading to aspiration pneumonia. The improper movement of the bolus through the pharynx and around the larynx contributes to increased aspiration risk (26).

Although the medical, social, and psychological effects of dysphagia are significant, dysphagia is often poorly diagnosed and managed (27). The early detection and proper management of dysphagia, including adequate nutritional management

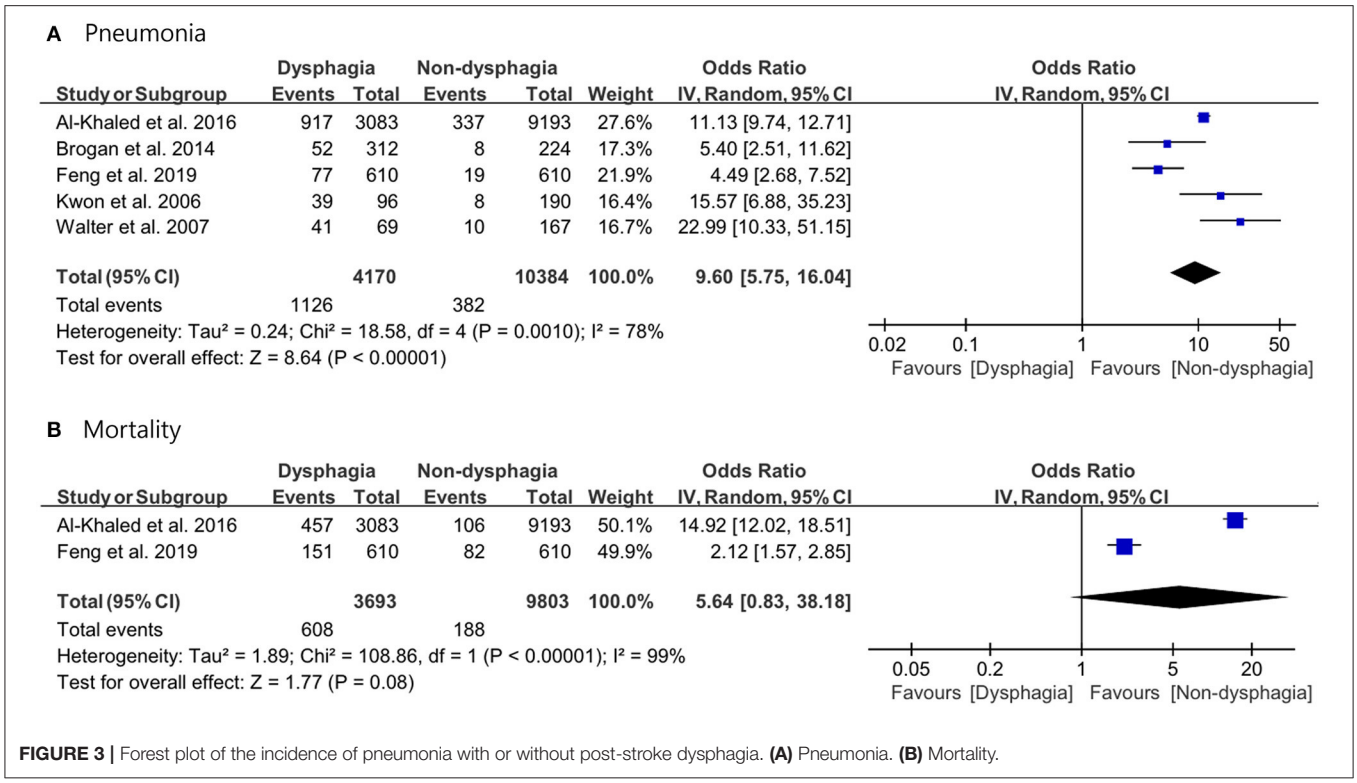


FIGURE 3 | Forest plot of the incidence of pneumonia with or without post-stroke dysphagia. **(A)** Pneumonia. **(B)** Mortality.

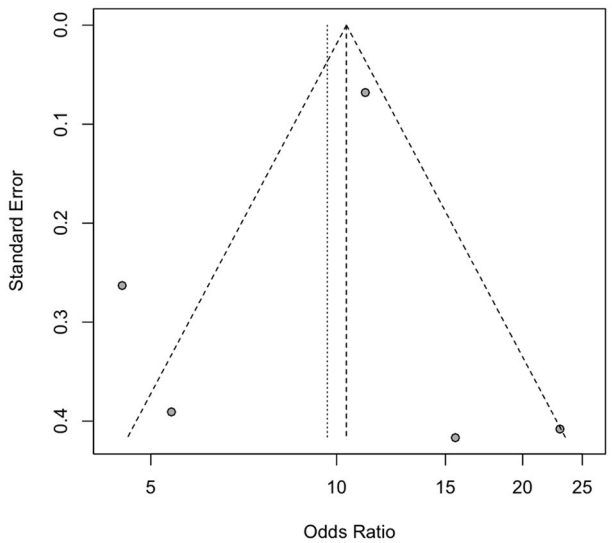


FIGURE 4 | The funnel plot assesses publication bias in the included studies.

and successful swallowing rehabilitation, may help prevent malnutrition and pneumonia in stroke patients (8, 11). Early pneumonia prevention is essential to reduce serious respiratory complications, such as respiratory failure, lung abscess, necrosis, sepsis, and death after stroke (8, 28).

During the acute phase of stroke, the development of pneumonia can be triggered by various factors. It has been hypothesized that stroke-induced immunodeficiency may promote bacterial infections, especially aspiration pneumonia (29). A large number of stroke patients are known to be elderly and immunocompromised (30). The complex relationship between infection and inflammatory responses may exist before and after stroke. A combination of brain-induced immunosuppression, aspiration, and dysphagia may trigger pneumonia in the acute phase after stroke (11). Dysphagia is known as a predisposing factor of aspiration pneumonia especially in elderly or patients with cognitive dysfunction (31). Impaired swallowing function in elderly is associated with physiologic decrement, including reduced tongue driving force, impaired pharyngeal constriction, and pharyngeal shortening. Patients with cognitive dysfunction also manifest dysfunctions in oral phase and pharyngeal phase (32). As most stroke patients were elderly, it may be possible that age and cognitive dysfunction may have led to susceptibility for swallowing dysfunction and post-stroke pneumonia.

Depending on the stroke severity, some patients are dependent on others for care, and some of them may be immobilized. Two studies included in this meta-analysis (20, 21). also demonstrated that a high NIHSS score, which reflects stroke severity, was associated with an increased risk of pneumonia. Decreased mobility may contribute to decreased air entry and impaired drainage of secretions from the lungs, which may result in an increased risk of pneumonia (19). In addition, it has been reported that the risk of aspiration may be high for patients with dysphagia who have a nasogastric tube, which can be associated with alterations in upper airway sensitivity,

glottis injury, and laryngeal muscular dysfunction (21). These findings may explain the close relationship between dysphagia and pneumonia development after stroke.

The mortality rate of patients with dysphagia was not significantly higher compared with that of patients without dysphagia after stroke in this meta-analysis. It is possible that other risk factors of ischemic stroke death, such as hypertension, history of heart disease, consciousness disorders, hyperthermia, hyperglycemia on admission, or urinary tract infection (33), may contribute to the overall mortality rate of stroke patients.

A limitation of this meta-analysis is that the diagnostic criteria were different across studies. Diagnoses of dysphagia and aspiration pneumonia were made based on clinical symptoms and signs and neurologic and physical assessment (8, 18–21). The videofluoroscopic swallowing study is known as the gold standard assessment tool for the diagnosis of dysphagia. The actual incidence of dysphagia can be underestimated with only clinical bedside assessments of swallowing, and the reliability of diagnosis cannot be confirmed. Some studies included in this meta-analysis were performed by retrospectively reviewing medical records (8, 19); thus, the diagnosis of stroke, dysphagia, and pneumonia may not be accurate. Retrospective chart reviews rely on accurate reporting and are subject to errors in documentation (19). Therefore, patients included in these studies might not have been examined thoroughly to ensure that they had dysphagia and aspiration pneumonia. In addition, the relationship of pneumonia and dysphagia may not directly reflect the medical causality and there may be a possibility of false-positive statistical results of this meta-analysis.

CONCLUSION

In conclusion, dysphagia is a significant risk factor for pneumonia after stroke. The early diagnosis and treatment of dysphagia in stroke patients are important to prevent the development of stroke-associated pneumonia. All stroke patients with clinical signs of dysphagia should be thoroughly assessed for dysphagia and should be provided with the appropriate treatment options if necessary. This study is a first step in establishing the evidence for the relationship between dysphagia and pneumonia and demonstrating the benefits of appropriate management of post-stroke dysphagia.

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/s.

AUTHOR CONTRIBUTIONS

MC and SY were responsible for the study concept and design, performed the data extraction and meta-analysis, and wrote the manuscript. KS, YC, MC, and SY completed the study selection and study evaluation. YC and KS reviewed and edited the manuscript. All authors read and approved the final manuscript.

FUNDING

The present study was supported by a National Research Foundation of Korea grant funded by the Korean government (grant no. NRF-2019M3E5D1A02068106).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.834240/full#supplementary-material

REFERENCES

1. Lo WL, Leu HB, Yang MC, Wang DH, Hsu ML. Dysphagia and risk of aspiration pneumonia: a nonrandomized, pair-matched cohort study. *J Dent Sci.* (2019) 14:241–7. doi: 10.1016/j.jds.2019.01.005
2. Xu Z, Gu Y, Li J, Wang C, Wang R, Huang Y, et al. Dysphagia and aspiration pneumonia in elderly hospitalization stroke patients: risk factors, cerebral infarction area comparison. *J Back Musculoskelet Rehabil.* (2019) 32:85–91. doi: 10.3233/BMR-170801
3. de Sire A, Moggio L, Demeco A, Fortunato F, Spanò R, Aiello V et al. Efficacy of rehabilitative techniques in reducing hemiplegic shoulder pain in stroke: systematic review and meta-analysis. *Ann Phys Rehabil Med.* (2021) 65:101602. doi: 10.1016/j.rehab.2021.101602
4. Monteiro KB, Cardoso MDS, Cabral V, Santos A, Silva PSD, Castro JBP, et al. Effects of motor imagery as a complementary resource on the rehabilitation of stroke patients: a meta-analysis of randomized trials. *J Stroke Cerebrovasc Dis.* (2021) 30:105876. doi: 10.1016/j.jstrokecerebrovasdis.2021.105876
5. Cheng I, Sasegbon A, Hamdy S. Effects of pharmacological agents for neurogenic oropharyngeal dysphagia: a systematic review and meta-analysis. *Neurogastroenterol Motil.* (2021) 34:e14220. doi: 10.1111/nmo.14220
6. Meng PP, Zhang SC, Han C, Wang Q, Bai GT, Yue SW. The occurrence rate of swallowing disorders after stroke patients in Asia: a PRISMA-compliant systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* (2020) 29:105113. doi: 10.1016/j.jstrokecerebrovasdis.2020.105113
7. Cho SY, Choung RS, Saito YA, Schleck CD, Zinsmeister AR, Locke, et al. Prevalence and risk factors for dysphagia: a USA community study. *Neurogastroenterol Motil.* (2015) 27:212–9. doi: 10.1111/nmo.12467
8. Feng MC, Lin YC, Chang YH, Chen CH, Chiang HC, Huang LC, et al. The mortality and the risk of aspiration pneumonia related with dysphagia in stroke patients. *J Stroke Cerebrovasc Dis.* (2019) 28:1381–7. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.011
9. Güleç A, Albayrak I, Erdur Ö, Öztürk K, Levendoglu F. Effect of swallowing rehabilitation using traditional therapy, kinesiology taping and neuromuscular electrical stimulation on dysphagia in post-stroke patients: a randomized clinical trial. *Clin Neurol Neurosurg.* (2021) 211:107020. doi: 10.1016/j.clineuro.2021.107020
10. Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke.* (2015) 46:1202–9. doi: 10.1161/STROKEAHA.114.007843
11. Eltringham SA, Kilner K, Gee M, Sage K, Bray BD, Pownall S, et al. Impact of dysphagia assessment and management on risk of stroke-associated pneumonia: a systematic review. *Cerebrovasc Dis.* (2018) 46:99–107. doi: 10.1159/000492730

12. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. *Neurology.* (2003) 60:620–5. doi: 10.1212/01.WNL.0000046586.38284.60
13. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Risk factors for aspiration pneumonia in frail older people: a systematic literature review. *J Am Med Dir Assoc.* (2011) 12:344–54. doi: 10.1016/j.jamda.2010.12.099
14. Wu CC, Huang HH, Lin HH, Chang WK. Oropharyngeal dysphagia increased the risk of pneumonia in patients undergoing nasogastric tube feeding. *Asia Pac J Clin Nutr.* (2020) 29:266–73. doi: 10.6133/apjcn.202007_29(2).0009
15. Teramoto S. The current definition, epidemiology, animal models and a novel therapeutic strategy for aspiration pneumonia. *Respir Investig.* (2022) 60:45–55. doi: 10.1016/j.resinv.2021.09.012
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* (2009) 62:1006–12. doi: 10.1016/j.jclinepi.2009.06.005
17. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res.* (2014) 14:579. doi: 10.1186/s12913-014-0579-0
18. Al-Khaled M, Matthis C, Binder A, Mudter J, Schattschneider J, Pulkowski U, et al. Dysphagia in patients with acute ischemic stroke: early dysphagia screening may reduce stroke-related pneumonia and improve stroke outcomes. *Cerebrovasc Dis.* (2016) 42:81–9. doi: 10.1159/000445299
19. Brogan E, Langdon C, Brookes K, Budgeon C, Blacker D. Respiratory infections in acute stroke: nasogastric tubes and immobility are stronger predictors than dysphagia. *Dysphagia.* (2014) 29:340–5. doi: 10.1007/s00455-013-9514-5
20. Walter U, Knoblich R, Steinhagen V, Donat M, Benecke R, Kloth A. Predictors of pneumonia in acute stroke patients admitted to a neurological intensive care unit. *J Neurol.* (2007) 254:1323–9. doi: 10.1007/s00415-007-0520-0
21. Kwon HM, Jeong SW, Lee SH, Yoon BW. The pneumonia score: a simple grading scale for prediction of pneumonia after acute stroke. *Am J Infect Control.* (2006) 34:64–68. doi: 10.1016/j.ajic.2005.06.011
22. Marin S, Serra-Prat M, Ortega O, Clavé P. Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review. *BMJ Open.* (2020) 10:e031629. doi: 10.1136/bmjopen-2019-031629
23. Schmidt J, Holas M, Halvorson K, Reding M. Videofluoroscopic evidence of aspiration predicts pneumonia and death but not dehydration following stroke. *Dysphagia.* (1994) 9:7–11. doi: 10.1007/BF00262752
24. Panebianco M, Marchese-Ragona R, Masiero S, Restivo DA. Dysphagia in neurological diseases: a literature review. *Neurol Sci.* (2020) 41:3067–73. doi: 10.1007/s10072-020-04495-2
25. Sonies BC. Evaluation and treatment of speech and swallowing disorders associated with myopathies. *Curr Opin Rheumatol.* (1997) 9:486–95. doi: 10.1097/00002281-199711000-00003
26. Pitts T. Airway protective mechanisms. *Lung.* (2014) 192:27–31. doi: 10.1007/s00408-013-9540-y
27. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. *Chest.* (2003) 124:328–36. doi: 10.1378/chest.124.1.328
28. Esposito S, Dal Canto G, Caramia MR, Fainardi V, Pisi G, Principi N. Complications in community acquired pneumonia: magnitude of problem, risk factors, and management in pediatric age. *Expert Rev Anti Infect Ther.* (2021) 20:1–7. doi: 10.1080/14787210.2021.1927710
29. Prass K, Braun JS, Dirnagl U, Meisel C, Meisel A. Stroke propagates bacterial aspiration to pneumonia in a model of cerebral ischemia. *Stroke.* (2006) 37:2607–12. doi: 10.1161/01.STR.0000240409.68739.2b
30. Langdon PC, Lee AH, Binns CW. Dysphagia in acute ischaemic stroke: severity, recovery and relationship to stroke subtype. *J Clin Neurosci.* (2007) 14:630–4. doi: 10.1016/j.jocn.2006.04.009
31. Ji EK, Wang HH, Jung SJ, Lee KB, Kim JS, Hong BY, et al. Is the modified Mann assessment of swallowing ability useful for assessing dysphagia in patients with mild to moderate dementia? *J Clin Neurosci.* (2019) 70:169–72. doi: 10.1016/j.jocn.2019.08.031
32. Ji EK, Wang HH, Jung SJ, Lee KB, Kim JS, Hong BY, et al. The changes for strength of oropharyngeal muscles in patients with dementia and dysphagia. *Brain Neurorehabil.* (2019) 12:e12. doi: 10.12786/bn.2019.12.e12
33. Dabilgou AA, Dravé A, Kyelem JMA, Ouedraogo S, Napon C, Kaboré J. Frequency and mortality risk factors of acute ischemic stroke in emergency department in Burkina Faso. *Stroke Res Treat.* (2020) 2020:9745206. doi: 10.1155/2020/9745206

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.

frontiers in Neurology

MINI REVIEW
published: 31 March 2022
doi: 10.3389/fneur.2022.786648

Transitional and Long-Term Rehabilitation Care System After Stroke in Korea

Ja-Ho Leigh[1,2], *Won-Seok Kim*[3]*, *Dong-Gyun Sohn*[4,5], *Won Kee Chang*[3] and *Nam-Jong Paik*[3]

[1] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, South Korea, [2] National Traffic Injury Rehabilitation Research Institute, National Traffic Injury Rehabilitation Hospital, Yangpyeong-gun, South Korea, [3] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [4] Graduate School of Public Health, Seoul National University, Seoul, South Korea, [5] Medical Rehabilitation Center, Korea Workers' Compensation Welfare Service Incheon Hospital, Incheon, South Korea

Stroke is one of the leading causes of mortality and disability in Korea. Patients who experience stroke require adequate management throughout the acute to subacute and chronic stages. Many patients with long-term functional issues require rehabilitative management even in the chronic stage. A comprehensive rehabilitation and care model for patients who experience stroke is necessary to effectively manage their needs during rehabilitation and allocate medical resources throughout the stages, thus ensuring reduced unmet needs and improved post-stroke quality of life. In Korea, the government and medical specialists are working on re-organizing the rehabilitation care model, including standardized triage and discharge planning after acute stroke treatment, and establishing systematic transitional and long-term rehabilitation care plans. This review briefly introduces the general rehabilitation triage after acute stroke and describes the current transitional and continuous care systems available for these patients in Korea. We also present the issues faced in transitional and long-term care plans of the current system and the efforts invested in resolving them and promoting long-term care in stroke cases.

Keywords: stroke, rehabilitation, transitional care, long-term care, community health service, Korea

OPEN ACCESS

Edited by:
Rocco Salvatore Calabrò, Bonino Pulejo Neurology Center (IRCCS), Italy

Reviewed by:
Seong Hoon Lim, Catholic University of Korea, South Korea

***Correspondence:**
Won-Seok Kim
wondol77@gmail.com

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *30 September 2021*
Accepted: *23 February 2022*
Published: *31 March 2022*

Citation:
Leigh J-H, Kim W-S, Sohn D-G, Chang WK and Paik N-J (2022) Transitional and Long-Term Rehabilitation Care System After Stroke in Korea. Front. Neurol. 13:786648. doi: 10.3389/fneur.2022.786648

INTRODUCTION

Stroke is one of the leading causes of mortality and disability in Korea (1). According to a recent executive summary of stroke statistics in Korea, the incidence of stroke is 232/100,000 persons/year. Mortality due to stroke is gradually decreasing due to early and adequate acute care; nonetheless, stroke remains a public health concern because one in forty adults lives with stroke (1). Approximately 30% of stroke survivors need assistance in their basic daily activities [modified Rankin Scale (mrs) 3 to 5] 3 months after stroke onset; this disability leads to higher costs and worse quality of life (2–4). On including patients who need assistance with their usual duties and activities (mRS 2) or have any stroke-related symptoms (mRS 1), the proportion increases up to 74% (2). Therefore, an adequate individualized rehabilitation plan is mandatory for patients with acute stroke to reduce long-term disabilities and socioeconomic burdens (5, 6). However, the time window for the effect of rehabilitation on functional recovery is limited as survivors reach their

functional plateau 6–12 months after stroke onset (7, 8). Thereafter, they must adapt their lives according to their disabilities.

Patients with stroke have long-term medical and functional problems and need adequate care to address these problems. For instance, patients with stroke in Korea may experience worsening problems in multiple domains associated with health-related quality of life (e.g., mobility, spasticity, pain, mood, communication, cognition, and life after stroke) during follow-up (9). In a recent systematic review of 19 studies on long-term unmet needs after stroke, the median number of self-reported unmet needs ranged from two to five in body functioning, activities/participatory, and environmental domains according to the International Classification of Functioning, Disability, and Health (10), and on an average, 73.8% of the patients reported at least one unmet need (11). Among service needs, unmet needs for information, transport, home help/personal care, and therapy were common (11). At 1 year after stroke, approximately 20% of patients reported unmet needs for rehabilitation services (12). Therefore, after patients with stroke are discharged from the hospital, a transitional and long-term rehabilitation care plan is required to reduce the worsening of various functional domains and fulfill unmet needs to improve post-stroke health-related quality of life.

Countries in the Asia-Pacific region have different strategic plans and public health policies for secondary prevention and rehabilitation after stroke (13). In Korea, the regional cardiocerebrovascular center program consisting of four subcenters in each regional center (cardiovascular, cerebrovascular, rehabilitation, and preventive center) was initiated by the Ministry of Health and Welfare (MOHW) of South Korea to promote the nationwide quality of acute care for patients with cardiovascular and cerebrovascular diseases since 2008 (14). A total of 14 regional cardiocerebrovascular centers have been installed. The rehabilitation center provides early and subacute rehabilitation after stroke and further triages patients to transitional or long-term care programs after inpatient rehabilitation. The Act on the Prevention and Management of Cardio-Cerebrovascular Diseases has been enforced since 2017 to alleviate the personal suffering and social burden resulting from cardiocerebrovascular diseases and promote patients' quality of life (15). A comprehensive management plan for cardiocerebrovascular disease from 2018 to 2022 has also been developed by the MOHW. It includes the agenda to promote appropriate and sufficient rehabilitation and continuous care after stroke (16).

This review briefly introduces the general rehabilitation triage after acute stroke in Korea and then describes the current transitional and continuous care systems available for patients with stroke in Korea. We also discuss the problems with the Korean system and the efforts to address problems and promote long-term care in stroke. By reviewing the current protocol in the country, we can learn from each other how to promote long-term care of stroke survivors and plan clinical research to provide important evidence for stroke care policy.

REHABILITATION AFTER ACUTE STROKE AND TRIAGES

In a comprehensive stroke center or regional cardiocerebrovascular center, stroke survivors are referred to physiatrists during hospitalization to evaluate the functional ability and rehabilitation needs. According to the initial evaluation for rehabilitation, patients who need comprehensive inpatient rehabilitation are usually transferred to a rehabilitation center (**Figure 1**). If the patients are not fully recovered and are not ready to be discharged to their homes after short-term intensive inpatient rehabilitation, they are transferred to long-term rehabilitation hospitals. If a patient has a mild impairment and is neurologically and medically stable at the initial evaluation after acute stroke, they can be discharged and can receive outpatient rehabilitation as per need. According to a report from the Korean Brain Rehabilitation Database from 2007 to 2011 ($n = 5{,}212$ patients from 46 hospitals), the transfer time to the rehabilitation center after stroke onset and length of stay in the rehabilitation center after transfer gradually decreased. The transfer time after stroke onset and median length of hospital stay during 2011 were 30 days and 28 days, respectively (17). The median transfer time after stroke onset was shorter for ischemic strokes (19 days) than for hemorrhagic strokes (35 days) (17). The Korean version of the modified Barthel index gained 18 points during the inpatient rehabilitation period (17). Based on the registry for 11 regional cardiocerebrovascular centers from June 2014 to December 2017, among 17,862 patients with stroke referred for rehabilitation, 3,716 (20.8%) patients were transferred to rehabilitation centers (18). The mean transfer time after stroke onset and length of stay at the rehabilitation center were 10.1 and 22.1 days respectively. Approximately 36% of patients were discharged to home from regional rehabilitation centers (18).

For acute stroke care quality control, the Health Insurance Review and Assessment Service of Korea evaluated nine indicators for care quality grading and fifteen indicators for monitoring in 2018 (19). Among these indicators, there are three rehabilitation-related indicators. The proportion of early assessment for rehabilitation needs within 5 days after admission due to acute stroke is one of the indicators for quality grading; 98% of patients with acute stroke in 242 hospitals received early rehabilitation assessments in 2018. The proportion of patients who received the required rehabilitation during admission among patients assessed as needing rehabilitation in early assessment was 93.7%, and the median number of days from admission to the provision of rehabilitation service was three (19). These results were obtained from the data in tertiary or general hospitals, and it seems that there is a regional discrepancy in these clinical indicators. Therefore, the comprehensive management plan for cardiocerebrovascular disease from 2018 to 2022 in Korea included an agenda to promote early assessments and services for rehabilitation after acute stroke based on the regional and primary cardiocerebrovascular centers (16).

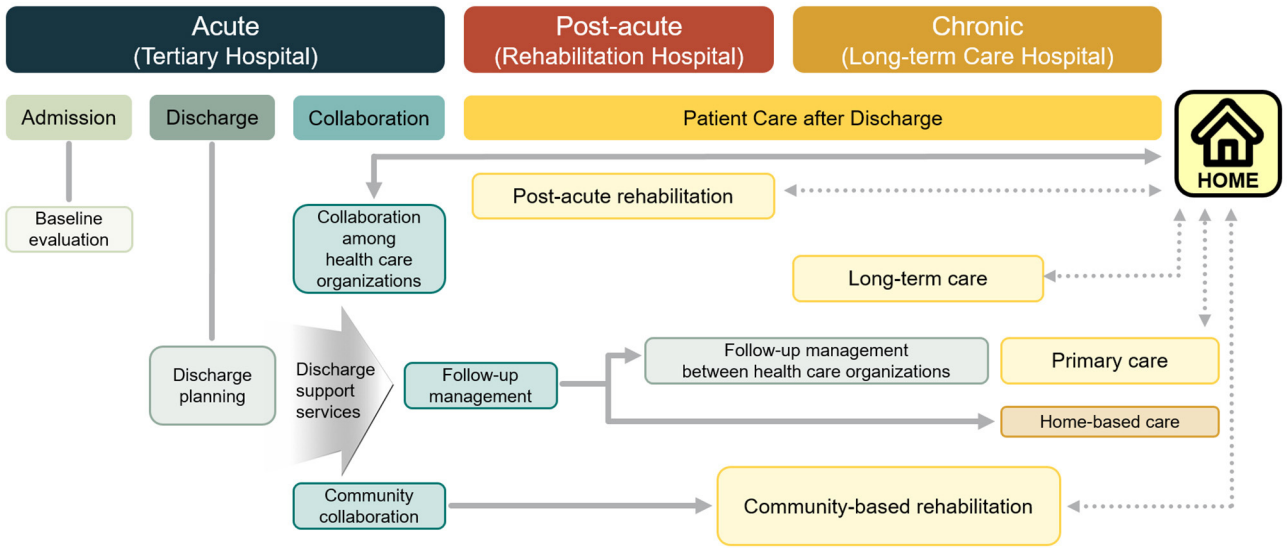


FIGURE 1 | Medical rehabilitation delivery system for patients with stroke.

TRANSITIONAL AND LONG-TERM REHABILITATION CARE SYSTEM

Status of Medical Rehabilitation Providers

Institutions that provide inpatient rehabilitation services for patients with stroke in Korea include tertiary and general hospitals where the department of rehabilitation medicine is established. These facilities also provide outpatient rehabilitation services, while community-based rehabilitation is mainly provided by public community healthcare centers and their collaborators (20). Recently, there has been a shift in the focus of rehabilitation for patients with stroke who have completed acute treatment from acute care hospitals to transitional and long-term care hospitals (LTCHs). In the past decade, the proportion of inpatient rehabilitation services provided by LTCHs has continued to increase. In comparison, outpatient rehabilitation services are still provided by acute care hospitals, indicating poor accessibility to rehabilitation for patients in the subacute and chronic stroke phases (21).

In the last 10 years, from 2007 to 2017, the proportion of inpatient rehabilitation services provided by the tertiary hospitals, general hospitals, and other hospitals decreased from 14.8%, 25.3%, and 29.5% to 5.8%, 10.9%, and 28.8% respectively. While the proportion of that provided by the LTCHs surged from 26.7 to 48.0%. For outpatient rehabilitation, the proportion provided by the tertiary, general, and other hospitals increased, and the proportion provided by LTCHs and primary clinics decreased. This result shows that outpatient rehabilitation services for patients with stroke are not yet institutionalized and enforced in Korea (21).

There is no consensus on the hospitalization period for rehabilitation delivery in Korea. The length of stay (LOS) for patients with stroke tends to be longer in Korea than in other countries. According to a study that used the Multicenter Prospective Observation Study data, the mean LOS, including rehabilitation from stroke onset to home discharge, was 115.6 days (median, 19.4 days) with a positively skewed distribution of LOS (22). Another previous study also showed that the mean LOS of patients with stroke in Korea was 191.5 days (23).

Studies have reported LOS after stroke in Spain (64.1 days), in the United States [16 days (acute inpatient rehab hospital), 28 days (skilled nursing facility)] (24, 25). Although a direct comparison cannot be made, the mean LOS for patients with stroke who were admitted to the rehabilitation wards was 16.8 days (the United States), 22.7 days (China), 24.3 days (Taiwan), 30.8 days (Singapore), 41.7 days (Canada), 54.5–76.3 days (France) (26–31). In Japan, the mean LOS from the time of stroke onset to the home discharge is more than 100 days, which is similar to that of Korea (32).

In addition, there is a lack of service providers who provide stroke rehabilitation services other than those provided in inpatient facilities. The National Health Insurance (NHI) claims data in Korea show that the ratio of inpatient rehabilitation to outpatient rehabilitation or day-patient rehabilitation is 81:19, which means that the proportion of rehabilitation services for patients with stroke in inpatient facilities is overwhelmingly high (33).

Provision of Transitional Rehabilitation and Chronic Long-Term Care Services

Transfer is based on the patient's decision rather than systematically transferring patients according to the post-onset period or severity. Within the NHI system, patients can receive specialized rehabilitation treatment for up to 2 h per day (1 h for physical therapy and another 1 h for occupational therapy) regardless of the type of medical institution for up to 2 years after stroke onset. If the patient wants to receive stroke rehabilitation

services in acute care hospitals, it is also possible to transfer from an acute or subacute care unit to another acute care facility. However, it is common to transfer the patient with stroke to a rehabilitation facility after acute stroke care because if a patient's hospitalization period is longer than the period set for each type of medical institution, the transfer is induced indirectly by deducting the patient's hospitalization fee.

While NHI recognizes the services provided by medical institutions as benefits to patients with stroke, long-term care insurance (LTCI) provides benefits such as physical activity or housework support through home-based and institution-based benefits, and special benefits in cash when patients with stroke need to receive care from their family caregivers (34). The LTCI, like NHI, is based on the social insurance system, and the finances of LTCI operate separately from the NHI. To be covered by LTCI, the patient has to be approved by the LTCI eligibility assessment committee. The introduction of LTCI reduced the burden of medical costs by rationalizing long-term health care utilization (35).

The distribution of institutions that provide rehabilitation services is uneven in Korea. Under such circumstances, a system in which a patient with a stroke can flexibly choose a rehabilitation facility has the advantage of receiving services according to the distribution and characteristics of medical resources in each region. The availability of a free selection of medical institutions also has the advantage of reflecting the preferences of medical consumers as much as possible.

Compared to general hospitals, LTCHs have less disincentive for long-term hospitalization and lack community- or home-based care and rehabilitation services after discharge. As a result, the number of inpatients in long-term care hospitals has increased steadily and tends to lead to long-term hospitalization (36).

LTCHs are rehabilitation service providers for patients with stroke. LTCHs have hospital beds to provide medical services for patients who need long-term hospitalization and are classified as hospitals along the same lines as general hospitals. LTCHs in Korea are required to provide inpatient subacute care to patients with geriatric diseases, chronic illnesses, and those who are recovering from surgery or other injuries, including stroke (37). Instead of a fee-for-service reimbursement method, which is a general payment model for NHI in Korea, LTCHs are reimbursed by the daily charge or per diem fee, depending on the physical or cognitive impairment, severity of behavioral problems, and functional status of patients with stroke. Some items, including specialized rehabilitation treatment, can be paid according to the fee-for-service method.

In Korea, LTCH resources only comprised 12,202 hospital beds in 92 institutions in 2005 but increased about 20 times to 268,084 beds in 1,472 institutions in 2020 (38). Considering that the total number of hospital beds in Korea has doubled over the same period, the increase in the number of beds in LTCHs is highly significant.

Community-based rehabilitation (CBR) has been implemented to provide long-term care for community-dwelling patients with disability (39). To support CBR, fourteen "Regional Health and Medical Center for Persons with Disability" have been established nationwide and the "Physician for the Disabled" system (40). The specific program for long-term rehabilitative care for stroke survivors has been provided under the CBR program, to the legally registered persons with disabilities and preliminary persons with disabilities, only for those who voluntarily visited public health centers. Nevertheless, generalized rehabilitation service in the community setting is yet to be established.

Medical Rehabilitation Delivery System

Comprehensive rehabilitation services for patients with stroke should be available along the continuum of care from the acute stage to the subacute and chronic phases. In general, after completing acute stroke treatment, medical staff, patients, and family caregivers determine whether to discharge the patient or transfer them to a comprehensive inpatient or outpatient rehabilitation facility based on the availability and affordability of informal or formal caregivers and the patient's functional status. When transferring a patient with stroke from a hospital to a rehabilitation facility, the patient and family caregivers must decide on the rehabilitation institution. However, there is no comprehensive or standardized approach to implement transition management protocols that consider patients' severity or medical needs during post-stroke rehabilitation in Korea.

If there is a discharge care team in an acute-stage medical institution, patients with stroke and their families receive help in transferring medical records and collecting hospital information. However, since the establishment of a discharge care team is not the duty of the medical institution, not all patients and caregivers receive systematic and uniform information in the triage scheme process.

For chronic stroke patients, researchers have made several attempts to assess the long-term disabilities and rehabilitative needs of the stroke patients (41, 42). However, there is no standardized assessment method in long-term stroke survivors supported by NHI or LTCI. Currently, the assessment of disability and rehabilitative planning in long-term stroke survivors are performed individually by the doctors.

CHALLENGES AND FUTURE PERSPECTIVES

Considering the status of the service delivery system for stroke rehabilitation in Korea described above, the problems of transitional and long-term care rehabilitation are as follows. First, there is still a lack of differentiation and designation of specialized medical rehabilitation institutions that will be in charge of the transitional phase and patient discharge. Second, patients are hospitalized for a long time in LTCHs because of a lack of outpatient rehabilitation services and home-based services in the local community and a bias toward inpatient rehabilitation treatment rather than outpatient services. Finally, the transfer for post-stroke rehabilitation or discharge after acute stroke treatment is not planned systematically.

The Korean government has undertaken three pilot projects and plans outlined below (**Figure 2**) to solve this problem.

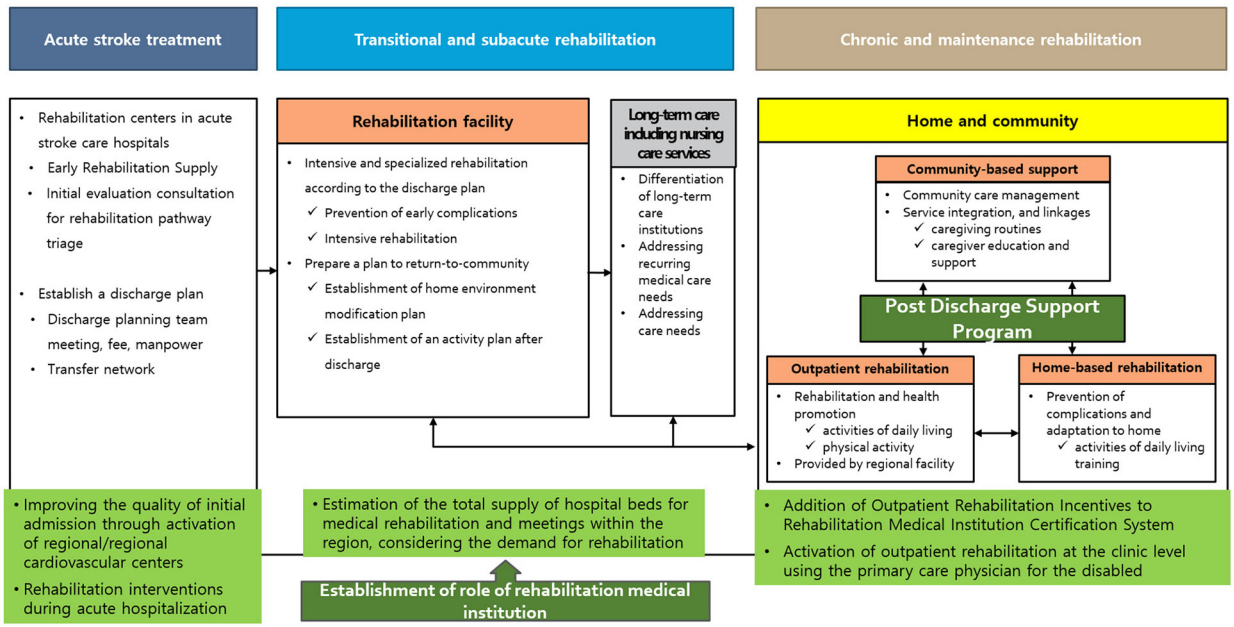


FIGURE 2 | Model of the medical rehabilitation supply system [adopted from (21)].

Designation of Medical Rehabilitation Institutions and Continuous Management of Outcome Indicators

Since 2020, hospitals with a certain level of quality have been designated as medical rehabilitation institutions so that intensive rehabilitation treatment is possible during the functional recovery period. A long-term care hospital can be designated as a secondary hospital after the conversion. The plan is to simultaneously increase the amount of rehabilitation treatment provided and incentives for the fee in these designated hospitals and recognize the fee related to discharge. In addition, pilot projects related to rehabilitation and social return centered on these medical rehabilitation institutions are planned. The outcome is scheduled to be evaluated and re-designated every 3 years, and by 2025, the project is planned to expand these resources to include 25,000 beds in 150 hospitals (43).

Activation of Outpatient Rehabilitation Service, Development of Home-Based Rehabilitation Service, and Designation of a Physician for the Disabled

Since 2019, the "Physician for the Disabled" system that treats patients with disabilities in the chronic phase, including stroke survivors, has been implemented, and incentives for counseling and treatment are provided to medical staff. After the COVID-19 pandemic, the number of care plans has increased in the pilot project for doctors who treat patients with disabilities. Moreover, non-face-to-face patient management services have been established and operated to facilitate home visitation. Lastly, standardized assessments of long-term disability and rehabilitative needs and planning of rehabilitative management are warranted to reduce the burden of disability in survivors with chronic stroke.

Operation of a Pilot Project to Establish a Rehabilitation Delivery System

A pilot project was started in 2021 to comprehensively evaluate the patient's condition on discharge from a general hospital-level medical institution to establish a system that enables a smooth return to the local community through an appropriate discharge plan. By designating representative tertiary hospitals, medical rehabilitation institutions, and long-term care hospitals in 19 districts in Korea, the patient linkage process was operationalized and service fees were determined for all processes such as consultation, conferences, and education.

CONCLUSION

Stroke care and rehabilitation requires a well-organized comprehensive model from acute stage to chronic stage with a standardized delivery system and proper allocation of medical resources. The current Korean medical practice for stroke rehabilitation is focused on inpatient rehabilitation and lacks the use of a systematic transitional care model including standardized triage system and relay of patients from acute inpatient rehabilitation to chronic community-based rehabilitation. Further, insufficient long-term community and outpatient rehabilitation resources contributes to unmet needs during long-term rehabilitation and care for patients with stroke. The Korean government and specialists are trying to address these problems by establishing standardized rehabilitation delivery system, developing and monitoring the outcome indicators of rehabilitative management

and developing pilot projects to promote outpatient or community-based rehabilitation.

AUTHOR CONTRIBUTIONS

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

FUNDING

This work was supported by the Research Program funded by the Korea National Institute of Health (2020ER630602), Rehabilitation Research & Development Support Program (#NRC RSP-2019017), National Rehabilitation Center, Ministry of Health and Welfare, Korea.

REFERENCES

1. Kim JY, Kang K, Kang J, Koo J, Kim DH, Kim BJ, et al. Executive summary of stroke statistics in Korea 2018: a report from the epidemiology research council of the Korean stroke society. *J Stroke.* (2019) 21:42–59. doi: 10.5853/jos.2018.03125
2. Kim SE, Lee H, Kim JY, Lee KJ, Kang J, Kim BJ, et al. Three-month modified rankin scale as a determinant of 5-year cumulative costs after ischemic stroke: an analysis of 11,136 patients in Korea. *Neurology.* (2020) 94:e978–91. doi: 10.1212/WNL.0000000000011295
3. Kwon S, Park JH, Kim WS, Han K, Lee Y, Paik NJ. Health-related quality of life and related factors in stroke survivors: data from Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2014. *PLoS ONE.* (2018) 13:e0195713. doi: 10.1371/journal.pone.0195713
4. Jang MU, Kang J, Kim BJ, Hong JH, Yeo MJ, Han MK, et al. In-hospital and post-discharge recovery after acute ischemic stroke: a nationwide multicenter stroke registry-base study. *J Korean Med Sci.* (2019) 34:e240. doi: 10.3346/jkms.2019.34.e240
5. Kim DY, Kim Y-H, Lee J, Chang WH, Kim M-W, Pyun S-B, et al. Clinical practice guideline for stroke rehabilitation in Korea 2016. *Brain Neurorehabil.* (2017) 10(Suppl 1). doi: 10.12786/bn.2017.10.e11
6. Chang WH, Sohn MK, Lee J, Kim DY, Lee S-G, Shin Y-I, et al. Role of intensive inpatient rehabilitation for prevention of disability after stroke: the Korean Stroke Cohort for Functioning and Rehabilitation (KOSCO) Study. *Brain Neurorehabil.* (2016) 9:e4. doi: 10.12786/bn.2016.9.e4
7. Winters C, Kwakkel G, van Wegen EEH, Nijland RHM, Veerbeek JM, Meskers CGM. Moving stroke rehabilitation forward: the need to change research. *NeuroRehabilitation.* (2018) 43:19–30. doi: 10.3233/NRE-172393
8. Horgan NF, O'Regan M, Cunningham CJ, Finn AM. Recovery after stroke: a 1-year profile. *Disabil Rehabil.* (2009) 31:831–9. doi: 10.1080/09638280802355072
9. Im HW, Kim WS, Kim S, Paik NJ. Prevalence of worsening problems using post-stroke checklist and associations with quality of life in patients with stroke. *J Stroke Cerebrovasc Dis.* (2020) 29:105406. doi: 10.1016/j.jstrokecerebrovasdis.2020.105406
10. Ustün TB, Chatterji S, Bickenbach J, Kostanjsek N, Schneider M. The international classification of functioning, disability and health: a new tool for understanding disability and health. *Disabil Rehabil.* (2003) 25:565–71. doi: 10.1080/0963828031000137063
11. Chen T, Zhang B, Deng Y, Fan JC, Zhang L, Song F. Long-term unmet needs after stroke: systematic review of evidence from survey studies. *BMJ Open.* (2019) 9:e028137. doi: 10.1136/bmjopen-2018-028137
12. Ullberg T, Zia E, Petersson J, Norrving B. Perceived unmet rehabilitation needs 1 year after stroke: an observational study from the Swedish stroke register. *Stroke.* (2016) 47:539–41. doi: 10.1161/STROKEAHA.115.011670
13. Unit TEI. *The Cost of Inaction:Secondary Prevention of Cardiovascular Disease in Asia-Pacific*. Unit TEI (2020).
14. Kim J, Hwang YH, Kim JT, Choi NC, Kang SY, Cha JK, et al. Establishment of government-initiated comprehensive stroke centers for acute ischemic stroke management in South Korea. *Stroke.* (2014) 45:2391–6. doi: 10.1161/STROKEAHA.114.006134
15. *Act on the Prevention and Management of Cardio-Cerebrovascular Diseases (Act No. 14217)* (2016).
16. Ministry of Health and Welfare. *The Comprehensive Management Plan for Cardiocerebrovascular Disease from 2018 to 2022.* Ministry of Health and Welfare (2018).
17. Joa KL, Han TR, Pyun SB, Rah UW, Park JH, Kim YH, et al. Inpatient stroke rehabilitation outcomes in Korea derived from the Korean brain rehabilitation centers' online database system for the years 2007 to 2011. *J Korean Med Sci.* (2015) 30:644–50. doi: 10.3346/jkms.2015.30.5.644
18. Ministry of Health and Welfare. *Regional Cardiocerebrovascular Center*. Ministry of Health and Welfare (2018).
19. Health Insurance Review & Assessment Service. *The Report for 8th Acute Stroke Care Quality Assessment*. Health Insurance Review & Assessment Service (2020).
20. Kim WH, Park YG, Shin HI, Im SH. The world report on disability and recent developments in South Korea. *Am J Phys Med Rehabil.* (2014) 93(Suppl. 1):S58–62. doi: 10.1097/PHM.0000000000000024
21. National Health Insurance Service. *Developing a model for an improved medical care supply system.* (2019). Available online at: http://www.alio.go.kr/download.dn?fileNo=2514663 (accessed July 11, 2021) (Korean).
22. Kang JH, Bae HJ, Choi YA, Lee SH, Shin HI. Length of hospital stay after stroke: a Korean nationwide study. *Ann Rehabil Med.* (2016) 40:675–81. doi: 10.5535/arm.2016.40.4.675
23. Jung SH, Lee KM, Park SW, Chun MH, Jung HY, Kim IS, et al. Inpatient course and length of hospital stay in patients with brain disorders in South Korea: a population-based registry study. *Ann Rehabil Med.* (2012) 36:609–17. doi: 10.5535/arm.2012.36.5.609
24. García-Rudolph A, Cegarra B, Opisso E, Tormos JM, Bernabeu M, Saurí J. Predicting length of stay in patients admitted to stroke rehabilitation with severe and moderate levels of functional impairments. *Medicine.* (2020) 99:e22423. doi: 10.1097/MD.0000000000022423
25. Main Line Health. *Acute Inpatient Rehab Hospital vs. Skilled Physician for the Disabled Facility* Available online at: https://www.mainlinehealth.org/specialties/rehab/inpatient/snf-vs-acute-rehab (accessed September 27, 2021).
26. Camicia M, Wang H, DiVita M, Mix J, Niewczyk P. Length of stay at inpatient rehabilitation facility and stroke patient outcomes. *Rehabil Nurs.* (2016) 41:78–90. doi: 10.1002/rnj.218
27. Zhang X, Qiu H, Liu S, Li J, Zhou M. Prediction of prolonged length of stay for stroke patients on admission for inpatient rehabilitation based on the international classification of functioning, disability, and health (ICF) generic set: a study from 50 centers in China. *Med Sci Monit.* (2020) 26:e918811. doi: 10.12659/MSM.918811
28. Hung CY, Wu WT, Chang KV, Wang TG, Han DS. Predicting the length of hospital stay of post-acute care patients in Taiwan using the Chinese version of the continuity assessment record and evaluation item set. *PLoS ONE.* (2017) 12:e0183612. doi: 10.1371/journal.pone.0183612
29. Tan WSM, Heng BHMMF, Chua KS, Chan KF. Factors predicting inpatient rehabilitation length of stay of acute stroke patients in Singapore. *Arch Phys Med Rehabil.* (2009) 90:1202–7. doi: 10.1016/j.apmr.2009.01.027
30. Grant CMD, Goldsmith CHP, Anton HA. Inpatient stroke rehabilitation lengths of stay in Canada derived from the national rehabilitation reporting system, 2008 and 2009. *Arch Phys Med Rehabil.* (2014) 95:74–8. doi: 10.1016/j.apmr.2013.08.014
31. Cassoudesalle H, Nozères A, Petit H, Cressot V, Muller F, Rouanet F, et al. Post-acute referral of stroke victims in a French urban area: results of a specific program. *Ann Phys Rehabil Med.* (2016) 59:248–54. doi: 10.1016/j.rehab.2016.02.003
32. Murata K, Hinotsu S, Sadamasa N, Yoshida K, Yamagata S, Asari S, et al. Healthcare resource utilization and clinical outcomes associated with acute

care and inpatient rehabilitation of stroke patients in Japan. *Int J Qual Health Care.* (2017) 29:26–31. doi: 10.1093/intqhc/mzw127
33. National Health Insurance Service. *Reform strategies for healthcare delivery system in Korea.* (2020). Available online at: http://www.alio.go.kr/download.dn?fileNo=2607762 (accessed July 11, 2021) (Korean).
34. National Health Insurance Service. *Insurance benefit of LTCI.* Available online at: https://www.nhis.or.kr/static/html/wbd/g/a/wbdga0503.html (accessed July 11, 2021).
35. Kim SH, Kim DH, Kim WS. Long-term care needs of the elderly in Korea and elderly long-term care insurance. *Soc Work Public Health.* (2010) 25:176–84. doi: 10.1080/19371910903116979
36. Choi JW, Park EC, Lee SG, Park S, Ryu HG, Kim TH. Does long-term care insurance reduce the burden of medical costs? A retrospective elderly cohort study. *Geriatr Gerontol Int.* (2018) 18:1641–6. doi: 10.1111/ggi.13536
37. Ga H. Long-term care system in Korea. *Ann Geriatr Med Res.* (2020) 24:181–6. doi: 10.4235/agmr.20.0036
38. Ministry of the Interior and Safety. Korea city statistics: the number of medical institutions and hospital beds. Available online at: https://kosis.kr/statisticsList/statisticsListIndex.do?parentId=B.1&vwcd=MT_ZTITLE&menuId=M_01_01#content-group (accessed July 11, 2021) (Korean).
39. Kim YH, Jo NK. Community-based rehabilitation in South Korea. *Disabil Rehabil.* (1999) 21:484–9. doi: 10.1080/096382899297297
40. National Rehabilitation Center. *Support by Regional Health & Medical Centers for Persons with Disabilities.* Available online at: http://www.nrc.go.kr/eng/html/content.do?depth=n_cc&menu_cd=03_06 (accessed January 31, 2022)
41. Chang WH, Sohn MK, Lee J, Kim DY, Lee SG, Shin YI, et al. Long-term functional outcomes of patients with very mild stroke: does a NIHSS score of 0 mean no disability? An Interim Analysis of the KOSCO. *Study Disabil Rehabil.* (2017) 39:904–10. doi: 10.3109/09638288.2016.1170214
42. Kim KT, Chang WK, Jung YS, Jee S, Sohn MK, Ko SH, et al. Unmet needs for rehabilitative management in common health-related problems negatively impact the quality of life of community-dwelling stroke survivors. *Front Neurol.* (2021) 12:758536. doi: 10.3389/fneur.2021.758536
43. Ministry of Health and Welfare. Medical institution policy: designated as a medical rehabilitation institution. Available online at: http://www.mohw.go.kr/react/policy/index.jsp?PAR_MENU_ID=06&MENU_ID=06290301&PAGE=1&topTitle= (accessed July 11, 2021) (Korean).

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: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 08 April 2022
doi: 10.3389/fneur.2022.698439

Safety and Efficacy of Early Rehabilitation After Stroke Using Mechanical Thrombectomy: A Pilot Randomized Controlled Trial

Wei Wang[1,2†], Ming Wei[3†], Yuanyuan Cheng[4], Hua Zhao[4], Hutao Du[4], Weijia Hou[4], Yang Yu[4], Zhizhong Zhu[4], Lina Qiu[2], Tao Zhang[5] and Jialing Wu[2]*

[1] Clinical College of Neurology, Neurosurgery and Neurorehabilitation, Tianjin Medical University, Tianjin, China, [2] Tianjin Key Laboratory of Cerebral Vascular and Neurodegenerative Diseases, Department of Neurorehabilitation and Neurology, Tianjin Neurosurgical Institute, Tianjin Huanhu Hospital, Tianjin, China, [3] Department of Neurosurgery, Tianjin Huanhu Hospital, Tianjin, China, [4] Department of Rehabilitation, Tianjin Huanhu Hospital, Tianjin, China, [5] Department of Intensive Care Unit, Tianjin Huanhu Hospital, Tianjin, China

OPEN ACCESS

Edited by:
Surjo R. Soekadar, Charité Universitätsmedizin Berlin, Germany

Reviewed by:
Domenico Antonio Restivo, Garibaldi Hospital, Italy
Xiaochuan Huo, Capital Medical University, China

****Correspondence:***
Jialing Wu
wywjl2009@hotmail.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *21 April 2021*
Accepted: *18 February 2022*
Published: *08 April 2022*

Citation:
Wang W, Wei M, Cheng Y, Zhao H, Du H, Hou W, Yu Y, Zhu Z, Qiu L, Zhang T and Wu J (2022) Safety and Efficacy of Early Rehabilitation After Stroke Using Mechanical Thrombectomy: A Pilot Randomized Controlled Trial. Front. Neurol. 13:698439. doi: 10.3389/fneur.2022.698439

Background: Early rehabilitation (ER) has been reported to be both safe and feasible for patients' post-stroke. To date, however, ER-related outcomes concerning patients who have undergone mechanical thrombectomy (MT) have not been investigated. This study aimed to determine the feasibility of ER and whether it improves prognosis in such patients.

Methods: In this single-center, double-blinded, randomized controlled study involving 103 patients who met the study criteria (i.e., has undergone MT), we randomly divided patients (1:1) into ER and conventional rehabilitation groups. The primary outcome was mortality, while secondary outcomes included favorable outcomes (modified Rankin scale of 0–2), the incidence of non-fatal complications, and Barthel Index (BI) scores. We assessed outcomes at 3 months and 1-year post-stroke.

Results: No significant between-group differences were found in terms of mortality and favorable outcomes at 3 months and 1-year post-stroke. At 3 months, 15 (28.8%) patients in the ER group and 29 (56.9%) in the conventional rehabilitation group ($p = 0.002$) had non-fatal complications. The BI in the ER and conventional rehabilitation groups was 100 (85–100) and 87.5 (60–100), respectively, ($p = 0.007$). At 1 year, the incidence of non-fatal complications was similar between both groups [BI in the ER group, 100 (90–100), $p = 0.235$; BI in the conventional rehabilitation group, 90 (63.8–100); $p = 0.003$].

Conclusion: Early rehabilitation (ER) reduces the incidence of early immobility-related complications and effectively improves patients' activities of daily living on a short- and long-term basis. Our results indicate that MT contributes to ER in patients with stroke.

Clinical Trial Registration: www.chictr.org.cn, identifier: ChiCTR1900022665.

Keywords: ischemic stroke, early rehabilitation, mobilization, mechanical thrombectomy, safety, efficacy

INTRODUCTION

Ischemic stroke accounts for 80% of cerebrovascular diseases, and cerebral infarction due to large vessel occlusion has a high fatality and disability rate. In total, 60–80% of patients with ischemic stroke die, have functional dependence despite alteplase treatment, or experience limited treatment efficacy because of low recanalization rates (1–3). In recent years, mechanical thrombectomy (MT) has been actively recommended in randomized controlled trials as the most effective treatment for acute ischemic stroke with large vessel occlusion (4–8). Despite the significant decrease in the mortality of patients undergoing MT, almost 50% present with varying degrees of neurological dysfunction, requiring functional rehabilitation (4, 5).

Rehabilitation is the key treatment to obtain a good functional prognosis in patients with stroke. Early rehabilitation (ER) is recommended in international clinical management guidelines for acute ischemic stroke (6, 7). Despite this, it still remains controversial in practice (8, 9) due to insufficiently conclusive clinical evidence. It has been reported that ER within 24 h of stroke onset did not increase the odds of a favorable outcome, nor did it have a negative effect on mortality rates (10–12). However, it has been reported that ER can reduce the incidence of severe complications, shorten the length of hospital stay for patients with stroke, and improve their ability to perform activities of daily living (13), all of which benefit patients in stroke care units (14).

Early rehabilitation (ER) is unlikely to have an extremely negative effect on stroke outcomes (15). Evidence suggests that ER is feasible for patients admitted to intensive care units and for those with cerebral hemorrhage to improve their functional independence (16–18). At present, there is a lack of research on ER interventions in patients with MT. Consequently, there is a need to assess the safety and efficacy of ER in such patients. We hypothesized that ER within 48 h after stroke onset was feasible and that it would improve functional outcomes for patients with MT at 3-month and 1-year follow-ups.

METHODS AND MATERIALS

Study Design and Patients

A prospective, single-center, randomized controlled study was performed in two groups who were followed up at 3 months and at 1 year with a blind outcome assessment. In total, we enrolled 103 patients with MT who attended our institution from April to September 2019. The study was registered with the Chinese Clinical Trial Registry (Clinical Trial Registration No. ChiCTR1900022665) and was approved by the Ethics Committee of the Tianjin Huanhu Hospital. After patients had been assured of their right to decline participation in our study or withdraw from our study at any time, all participating patients signed an informed consent form.

Abbreviations: BI, Barthel Index; CI, confidence interval; CRG, conventional rehabilitation group; ER, Early rehabilitation; ERG, early rehabilitation group; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; MT, mechanical thrombectomy; OR, odds ratio; RR, relative risk.

Inclusion criteria comprised of patients: (i) aged >18 years; (ii) with a history of stroke with an accompanying neurological deficit, confirmed using magnetic resonance imaging (MRI) or computed tomography (CT) scans; (iii) able to undergo MT; (iv) who had a modified Rankin scale (mRS) score <3 prior to the occurrence of stroke; (v) who could understand and execute therapy instructional programs; and (vi) who had no contraindications in terms of commencing rehabilitation within 48 h post-stroke. Exclusion criteria comprised those: (i) unable to undergo cooperative rehabilitation therapy due to severe aphasia, unconsciousness, or cognitive deficits; (ii) with progressive stroke [National Institute of Health Stroke Scale (NIHSS) score that increased ≥4 points 24 h postoperatively]; (iii) with postoperative symptomatic intracranial hemorrhage or massive infarction with midline shift; (iv) with unstable vital signs; (v) with other medical conditions preventing early mobilization, such as severe heart disease, fracture, or other disorders; and (vi) enrolled in another intervention trial or those who declined to provide written informed consent to participate in the study.

Enrolled patients were randomly assigned in a 1:1 manner to an early rehabilitation group (ERG) and a conventional rehabilitation group (CRG) according to a random computer-generated code. Mortality, non-fatal complications, the number of favorable outcomes (mRS, 0–2), and Barthel Index (BI) scores were assessed at 3 months and at 1 year follow-up.

Intervention

The start time and the plans for rehabilitation intervention differed between the two groups. The CRG group underwent routine rehabilitation treatment only in the stroke unit. Routine rehabilitation was initiated when a patient's condition was relatively stable ≥48 h post-stroke. Routine rehabilitation activities included correct bed positioning, passive and active mobilization in bed, sitting balanced-limb control activities, and activities of daily living. Early out-of-bed mobilization and routine rehabilitation training in the stroke care unit were performed for patients in the ERG. The first out-of-bed activities were started as soon as possible (within 48 h of stroke symptom onset). The following out-of-bed activities were implemented in the ERG: supported or unsupported sitting, transfer with or without assistance, standing, and transfer of feet activities. This group received out-of-bed mobilization therapy for a minimum of 5–10 min per session, with four sessions per day (depending on the patient's tolerance) for ≥4 days a week until discharge. Vital signs were closely monitored during the out-of-bed procedures. Both groups received routine rehabilitation for 30–40 min daily until discharge.

Routine monitoring was continued for the first 3 days. If a patient's vital signs were unstable or if neurological function deteriorated during out-of-bed activities, then the patient was laid flat on the bed and activities were immediately stopped. The program was developed by specialized rehabilitation physicians, while patient instructions and education were provided by specialized rehabilitation therapists and nurses. The patients were unaware of their grouping. The rehabilitation treatment process was supervised by a rehabilitation therapist and a nurse to minimize medical risks.

Baseline Data

Baseline patient characteristics were collected, including age, sex, risk factors for stroke (hypertension, diabetes mellitus, cardiovascular disease, atrial fibrillation, cerebral infarction, smoking, and alcohol consumption), the NIHSS score, premorbid disability, and stroke type. Stroke severity was classified as mild (NIHSS score, <8), moderate (NIHSS score, 8–16), or severe (NIHSS score, >16) (19). The time to first mobilization, total amount of mobilization, and time spent in hospital were also recorded.

Outcomes

The primary outcome was the mortality rate. Secondary outcomes included the number of patients with a favorable outcome (mRS, 0–2), the incidence of non-fatal complications, and the BI score. mRS usually ranges from 0 to 5, with a score of 6 indicating death. We defined a favorable outcome as an mRS of 0–2 (no/minimal disability) and poor outcomes as an mRS between 3 and 6 (moderate or severe disability, or death). Complications included immobility-related and neurological complications. Immobility-related complications included pneumonia, deep vein thrombosis, urinary tract infection, pulmonary embolism, and neurological progressive and recurrent stroke. Activities of daily living were measured using the BI. BI scores ≥85 were defined as indicating mild dependance or independence (20). Blinded evaluation of both primary and secondary outcomes was undertaken by trained research staff.

Statistical Analysis

We analyzed data concerning all patients who completed the protocols and the follow-ups. Descriptive statistics were used to analyze all baseline and clinical characteristics. A chi-square test was used to compare differences in categorical variables, a *t*-test was used to compare parametric continuous variables, and a Mann-Whitney *U* test was used to compare non-parametric continuous variables. Logistic regression analysis was used to investigate whether the intervention influenced outcomes at 3 months and at 1 year (adjusted for age, premorbid mRS score, and baseline NIHSS score). All analyses were performed using Statistical Package for Social Science 20.0 (IBM SPSS, Inc., Chicago, IL, USA) software. Statistical significance was set at $p < 0.05$.

RESULTS

Between April 2019 and September 2019, 168 patients had undergone MT evaluation, of whom 54 patients did not meet the study inclusion criteria due to postoperative bleeding ($n = 16$), massive infarction with midline shift ($n = 9$), conscious disturbances ($n = 12$), unstable vital signs ($n = 9$), severe aphasia ($n = 3$), progressive stroke ($n = 5$), and limb disease ($n = 2$). Nine patients declined to participate in the study. In total, 103 patients were recruited (**Figure 1**).

The enrolled patients were randomly assigned into two groups, namely, the ERG and the CRG ($n = 52$ and $n = 51$ patients, respectively). Baseline characteristics between the groups were similar (**Table 1**). Patients in the ERG commenced mobilization soon after randomization at a median of 42 h (range, 20–48 h) after stroke onset, whereas mobilization in the CRG commenced at a median of 101 h (range, 53–216 h) after stroke onset. This particular between-group difference was significant ($p < 0.001$, **Table 2**). The time of first mobilization was earlier than 60 h for only two patients in the CRG. The average hospital stay was 11 (range, 7–14) days for the ERG and 15 (9–19) days for the CRG ($p = 0.002$, **Table 2**). The total duration of mobilization in the ERG was 350 (225–480) min and 240 (150–330) min in the CRG ($p < 0.001$, **Table 2**).

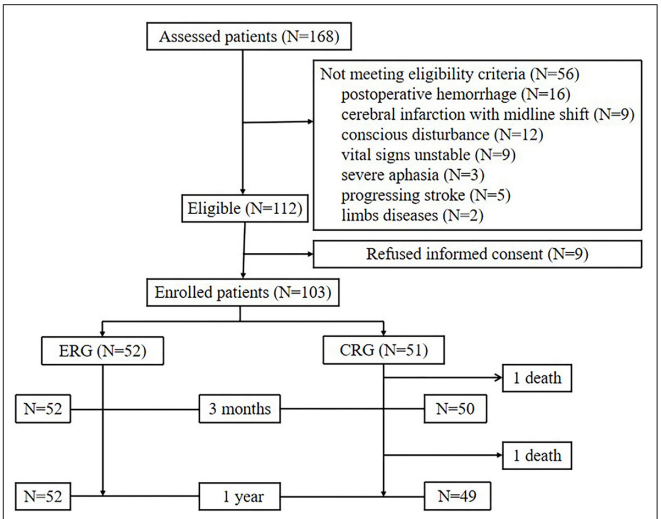


FIGURE 1 | Study profile. ERG, early rehabilitation group; CRG, conventional rehabilitation group.

Mortality

None of the 52 patients in the ERG died (0%), and only 1 (2%) of 51 patients in the CRG died due to progressive stroke that occurred after 3 months ($p = 0.997$). Similarly, at the 1-year follow-up, there were no deaths in the ERG and only 1 (2%) death among 50 patients in the CRG due to recurrent stroke ($p = 0.999$, **Tables 3**, **4**).

mRS

Favorable outcomes did not differ significantly between the two groups at the 3-month follow-up [odds ratio (OR) 1.941, 95% confidence interval (CI) 0.830–4.541; $p = 0.126$] or at the 1-year follow-up (OR 2.018, 95% CI.771–5.283; $p = 0.153$). However, the percentage of patients with favorable outcomes (mRS, 0–2) was higher in the ERG at the 3-month follow-up (73.1 vs. 56.9%), and this difference between the groups was maintained at the 1-year follow-up (82.7 vs. 66%, **Tables 3**, **4**). The assumption-free ordinal analysis showed a significant difference between the groups across all mRS scores (0–6, **Figure 2**).

TABLE 1 | Baseline characteristics of enrolled patients.

	ERG ($n = 52$)	CRG ($n = 51$)	*P*-value
Age (years)	58 (48–66.8)	62 (55–69)	0.077
≤65	37 (71.2)	34 (66.7)	0.247
>65	15 (28.8)	17 (33.3)	
Sex, male	41 (78.8)	42 (82.4)	0.653
Stroke risk factors			
Hypertension	29 (55.8)	36 (70.6)	0.119
Diabetes mellitus	9 (17.3)	13 (25.5)	0.311
Cardiovascular disease	9 (17.3)	11 (21.6)	0.626
Atrial fibrillation	6 (11.5)	7 (13.7)	0.738
Previous stroke or TIA	3 (5.8)	7 (13.7)	0.173
Smoking	35 (67.3)	32 (62.7)	0.682
Alcoholics	26 (50)	23 (45.1)	0.695
NIHSS score	10 (7.25–12.75)	12 (8–17)	0.123
0–7	13 (25)	11 (21.6)	
8–16	28 (53.8)	26 (51)	
>16	11 (21.2)	14 (27.4)	
NIHSS score after MT	8 (5–10.75)	8 (6–12)	0.234
0–7	20 (38.5%)	19 (37.3)	
8–16	28 (53.8%)	27 (52.9%)	
>16	4 (7.7%)	5 (9.8%)	
rtPA treatment (yes)	50 (96.2)	50 (98)	0.569
Pre-morbid mRS	0 (0–0)	0 (0–0)	0.677
0	49 (94.2)	47 (92.2)	
1	3 (5.8)	4 (7.8)	
2	0 (0)	0 (0)	
Stroke type			0.311
anterior circulation infarct	43 (82.7)	38 (74.5)	
posterior circulation infarct	9 (17.3)	13 (25.5)	

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; rtPA, tissue plasminogen activator; TIA, transient ischemic attack; mRS, modified Rankin Scale.
Data are expressed as medians (IQR) and n (%).

TABLE 2 | Intervention summary and average days of hospitalization in both groups.

	ERG	CRG	*P*-value
Time to first mobilization (h)	42 (20–48)	101 (53–216)	<0.001
Total amount of mobilization (min)	350 (225–480)	240 (150–330)	<0.001
Days in hospital (d)	11 (7–14)	15 (9–19)	0.002

CRG, conventional rehabilitation group; d, days; ERG, early rehabilitation group; h, hours; IQR, interquartile range; min, minutes.
Data are expressed as medians (IQR).

Non-fatal Complications

At the 3-month follow-up, there was a significant between-group difference in the number of patients who experienced non-fatal complications in the earlier period of their rehabilitation treatment course. Non-fatal complications occurred in 15 (28.8%) patients in the ERG and in 29 (56.9%) patients in the CRG (OR 3.740, 95% CI 1.604–8.718; $p = 0.002$, **Table 3**). Immobility-related complications also significantly differed between groups. An in-depth description of the development of immobility-related and neurological complications is shown in **Table 3**. At the 1-year follow-up, recurrent stroke complications occurred in 3 (5.8%) and 7 (14%) patients in the ERG and CRG, respectively (OR 2.421, 95% CI 0.563–10.422; $p = 0.235$, **Table 4**).

TABLE 3 | Outcomes at 3-months.

	ERG ($n = 52$)	CRG ($n = 51$)	OR (95% CI)	*P*-value
Primary outcome				
Mortality	0 (0)	1 (2)		0.997
Secondary outcomes				
Favorable outcome (mRS 0–2)	38 (73.1)	29 (56.9)	1.941 (0.830–4.541)	0.126
mRS category				
0	19 (36.5)	11 (21.6)		
1	15 (28.8)	14 (27.5)		
2	4 (7.7)	4 (7.8)		
3	12 (23.1)	10 (19.6)		
4	1 (1.9)	8 (15.7)		
5	1 (1.9)	3 (5.9)		
6	0 (0)	1 (2.0)		
Non-fatal complications	15 (28.8)	29 (56.9)	3.740 (1.604–8.718)	0.002
Pulmonary infection	8 (15.4)	18 (35.3)	2.701 (1.020–7.154)	0.046
Vein thrombus	2 (3.8)	8 (15.7)	5.488 (1.112–27.079)	0.037
Urinary infection	1 (1.9)	2 (3.9)	4.270 (0.259–70.421)	0.310
Recurrent stroke	2 (3.8)	5 (9.8)	3.144 (0.542–18.224)	0.201
Progressive stroke	0 (0)	1 (2)		0.997
Vascular occlusion	3 (5.8)	1 (2)	0.247 (0.022–2.827)	0.261
Other adverse events	1 (1.9)	3 (5.9)	1.407 (0.103–19.138)	0.798
BI	100 (85–100)	85 (60–100)	0.924 (0.873–0.979)	0.007
≥85	43 (82.6)	27 (52.9)	4.055 (1.595–10.309)	0.003

BI, Barthel Index; CI, confidence interval; CRG, conventional rehabilitation group; ERG, early rehabilitation group; IQR, interquartile range; mRS, modified Rankin Scale; RR, relative risk.
Data are expressed as medians (IQR) and n (%).
All analyses are adjusted for the baseline National Institutes of Health Stroke Scale score, age, and the premorbid mRS score.

Activities of Daily Living

Significant differences in activities of daily living between the two groups were observed at the 3-month and 1-year follow-ups. At the 3-month follow-up (**Table 3**), the median BI was 100 in the ERG vs. 87.5 in the CRG (OR 0.924, 95% CI 0.873–0.979; $p = 0.007$), and 43 (82.6%) patients in the ERG and 27 (52.9%) patients in the CRG showed mild dependence or independence, respectively (BI ≥85, OR 4.055, 95% CI 1.595–10.309; $p = 0.003$). At the 1-year follow-up (**Table 4**), the median BI was 100 in the ERG vs. 90 in the CRG (OR 0.951, 95% CI 0.920–0.983; $p = 0.003$), and 47 (90.3%) and 29 (58%) patients in the ERG and CRG showed mild dependence or independence (BI ≥85), respectively (OR 6.308, 95% CI 2.104–18.914; $p = 0.001$).

TABLE 4 | Outcomes at the 1-year follow-up.

	ERG ($n = 52$)	CRG ($n = 50$)	OR (95% CI)	*P*-value
Primary outcome				
Mortality	0 (0)	1 (2)		0.999
Secondary outcomes				
Favorable outcome (mRS 0–2)	43 (82.7)	33 (66)	2.018 (0.771–5.283)	0.153
mRS category				
0	26 (50)	12 (24)		
1	10 (19.2)	12 (24)		
2	7 (13.5)	9 (18)		
3	8 (15.4)	10 (20)		
4	1 (1.9)	4 (8)		
5	0 (0)	2 (4)		
6	0 (0)	1 (2)		
Non-fatal complications	3 (5.8)	7 (14)	2.421 (0.563–10.422)	0.235
BI	100 (90–100)	90 (63.8–100)	0.951 (0.920–0.983)	0.003
≥85	47 (90.3)	29 (58)	6.308 (2.104–18.914)	0.001

BI, Barthel Index; CI, confidence interval; CRG, conventional rehabilitation group; ERG, early rehabilitation group; IQR, interquartile range; mRS, modified Rankin scale; RR, relative risk.

Data are expressed as medians (IQR) and n (%).

All analyses are adjusted for the baseline National Institutes of Health Stroke Scale score, age, and the premorbid mRS score.

DISCUSSION

This was a randomized, double-blind, controlled study on the safety and efficacy of ER in patients who had MT. Our findings showed that postoperative ER did not contribute to increased short- and long-term mortality rates. The incidence of non-fatal complications was significantly lower in the ERG than in the CRG. ER can reduce immobility-related complications, mainly due to a reduction in the incidence of pulmonary infections and venous thrombosis without increasing the incidence of neurological complications. We defined an mRS of 0–2 (minimum or no disability) as a favorable outcome. Although no significant differences between the groups at 3-month and 1-year follow-ups were found, the percentage of favorable outcomes was higher in the ERG than in the CRG. ER improved the patients' abilities to perform daily activities based on our observations at both 3 months and 1 year. Therefore, our study findings provide preliminary clinical evidence of the benefits of ER in patients who had undergone MT.

In preliminary findings, the A very early rehabilitation trail (AVERT) has shown the safety and feasibility of very early rehabilitation for patients with acute ischemic stroke (11, 21). However, this trial lacked clinical evidence concerning ER for patients having undergone MT. In our study, we included patients undergoing endovascular MT in our safety and feasibility assessment and noted the potential benefits of early out-of-bed rehabilitation. Despite showing the feasibility of an early ambulation protocol, no consensus was identified concerning the start time for the intervention. The follow-up AVERT III trial indicated that earlier, more frequent, and more intense out-of-bed activity within 24 h post-stroke was associated with unfavorable outcomes at 3-month follow-up (11). This finding may be related to the timing of ER intervention within 24 h of stroke onset, as some randomized controlled trials regarding early stroke rehabilitation have shown that patients with mild to severe stroke (ischemic and hemorrhagic) may benefit from high-intensity rehabilitation 24 h after stroke occurrence (10, 22). One study from southern Brazil reported that early mobilization had no negative effect on the rates of immobility complications and mortality within 48 h of stroke symptom onset (23). Therefore, based on the above, we set our early out-of-bed activity intervention to within 48 h post-stroke.

Due to cerebral autoregulation impairment, blood pressure changes may aggravate brain tissue reperfusion injury and increase the risk of hemorrhage transformation (24), whereas postural changes may affect the ischemic penumbra area and normal brain tissue blood supply due to residual stenosis of intracranial vessels after surgery, which suggests that an ER rehabilitation intervention for patients undergoing MT may be unsafe (25). However, no fatal complications, such as symptomatic cerebral hemorrhage or progressive stroke, were observed in the ERG. Moreover, there was no significant between-group difference found in terms of mortality. This result is consistent with those of other ER randomized controlled trials (16), which indicates that early out-of-bed sitting is unlikely to have major negative effects on stroke outcomes. Additionally, no similar complications were found to be associated with ER (15, 23). Although ER did not improve the prognosis of patients, it had no serious adverse effects. This result shows that ER is effective for reducing early immobility-related complications in patients who have undergone MT and has guiding significance for the postoperative management of such patients.

The incidence of pulmonary infection and lower limb venous thrombosis was also found to be significantly lower in the ERG than in the CRG. This may be due to the disturbance of consciousness and bed rest after surgery in patients who have undergone MT, which increases the probability of aspiration and hypostatic pneumonia. This, in turn, increases the probability of lower limb venous thrombosis in patients with limb paralysis and immobility (26). Extended immobility has been associated with medical complications during hospitalization, and patients with stroke are more likely to have acute complications which significantly negatively correlates with functional prognoses (27) in the early stages of their hospitalization. ER promotes recovery and reduces immobility-related complications and may, therefore, consequently reduce the length of hospital stay (28, 29). This may explain why patients in the ERG were better able to perform activities of daily living than those in the CRG. Furthermore, early rehabilitation can effectively prevent complications, such as infection, which is a possible reason for low mortality rates found in this study (14). Similar to previous studies (29, 30), our study findings provide further evidence in support of the safety and efficacy of ER (within 48 h postoperatively) commencement after MT. We found that ER can reduce early complications in patients undergoing MT

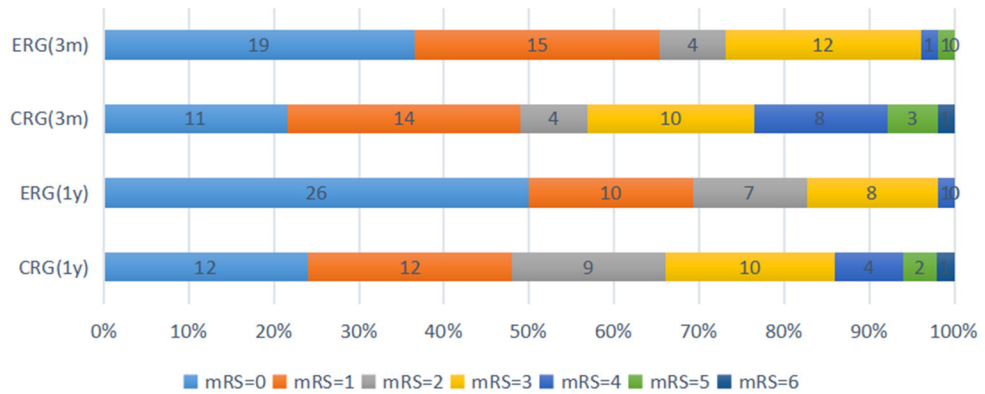


FIGURE 2 | Modified ranking scale (mRS) shift: patients achieving each mRS score at 3-months and 1-year. ERG, early rehabilitation group; CRG, conventional rehabilitation group; mRS, modified Rankin Scale; M, months; Y, year.

in addition to shortening hospital stay, thereby resulting in a favorable prognosis.

This study had some limitations. First, our study was a single-center trial. Second, as a small pilot trial, it intended to preliminarily explore the safety and feasibility of ER of patients with MT. Critical and unstable conditions are contraindications for early out-of-bed rehabilitation. Therefore, the trial did not include patients with critical and unstable conditions. Although there were some limitations in the study, our trial showed that ER is safe and feasible. However, multicenter randomized controlled trials with larger sample sizes are needed to validate our study findings in future.

In conclusion, ER did not increase the probability of a favorable prognosis for patients undergoing MT. However, ER reduced the incidence of early immobility-related complications, shortened hospital stay, and effectively improved the activities of daily living on a short- and long-term basis without increasing mortality and neurological-related complications.

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 human participants were reviewed and approved by the Ethics Committee of the Tianjin Huanhu Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW, ZZ, MW, YY, and JW conceptualized and designed the study. WW drafted the initial manuscript and revised the report. JW coordinated and critically revised the study for important intellectual content. YY, YC, HZ, HD, and WH completed the rehabilitation intervention-related work. TZ coordinated with the hospitalized patients. LQ conducted the statistical analysis. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Tianjin Key Medical Discipline (Specialty) Construction Project, Tianjin Key Research and Development Program in Science and Technology (No. 19YFZCSY00260), and Tianjin Health Science and Technology Project (No. MS20015).

ACKNOWLEDGMENTS

We are grateful to the patients and their families. We would also like to thank our colleagues for their assistance. Finally, we wish to thank Editage (www.editage.cn) for English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.698439/full#supplementary-material

Supplementary Figure 1 | Comparison of first mobilization time between two groups. ERG, early rehabilitation group; CRG, conventional rehabilitation group; The abscissa represents the number of patients in the two groups; the ordinate represents first mobilization time of each enrolled patient (hour); The blue and yellow lines represent the fluctuation range of first mobilization time in the early rehabilitation group and the conventional rehabilitation group respectively.

REFERENCES

1. Broderick J, Palesch Y, Demchuk A, Yeatts S, Khatri P, Hill M, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. *N Engl J Med.* (2013) 368:893–903. doi: 10.1056/NEJMoa1214300
2. Berkhemer O, Fransen P, Beumer D, van den Berg L, Lingsma H, Yoo A, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med.* (2015) 372:11–20. doi: 10.1056/NEJMoa1411587
3. Bhatia R, Hill M, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke.* (2010) 41:2254–8. doi: 10.1161/STROKEAHA.110.592535
4. Goyal M, Demchuk A, Menon B, Eesa M, Rempel J, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med.* (2015) 372:1019–30. doi: 10.1056/NEJMoa1414905
5. Jovin T, Chamorro A, Cobo E, de Miquel M, Molina C, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med.* (2015) 372:2296–306. doi: 10.1056/NEJMoa1503780
6. Powers W, Rabinstein A, Ackerson T, Adeoye O, Bambakidis N, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
7. Winstein C, Stein J, Arena R, Bates B, Cherney L, Cramer S, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2016) 47:e98–169. doi: 10.1161/STR.0000000000000098
8. Lynch EA, Cumming T, Janssen H, Bernhardt J. *Early mobilization after stroke: Changes in clinical opinion despite an unchanging evidence base. J Stroke Cerebrovasc Dis.* (2017) 26:1–6. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.021
9. Bernhardt J, English C, Johnson L, Cumming TB. Early mobilization after stroke: Early adoption but limited evidence. *Stroke.* (2015) 46:1141. doi: 10.1161/STROKEAHA.114.007434
10. Tong Y, Cheng Z, Rajah GB, Duan H, Cai L, Zhang N, et al. High intensity physical rehabilitation later than 24 h post stroke is beneficial in patients: A pilot randomized controlled trial (rct) study in mild to moderate ischemic stroke. *Front Neurol.* (2019) 10:113. doi: 10.3389/fneur.2019.00113
11. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (avert): a randomised controlled trial. *Lancet.* (2015) 386:46–55. doi: 10.1016/S0140-6736(15)60690-0
12. Fure B, Holte H, Hov L, Vist GE, Kateraas LH, Indredavik B. Very early mobilisation in cases of acute stroke. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke.* (2018) 138. doi: 10.4045/tidsskr.17.0924
13. Li Z, Zhang X, Wang K, Wen J. Effects of early mobilization after acute stroke: a meta-analysis of randomized control trials. *J Stroke Cerebrovasc Dis.* (2018) 27:1326–37. doi: 10.1016/j.jstrokecerebrovasdis.2017.12.021
14. Govan L, Langhorne P, Weir C. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care? Further analysis of a systematic review. *Stroke.* (2007) 38:2536–40. doi: 10.1161/STROKEAHA.106.478842
15. Herisson F, Godard S, Volteau C, Le Blanc E, Guillon B, Gaudron M. Early sitting in ischemic stroke patients (sevel): a randomized controlled trial. *PLoS ONE.* (2016) 11:e0149466. doi: 10.1371/journal.pone.0149466
16. Liu N, Cadilhac D, Andrew N, Zeng L, Li Z, Li J, et al. Randomized controlled trial of early rehabilitation after intracerebral hemorrhage stroke: difference in outcomes within 6 months of stroke. *Stroke.* (2014) 45:3502–7. doi: 10.1161/STROKEAHA.114.005661
17. Yen H, Jeng J, Chen W, Pan G, Chuang Pt Bs W, Lee Y, et al. Early mobilization of mild-moderate intracerebral hemorrhage patients in a stroke center: a randomized controlled trial. *Neurorehabil Neural Repair.* (2020) 34:72–81. doi: 10.1177/1545968319893294
18. Alamri M, Waked I, Amin F, Al-Quliti K, Manzar M. Effectiveness of an early mobility protocol for stroke patients in intensive care unit. *Neurosciences.* (2019) 24:81–8. doi: 10.17712/nsj.2019.2.20180004
19. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
20. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the barthel index for stroke rehabilitation. *J Clin Epidemiol.* (1989) 42:703–9. doi: 10.1016/0895-4356(89)90065-6
21. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (avert): Phase ii safety and feasibility. *Stroke.* (2008) 39:390–6. doi: 10.1161/STROKEAHA.107.492363
22. Langhorne P, Wu O, Rodgers H, Ashburn A, Bernhardt J. A very early rehabilitation trial after stroke (avert): A phase iii, multicentre, randomised controlled trial. *Health Technol Assess.* (2017) 21:1–120. doi: 10.3310/hta21540
23. Poletto S, Rebello L, Valença M, Rossato D, Almeida A, Brondani R, et al. Early mobilization in ischemic stroke: a pilot randomized trial of safety and feasibility in a public hospital in brazil. *Cerebrovasc Dis Extra.* (2015) 5:31–40. doi: 10.1159/000381417
24. Maier IL, Tsogkas I, Behme D, Bähr M, Knauth M, Psychogios MN, et al. High systolic blood pressure after successful endovascular treatment affects early functional outcome in acute ischemic stroke. *Cerebrovasc Dis.* (2018) 45:18–25. doi: 10.1159/000484720
25. Bösel J. Blood pressure control for acute severe ischemic and hemorrhagic stroke. *Curr Opin Crit Care.* (2017) 23:81–6. doi: 10.1097/MCC.0000000000000394
26. Balami J, White P, McMeekin P, Ford G, Buchan A. Complications of endovascular treatment for acute ischemic stroke: prevention and management. *Int J Stroke.* (2018) 13:348–61. doi: 10.1177/1747493017743051
27. Janus-Laszuk B, Mirowska-Guzel D, Sarzynska-Dlugosz I, Czlonkowska A. Effect of medical complications on the after-stroke rehabilitation outcome. *NeuroRehabilitation.* (2017) 40:223–32. doi: 10.3233/NRE-161407
28. Kim B, Lee J, Sohn M, Kim D, Lee S, Shin Y, et al. Risk factors and functional impact of medical complications in stroke. *Ann Rehabil Med.* (2017) 41:753–60. doi: 10.5535/arm.2017.41.5.753
29. Chippala P, Sharma R. Effect of very early mobilisation on functional status in patients with acute stroke: a single-blind, randomized controlled trail. *Clin Rehabil.* (2016) 30:669–75. doi: 10.1177/0269215515596054
30. Langhorne P, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. *Cerebrovasc Dis.* (2010) 29:352–60. doi: 10.1159/000278931

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.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership