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Volume 49, Number 1, February 2025

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Aims and Scope

Annals of Rehabilitation Medicine (*ARM*) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, more than 3,500 physiatrists regularly receive this journal's table of contents via email, and the number is continually increasing. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM). International members comprise approximately half the editorial board, conducting peer-reviews of submitted manuscripts or acting as handling editors by assigning peer-review tasks to other reviewers.

The journal encompasses all aspects of physical medicine and rehabilitation, including basic, translational, clinical, and policy research, as well as rehabilitation education. Research areas covered by this journal include rehabilitation for brain disorders, spinal cord injuries, neuromuscular diseases, and dysphagia; cancer, cardiopulmonary, geriatric, pain & musculoskeletal, and pediatric rehabilitation; electrodiagnosis, orthosis & prosthesis, physical therapy, and sports medicine; and other emerging fields in rehabilitation medicine.

General Information

Annals of Rehabilitation Medicine is published in English bi-monthly on the last days of February, April, June, August, October, and December. Publication type includes original research, reviews, and other types of articles that reflect the depth and breadth of this specialty. The editorial board consists of members from 13 different countries. Articles are welcome for submission from all over the world. Full text is available from: http://www.e-arm.org/. All or part of the journal articles is indexed/tracked/covered by SCOPUS, EBSCO, PubMed Central/PubMed, KoreaMed, KoMCI, DOI/Crossref, Google Scholar, and Web of Science Core Collection as Emerging Sourc es Citation Index (ESCI) journal.

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Letter to the Editor

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Letter to the Editor: Efficacy and Safety of High Density LED Irradiation Therapy for Patients With Hand Osteoarthritis: A Single-Center Clinical Study

Vanshika Agarwal, BPT, MPT, Jeyanthi. S, BPT, MPT, PhD, Adarsh Sharma, BPT, MPT, (PhD)

Department of Physiotherapy, Amar Jyoti Institute of Physiotherapy, University of Delhi, Delhi, India

Dear Editor,

We read the article by Kim et al. [1], with attention and would like to congratulate them for their valuable research on efficacy and safety of high density light-emitting diode (LED) irradiation therapy for patients with hand osteoarthritis. However, we would like to provide some feedback on the study presented by authors.

Firstly, we would like to appraise the information outlined in the introduction section concerning hand osteoarthritis, including its prevalence, symptoms, deformity and limitations individuals experience due to the condition. Additionally, the introduction emphasizes the scarcity of literature on hand osteoarthritis, attributing it to a shift in focus towards osteoarthritis affecting larger joints. Our understanding is further deepened by reading the physiology and mechanism of action of photobiomodulation therapies in alleviating symptoms due to arthritis. But we would like to draw attention towards the missing hypothesis in text. In our view, the authors should use two-tailed hypothesis, for which "high-density LED irradiation therapy might have significant difference in improving pain, hand swelling and joint mobility in patients with hand osteoarthritis" would be an alternate hypothesis, and the null hypothesis would be "high-density LED irradiation therapy might not have significant difference in improving pain, hand swelling and joint mobility in patients with hand osteoarthritis."

Secondly, the stated inclusion and exclusion criteria need to be modified. The amount of time since the disease's inception and the reference for the selected American College of Rheumatology criteria [2] should have been mentioned in the inclusion criteria. Along with this, patients with any congenital hand deformities, a history of hand injury, patients taking prior physiotherapy sessions and patients contraindicated for LED irradiation (such as in case of epilepsy, active cancer, photosensitizing medications or highly sensitive skin) should have been excluded from the study [3]. Further, the text also lacked the method of sample size calculation and its parameters.

However, we appreciate the number of therapy sessions given per week for 4 weeks along with parameters of irradiation and safety assessment before application has been well mentioned.

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Next, we would like to draw attention towards the fact that the methodology did not specify any follow-up time, but it was directly mentioned in results, which initially made the statistical analysis less comprehensible. Explanation of the statistical tests applied, such as paired-t test, one-way ANOVA and chi-square test was unclear. Also the normality of the demographic data in the form of p-values could have been notified for better clarity [4]. However, results were well presented along with graphs and figures. The findings of the study were intriguing, informative, and aligned with other recent evidence, thereby contributing additional insights to the existing literature.

We are interested in hearing the author's thoughts on these remarks.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Response

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Response: Efficacy and Safety of High Density LED Irradiation Therapy for Patients With Hand Osteoarthritis: A Single-Center Clinical Study (*Ann Rehabil Med* 2024;48:50-6)

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We appreciate your interest in our manuscript, "Efficacy and safety of high density LED irradiation therapy for patients with hand osteoarthritis: a single-center clinical study" [1]. We are grateful for your thorough review and for providing constructive feedback.

Firstly, regarding the hypothesis: As you noted, the use of ANOVA indicates that a two-sided hypothesis was applied in our study. The specific hypotheses were as follows:

Null hypothesis: high-density light-emitting diode (LED) irradiation therapy might not have a significant difference in the visual analogue scale (VAS), ring size, or passive joint range of motion at baseline, post-treatment (week 4), and two weeks post-treatment (week 6).

Alternative hypothesis: high-density LED irradiation therapy might have a significant difference in VAS, ring size, or passive joint range of motion at baseline, post-treatment (week 4), and two weeks post-treatment (week 6).

Secondly, regarding the selection and exclusion criteria for study participants: While disease duration wasn't considered, we agree this should have been included. Although not detailed in the manuscript, two specialists in Physical and Rehabilitation Medicine verified that patients met the American College of Rheumatology criteria, excluding those with congenital hand deformities or prior injuries. Additionally, we screened for conditions such as autoimmune diseases, myocardial infarction, severe heart disease, or uncontrolled hypertension, which may affect outcomes. We appreciate your comments on the contraindications for LED irradiation, including photosensitizing medications, skin sensitivity, and prior physiotherapy.

Thirdly, regarding the sample size calculation: Although this was performed during the research design, it was not included in the manuscript. The details are as follows:

Due to the lack of prior clinical studies using LED phototherapy for hand osteoarthritis, we referenced data from studies using laser therapy [2]. It was hypothesized, based on clinical judgment, that the improvement in VAS scores with LED phototherapy would not exceed 80% of that observed with laser therapy, with reported changes ranging from 1.75 to 1.86 after six weeks.

Assuming a two-sided significance level of $\alpha=0.05$ and a standard deviation of 3.0, the calculated sample size was 18 participants. The mean change in VAS score for LED phototherapy is estimated to be 1.4. To accommodate a potential dropout rate of 20%, the total target recruit-

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ment was set at 23 participants.

Lastly, regarding the methodology: As you rightly indicated, the study design should have included an observation period extending to week 6.

We acknowledge that the explanation of the statistical tests in the manuscript was insufficient. We used a chi-square test to examine sex differences among the 23 participants and found a significant difference in the sex ratio within the group ($p<0.05$). Additionally, although not included in the manuscript, we performed a t-test to assess age differences between sexes, which was not statistically significant. ANOVA was then used to evaluate changes in pain, finger circumference, and range of motion across three time points followed by a post-hoc Bonferroni test to identify specific differences between these time points. The mention of Pearson's was mistakenly included and should have been removed during revision.

Thanks for your feedback.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Original Article

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Validation of Korean Version of the Oxford Cognitive Screen (K-OCS), a Post Stroke-Specific Cognitive Screening Tool

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Objective: To establish and evaluate the validity of the recently developed Korean version of the Oxford Cognitive Screen (K-OCS), this study verified its reliability, validity, and diagnostic accuracy.

Methods: Between November 2021 and December 2023, we recruited 72 patients with stroke from our hospital who agreed to participate in the study. The patients were repeatedly tested using K-OCS by the same or different assessors to estimate inter- and intra-rater reliability. To demonstrate the validity and usability of K-OCS, the test results of screening tools currently used in clinical practice, including the Korean-Mini Mental State Examination and the Korean version of the Montreal Cognitive Assessment, were used in comparison analyses.

Results: The subtests of K-OCS demonstrated excellent inter-rater reliability (intra-class correlation coefficient [ICC]=0.914–0.998) and test–retest reliability (ICC=0.913–0.994). We found moderate-to-strong correlations for convergent validity for the subsets (r=0.378–0.979, p<0.01), and low-to-moderate discriminant validity correlations. The optimal cut-offs estimated for the subtests of the K-OCS showed a good-to-high range of specificity (94.8%–100%). The positive predictive value was 58.2%–100% and negative predictive value was 65.6%–98.4%. Sensitivity was estimated at 25.6%–86.9%.

Conclusion: The results of this study indicate that K-OCS is a reliable and valid tool for screening cognitive impairment in patients post-stroke.

Keywords: Cognitive screening, Cognition, Stroke, Neurocognitive test, Validation study

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INTRODUCTION

More than 70% of the patients with stroke experience post-stroke cognitive impairment (PSCI), depending on the type of stroke, definition, and time point of assessment [1,2], and 32% of the survivors experience persistent cognitive decline up to 3 years after stroke [3]. Assessment of potential PSCI is important, as the phenomenon may be reversible in the early phase and presence of co-morbid conditions may affect cognition [4]. Numerous international clinical treatment guidelines for stroke

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recommend that survivors be routinely assessed for cognitive impairment using cognitive screening tools, followed by a comprehensive assessment according to the results [5,6]. In terms of measuring cognitive impairment after stroke, improvements in the screening tools are required to reflect better insights into the disease pathophysiology and symptoms [7]. The Mini-Mental State Examination (MMSE) [8] and Montreal Cognitive Assessment (MoCA) [9] have been developed to screen for dementia in general and are currently being used to evaluate post-stroke cognitive function, but their application in the field of stroke care faces numerous challenges. As a representative example, difficulties may emerge after lesions in the brain language domain owing to limitations in the expressive or receptive language abilities of the patients with stroke [10,11]. In practical terms, approximately 20% of stroke patients are unable to undergo dementia screening [12].

The Oxford Cognitive Screen (OCS) [13] addresses cognitive functioning in a comprehensive manner across several domains to identify impairments beyond the limitations of assessment from language, spatial-temporal, memory, or executive functions commonly affected by stroke. OCS employs a multiple-choice format to enhance the participation of patients with language impairments and vertical layouts to maximize the evaluation of patients who have neglect symptoms. The tool allows for rapid screening within approximately 15 minutes. Other notable advantages of OCS is applicability at bedside and ease of use for patients with hemiplegia that spares a single upper limb. As for the criteria to determine impairment, the OCS uses 5th-percentile cut-offs. The test's utility is further enhanced by incorporating a "visual snapshot" (Fig. 1), which facilitates communication of the assessment results. The results in the Korean version (K-OCS) are summarized in a snapshot report that displays scores alongside brief descriptions of each subtask, making it easy to understand the patient's cognitive performance at a glance. The snapshot report serves not only as a tool to indicate areas of impairment but also to record additional notes. For instance, if a patient experiences difficulties only in reading but performs well on other language tasks, only the relevant segment of the "domain" is shaded and explanatory comments can be provided in the adjacent area (e.g., "Deficit in reading only - score 11/15"). Observation of the behavior and medical condition, such as "T-tube limitations or not wearing reading glasses" or "Excited emotional status," can also be described to provide additional information.

The initial development of OCS in the United Kingdom was followed by normative studies in various countries, including Italy, Hong Kong, Denmark, Russia, Spain, Portugal, Netherlands, Australia, and Germany [14-22]. Recently, a normative study for K-OCS that considered and adapted cultural and linguistic characteristics has been published (https://process.innovation.ox.ac.uk/clinical/p/ocs/questionnaire/1). The K-OCS was translated and reverse-translated according to a systematic translation procedure in a previous study, adapted to align with the linguistic and cultural characteristics of Korea, and ultimately approved by the original author [23]. As for the criteria to determine impairment, the OCS uses 5th-percentile cut-offs. Detailed information on how to translate and score can be found in the K-OCS normative study [23]. To serve as a useful cognitive assessment tool for stroke, its reliability in patients with stroke must be established. In addition, securing a validity consistent with the results of existing evaluations would be essential. The original OCS has become recognized as a screening test for evaluating PSCIs because of its strong reliability and validity [13], and the latter has been demonstrated in comparison analyses with existing screening tools [10,11]. Additionally, reports have revealed the neurological validity of OCS by demonstrating its ability to detect cognitive impairments characteristic of hemispheric lesions [10].

This study aimed to estimate the feasibility of using K-OCS, which may be a new avenue for post-stroke cognitive screening. For this purpose, we conducted a prospective clinical study and analyzed inter-rater reliability, test–retest reliability, convergent and discriminant validities, specificity, sensitivity, and predictive values, which adopted results of MMSE, MoCA, and other

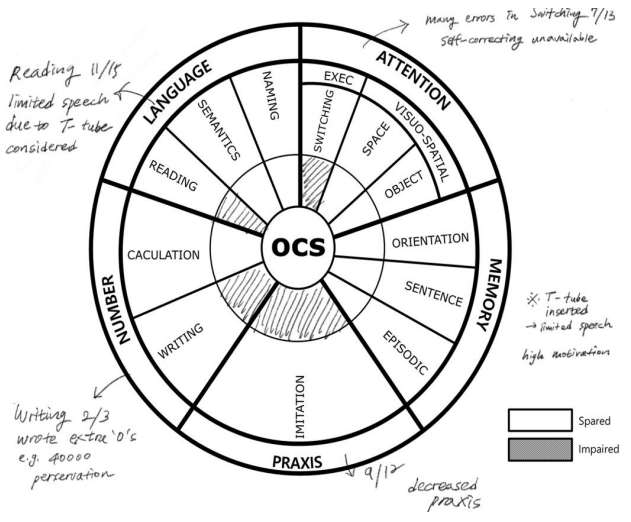

Fig. 1. Cognitive profile. OCS, Oxford Cognitive Screen.

functional evaluation tests.

METHODS

Participant selection

This study enrolled patients with stroke who were hospitalized or visited the outpatient department in a university-affiliated institute, the CHA Bundang Medical Center, for comprehensive rehabilitation from November 2021 to December 2023. The study protocol was approved by the Institutional Review Board of CHA Bundang Medical Center (2021-09-001-001) and registered at clinicaltrials.gov (NCT 06367920). All patients received written and oral information about the study and provided their consent before study participation.

The inclusion criteria were a diagnosis of ischemic or hemorrhagic stroke based on the results from brain magnetic resonance imaging or computed tomography, adults aged 20 years and older, time points of at least 72 hours after stroke onset, and ability to attend for at least 20 minutes, as determined by the medical team. Written informed consent was provided by the patient or a legal representative in case of difficulty in understanding the consent form. The exclusion criteria were a previous history of stroke and pre-existing psychiatric or neurological conditions.

Evaluations for cognition and neurological function

An expert clinical psychologist (Researcher E.C.) and two trained psychology graduate students performed the cognitive evaluations. The assessor was educated on the basic theory underlying OCS, including its purpose, methods to use the tool, and interpretation of test results, through a manual. Simultaneously, the assessors practiced administering the test by watching examination videos provided by the original UK research team (available at https://www.ocs-test.org/ocs-background/how-to). Subsequently, each trained assessor completed five practice sessions using the actual test tools under the supervision of a licensed clinical psychologist (E.C.) and received training in scoring and interpreting the results. The tests were administered to each patient sequentially, with a minimum time gap of 30 min between tests, following the order of the Korean version of the MoCA (K-MoCA) [24], Korean-MMSE (K-MMSE) [25], and K-OCS [23]. We ensured that tasks directly involving memory recall (e.g., word lists) were not performed consecutively, thereby reducing the likelihood of carryover effects. Patient interviews or non-verbal tasks were conducted between assessments to minimize the possibility of unnecessary interference caused by administering similar tests consecutively or by overlapping verbal tasks. The Birmingham Cognitive Screen (BCoS) imitation task [26] was administered by the clinical psychologist for comparison with the result of the K-OCS imitation task. Lastly, to assess general neurological impairments, rehabilitation medicine physicians (Researcher I.L.) examined the patients using the Korean National Institutes of Health Stroke Scale (K-NIHSS) [27].

In this institute, the enrolled patients were periodically evaluated for physical and cognitive function as a routine practice for timely and appropriate rehabilitation. Data generated during the routine clinical work-up, such as test results of the "line bisection test" [28] and "Functional Independence Measurement (FIM)" [29] administered by licensed and trained occupational therapists, were also included for analysis in available cases. Detailed information on the matching of each subset between the tests is provided in Supplementary Table S1.

Procedures for reliability, validity, and diagnostic accuracy analyses of K-OCS

As a first step, the inter-rater reliability of K-OCS was assessed by three raters. The first rater (E.C.) conducted the K-OCS evaluation and recorded the assessment process on video. The second and third raters independently scored the video recordings. Test–retest (intra-rater) reliability was assessed by conducting a re-evaluation within 5 days of the initial assessment.

To assess convergent and discriminant validity correlations, the K-OCS scores were compared to those of conventional cognitive screening tools (K-MMSE and K-MoCA). Evaluation of convergent validity included within-test and between-test assessments. Within-test convergent validity was evaluated by correlating scores from different components of the same assessment tool. Between-test convergent validity involved comparing the scores of the assessment tool with those of established cognitive tests known to measure similar constructs. To confirm discriminant validity, we conducted an analysis to demonstrate a low correlation between OCS and other instruments measuring different constructs. Lastly, diagnostic accuracy was assessed by analyzing the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). These analyses were performed using the evaluation results of not only K-MoCA and K-MMSE but also of other tests, including the line bisection test, NIHSS, and FIM for all available subtask items.

Measures to assess neuropsychological and functional abilities

K-OCS [23] comprises a test manual, stimulus booklet, evaluator scoring sheet, and examinee assessment sheet. With 10 items, it assesses five cognitive domains: language, attention and executive function, memory, numerical processing, and executive function. K-MoCA [24] was designed to identify mild cognitive impairment in older adults with memory deficits. This assessment comprises 30 points and evaluates spatial-temporal function, frontal lobe executive function, short-term memory, attention, concentration and working memory, language function, and time and place orientation. K-MMSE is an adapted test tailored to the Korean context; it assesses time and place orientation, attention, immediate and delayed recall, constructional ability, and language ability on a 30-point scale [25]. BCoS was developed to identify different forms of praxic deficits using procedures designed to include patients with aphasia and/or spatial neglect [26]. In this study, the results of the BCoS imitation task were compared with those of the OCS imitation task. The line bisection test is a quick measure to detect the presence of unilateral spatial neglect [28]. K-NIHSS [27] is widely used to score severity in acute stroke and allows evaluation of neurological impairment across 10 categories: consciousness, gaze, visual field, strength of face, upper limb, and lower limb, motor control, sensory function, language, articulation, and perception. FIM is a reliable evaluation tool to measure performance in daily life activities in patients with disability using two subscale scores—motor and cognitive [29].

Data and statistical analysis

The collected data were analyzed using IBM SPSS 21 (IBM Corp.) and R 4.1.3. Descriptive analysis was used for the demographic data. Intra-class correlation coefficients (ICCs) were calculated to evaluate the inter- and intra-rater consistency for total, each domain, and each task of the K-OCS assessment.

Using data from K-OCS, K-MMSE, K-MoCA, and other tests, several components were checked to assess the validity of K-OCS. Convergent and discriminant validity correlations between K-OCS and the other tests was assessed using the Spearman correlation coefficient. Items related to diagnostic accuracy in addition to specificity, sensitivity, PPV, and NPV of K-OCS were computed using the reportROC (Receiver Operating Characteristic) package. Using normative data from the K-OCS study [23], impairment cut-off scores were set based on the fifth percentile score for each subtask of K-MoCA. Subtest scores of K-OCS and K-MoCA were compared in the language, memory, numeric ability, and executive function domains. Specificity≥80% confirms effective exclusion of non-impairment cases; sensitivity≥80% indicates strong detection of cognitive impairment; PPV≥70% is reliable in high-prevalence settings; and NPV≥70% ensures accuracy in excluding the condition [30]. Two subtasks were not available for the diagnostic accuracy analysis: the cutoff point of the "recall" subtask in the "memory" domain was 0 and there was no corresponding MoCA subtest for the "heart cancellation" in the "visual attention" domain of OCS.

RESULTS

Collectively, 72 participants were recruited (46 male and 26 female). The ages ranged from 31 to 93 years, with a mean age of 62.35±13.80 years and their education level ranged from 1 to 19 years, with a mean of 13.03±3.60 years. The demographic variables and characteristics related to brain damage in the stroke cohort, including the time elapsed after stroke, are presented in Table 1. The onset of the period was less than 3 months in 22 participants (30.6%), between 3 and 12 months in 16 participants (22.2%), and more than 12 months in 34 participants (47.2%). To evaluate inter-rater reliability, 24 participants were

Table 1. Patient sample characteristics (n=72)

Sample characteristic	Category	Proportion of patients
Age (yr)	<50	13 (18.1)
	50–59	13 (18.1)
	>59	46 (63.9)
Sex, female		26 (36.1)
Education (yr)	≤6	7 (9.7)
	7–12	28 (38.9)
	>12	37 (51.4)
Etiology	Hemorrhagic	31 (43.1)
	Ischemic	41 (56.9)
Onset of period (mo)	<3	22 (30.6)
	3–12	16 (22.2)
	>12	34 (47.2)
Lesion lateralization	Unilateral left hemisphere	38 (52.8)
	Unilateral right hemisphere	29 (40.3)
	Bilateral/cerebellar	5 (6.9)
Stroke severity NIHSS	Mild	44 (61.0)
	Moderate	22 (30.6)
	Moderate to severe	3 (4.2)
	Severe	3 (4.2)

Values are presented as number (%).
NIHSS, National Institutes of Health Stroke Scale.

randomly selected and their performances in the K-OCS test were video-recorded. Of these, 17 patients were re-tested for evaluation of intra-rater reliability.

Reliability verification

Three raters participated in the inter-rater reliability analysis using a sample of 24 participants. Reliability is classified as follows: a coefficient value of 0–0.4 indicates poor, 0.4–0.6 fair, 0.6–0.75 good, and 0.75–1 excellent reliability [31]. The results suggested excellent inter-rater reliability for the scoring of most subtests in K-OCS (Table 2). Test–retest reliability was analyzed in a sample of 17 participants with an average interval of 2.88±0.82 days between evaluations. We obtained ICC values between 0.913 and 0.994 (p<0.001), which also demonstrated excellent level of agreement (Table 3).

Validity verification

Data from 72 participants were included in the analysis to ver-

Table 2. Inter-rater reliability (rater n=3, stroke patient n=24)

Domain	Task	ICC	95% CI	p-value
Language	Picture naming	0.994	0.989–0.997	<0.001
	Semantics	0.995	0.991–0.998	<0.001
	Sentence reading	0.995	0.990–0.997	<0.001
Memory	Orientation	0.971	0.990–0.997	<0.001
	Orientation MCQ	0.914	0.830–0.960	<0.001
	Recall	0.988	0.976–0.994	<0.001
	Recognition	0.983	0.967–0.992	<0.001
	Episodic memory	0.997	0.995–0.999	<0.001
Attention	Hearts cancelation	0.998	0.997–0.999	<0.001
	Space asymmetry	0.946	0.789–0.975	<0.001
	Object asymmetry	0.950	0.902–0.977	<0.001
Number	Number writing	0.997	0.995–0.998	<0.001
	Calculation free	0.971	0.943–0.987	<0.001
	Calculation MCQ	0.944	0.890–0.974	<0.001
Praxis	Imitation	0.988	0.976–0.994	<0.001
Executive function	Executive mixed	0.996	0.993–0.998	<0.001
	Executive total	0.989	0.979–0.995	<0.001

ICC, intra-class correlation coefficient; CI, confidence interval; MCQ, multiple choice question.

Table 3. Test–retest reliability for each subtest of the K-OCS (n=17)

Domain	Task	ICC	95% CI	p-value
Language	Picture naming	0.968	0.913–0.988	<0.001
	Semantics	0.986	0.962–0.994	<0.001
	Sentence reading	0.994	0.984–0.997	<0.001
Memory	Orientation	0.947	0.857–0.980	<0.001
	Orientation MCQ	0.967	0.918–0.989	<0.001
	Recall	0.956	0.880–0.984	<0.001
	Recognition	0.906	0.748–0.965	<0.001
	Episodic memory	0.956	0.881–0.983	<0.001
Attention	Hearts cancelation	0.992	0.985–0.994	<0.001
	Space asymmetry	0.960	0.889–0.985	<0.001
	Object asymmetry	0.933	0.814–0.976	<0.001
Perception	Visual field	0.942	0.846–0.979	<0.001
Number	Number writing	0.959	0.890–0.985	<0.001
	Calculation	0.960	0.891–0.985	<0.001
Praxis	Imitation	0.983	0.954–0.993	<0.001
Executive function	Executive mixed	0.913	0.759–0.969	<0.001
	Executive total	0.927	0.795–0.974	<0.001

K-OCS, Korean version of the Oxford Cognitive Screen; ICC, intra-class correlation coefficient; CI, confidence interval; MCQ, multiple choice question.

ify convergent and discriminant validity correlations. K-OCS and existing tools that assess similar functions demonstrated a moderate-to-strong association (r range, 0.378–0.979, p<0.001; Table 4). We obtained relatively high correlations for K-OCS subscores—imitation (r=0.979), orientation (r=0.849), calculation (r=0.698), and executive mixed tasks (r=0.671). In contrast, relatively low correlations were noted for the executive total (r=|0.386|), recall MoCA (r=0.378), recall MMSE (r=0.430), recognition MoCA (r=0.455), recognition MMSE (r=0.461), episodic memory MoCA (r=0.498), and number writing (r=0.455) tasks (all p<0.01). In the executive total task, a higher total score indicates poorer performance; thus, the correlation is presented as a negative value. To facilitate comparison with findings from other subtests, the values were presented as absolute values, which were then used to compute the r-values; this strategy helps avoiding misinterpretation of negative values that resulted from the reverse scoring system. The results show that correlation is superior for subtasks with content and methods similar to those of existing assessments, while subtasks that highlight the unique features of K-OCS are associated with decreased correlations. As indicated in Supplementary Table S2, the analysis of correlations between cognitive subtests within K-OCS revealed predominantly strong associations, excluding the orientatios (r=0.387, p<0.01) and the orientation multiple-choice items (r=0.304, p<0.01). To confirm rationality in the correlation analysis for validity, we chose the FIM motor subscale score as a negative control for discriminant validity. The results mostly revealed no correlation and only a few correlations were noted among the 15 subtasks of K-OCS (Supplementary Table S3).

Diagnostic accuracy

In this study, we assessed diagnostic accuracy by comparing the results between the K-OCS cognitive subtests and a representative selective test—K-MoCA memory subtest—which has been widely used in PSCI screening. Specificity, sensitivity, PPV, and NPV were computed and the corresponding values are presented in Table 5. Specificity in the subtasks ranged from 94.8% to 100%, indicating low false positive probability in K-OCS. Sensitivity was relatively lower for specific memory tasks such as recognition (32.2%), episodic memory (25.6%), and calculations in multiple choice questions (35.2%). The PPV for K-OCS, representing the probability of cognitive impairment based on positive results, was notably high for episodic memory and

Table 4. Convergent validity: correlations between performance on subtests of the K-OCS and other measures of cognition (n=72)

Domain	Task	Validation task	r
Language	Picture naming	MoCA picture naming	0.619**
		MMSE picture naming	0.566**
	Semantics	MMSE comprehension	0.553**
	Sentence reading	MMSE reading	0.598**
Memory	Orientation	MoCA orientation	0.849**
	Orientation MCQ	MoCA orientation	0.838**
	Recall	MoCA recall	0.378**
		MMSE recall	0.430**
	Recognition	MoCA recall	0.455**
		MMSE recall	0.461**
	Episodic memory	MoCA recall	0.498**
		MMSE recall	0.607**
Attention	Hearts cancellation	Line bisection	-0.508**[a]
Number	Number writing	MoCA clock number	0.455**
	Calculation	MMSE minus7	0.698**
	Calculation MCQ	MMSE minus7	0.666**
Praxis	Imitation	BcoS imitation	0.979**
Executive function	Executive mixed	MoCA executive	0.671**
	Executive total	MoCA executive	-0.386**[b]

K-OCS, Korean version of the Oxford Cognitive Screen; MCQ, multiple choice question; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination; BCoS, Birmingham Cognitive Screen.
**p<0.01.
[a]In the line bisection task, a higher total score indicates poorer performance, so the correlation is presented as a negative value.
[b]The executive total task, a higher total score indicates poorer performance, so the correlation is presented as a negative value.

Table 5. Diagnostic accuracy (n=72)

Domain	K-OCS	K-MoCA	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Language	Picture naming	Picture naming	73.5	95.4	58.2	97.1
Memory	Orientation MCQ	Orientation	86.9	98.6	87.1	98.4
	Recall	Recall			a	
	Recognition	Recall	32.2	96.8	87.5	65.6
	Episodic memory	Recall	25.6	100	100	69.5
Attention	Hearts cancelation				b	
Number	Calculation MCQ	Calculation	35.2	100	100	81.3
Executive function	Executive mixed	Executive	52.7	94.8	68.5	90.2

a, impairments cannot be distinguished because the K-OCS recall task has zero cutting points; b, not unambiguously assessed in MoCA.
K-OCS, Korean version of the Oxford Cognitive Screen; K-MoCA, Korean version of the Montreal Cognitive Assessment; PPV, positive predictive value; NPV, negative predictive value; MCQ, multiple choice question.

calculation tasks (100%), whereas executive mixed (68.5%) and picture naming tasks (58.2%) showed relatively lower values (Table 5). The NPV of K-OCS, with negative values indicating that cognitive impairment is likely not present, was significantly high for orientation MCQ (98.4%), picture naming (97.1%), and executive mixed tasks (90.2%). In contrast, recognition (65.6%) and episodic memory tasks (69.5%) had comparatively lower values.

DISCUSSION

The World Health Organization's Wilson-Jungner criteria, published in 2018, recommend cognitive and emotional screening assessments for all patients with stroke. Additionally, the global focus is on cognitive impairment and rehabilitative interventions after stroke, emphasizing the need to assess function across different cognitive domains [32]. In this study, we reported data on the reliability and validity of K-OCS, which seems appropriate for screening for cognitive impairment in stroke. Verification of the reliability and validity of an assessment tool is crucial for ensuring accuracy and dependability of the measurements in research and clinical practice.

The inter-rater ICC values of K-OCS were 0.914–0.998 across the subset tests, indicating excellent inter-rater reliability [33]. For comparison with prior research results, the Hong Kong-OCS study yielded values of 0.952–1 [15] and the Spanish-OCS study, of 0.790–1 [18]. The test–retest reliability values were 0.906–0.992, which also indicates excellent inter-rater reliability. The original OCS test–retest reliability values were 0.331–0.776 [13], the Hong Kong-OCS study reported values of 0.578–0.989 [15], and the Russian-OCS study, of 0.48–0.96 [17]. There is a notable difference between the present and previous results that showed a significant increase in the re-test score for language [13,15,17]. The average interval between test and retest in this study was 2.88 days, while it was 3.3 days in the original OCS study [13] and sampling was performed at an average of 6 days post-stroke. In contrast, in this study, 30.6% of sampling occurred within 3 months post-stroke. The different condition has likely contributed to the narrower variations in the test–retest scores, particularly in the language domain, in the present study. This is consistent with previous findings, which indicate that patients with acute stroke rapidly recover their language expression abilities early after stroke [34].

Regarding validity, the range of the correlation coefficients between K-OCS subtasks and the corresponding test results of other assessments was |0.386–0.979|, which represents an acceptable level of convergent validity in reference to the values in the original OCS (|0.346–0.902|) [13], Hong Kong-OCS (|0.368–0.732|) [15], Russian-OCS (|0.330–0.950|) [17], and Spanish-OCS (|0.466–0.908|) [18]. The convergent correlations within K-OCS for each subtask value were 0.304–0.676. Similarly, the original OCS study reported values of 0.260–0.680 [13]. Overall, convergent validity appeared somewhat lower than that in other gold-standard neurocognitive assessments. However, according to prior research, MMSE may underestimate non-verbal domains such as memory when evaluating language expression deficits following stroke, and MoCA has also been reported to have limitations in distinguishing between cognitive decline in Alzheimer's disease and PSCI [35]. The relatively low convergent validity for some K-OCS subtasks may be attributed to the unique ability of this test to measure neuropsychological functions that were indistinguishable with existing cognitive-screening tools. To minimize the impact of aphasia, OCS includes a multiple-choice response format, and to reduce the influence of neglect symptoms, it presents stimuli in vertical layouts. This innovative approach was designed to address the

limitations of existing assessment tools by reducing previously recognized confounding effects and enhancing the accuracy of cognitive screening [32,36]. Therefore, compared with existing tools, OCS seems to have enabled a more comprehensive understanding of the intended target component to be measured by enriching insights about the evaluation process.

In this study, discriminant validity assessed the correlation between the FIM-motor task and subtasks in K-OCS; among 15 tasks, we found a moderate degree of correlation in only four (sentence reading, orientation, orientation MCQ, and hearts cancellation). In the original OCS study, subtasks from the Barthel and OCS were used, and correlations were reported only for Broken Hearts [13].

In terms of diagnostic accuracy, relatively low sensitivity scores were observed in certain subtasks, such as recognition (32.2%), episodic memory (25.6%), and the multiple-choice question on calculations (35.2%). These findings may be due to the K-OCS design that differs from traditional assessment tools in aspects that include use of multiple-choice responses and of cued rather than simple recall.

Regarding the study's limitations, we note that post-injury duration for most of the patients (47.2%) exceeded one year, with 30.6% within three months, and 22.2% between three and 12 months (Table 1). Given that K-OCS is internationally recommended as a screening tool for patients with acute stroke, future research should prioritize validating its use in a large-scale population with acute stroke within the first three months of injury. Another consideration is the absence of a parallel test for K-OCS. Patients with acute stroke often exhibit rapid changes in cognitive function over a short period. Therefore, developing a parallel test with the same content but different items is necessary to enable short-term follow-up. Furthermore, development of parallel forms of testing would be essential to avoid learning effects of repetitive evaluation in patients with rapid recovery.

In conclusion, according to the results of this study, K-OCS overall demonstrated a fair level of validity, supporting its recommendation for clinical use in Korea and conforming to its designation as a stroke-specialized tool with distinct characteristics from those in existing tools. As a tool that is friendly toward common post-stroke symptoms such as aphasia and neglect, K-OCS enables a rapid and comprehensive assessment of patients' cognitive strengths and weaknesses. Therefore, K-OCS can be applied to patients with stroke in clinical settings, and we expect that future research will continue to validate its clinical utility.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Cho E. Methodology: Cho E. Formal analysis: Cho E. Funding acquisition: Kim MY. Project administration: Cho E, Kim MY, Choi S. Visualization: Cho E. Writing – original draft: Cho E, Kim MY, Lim I, Kim R. Writing – review and editing: Cho E, Kim MY, Choi S, Demeyere N. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS

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Associations Between Stroke Outcome Assessments and Automated Tractography Fractional Anisotropy Incorporating Age

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Objective: To evaluate the association between outcomes, including affected extremity functions and activities of daily living (ADL), and fractional anisotropy (FA) derived from automated tractography incorporating age among patients after stroke.
Methods: This study enrolled stroke patients, and diffusion-tensor imaging was conducted during the second week. Standardized automated tractography was utilized to compute FA values in the corticospinal tract (CST), the inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF). Outcome evaluations were performed at discharge from our affiliated rehabilitation facility. Extremity functions were assessed using the total scores of the motor component of the Stroke Impairment Assessment Set (SIAS-motor). Independence levels in ADL were appraised through the motor and cognition components of the Functional Independence Measure (FIM). For each outcome measure, multivariate regression analysis incorporated the FA values of the CST, the IFOF, and the SLF, along with age.
Results: Forty-two patients were enrolled in the final analytical database. Among the four explanatory variables, the CST emerged as the most influential factor for SIAS-motor scores. Conversely, age proved to be the primary determinant for both the motor and cognition components of FIM, surpassing the impact of FA metrics, including the CST and the IFOF.
Conclusion: The key influencing factors exhibited significant variations based on the targeted outcome assessments. Clinicians should be aware of these differences when utilizing neuroimaging techniques to predict stroke outcomes.

Keywords: Neuroimaging, Prognosis, Recovery of function, White-matter

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INTRODUCTION

Neuroimaging is an important diagnostic tool in stroke rehabilitation [1-5]. Among various neuroimaging modalities, diffusion-tensor imaging (DTI) is unique for its ability to evaluate neural fibers in vivo [6]. Of the various parameter estimates obtained from DTI, fractional anisotropy (FA) is frequently employed to assess neural integrity in the brain, particularly as an indicator of Wallerian degeneration [6]. DTI is partially used for outcome prediction in clinical practice [4,7,8].

The vast majority of DTI studies in relation to stroke outcomes have focused on upper extremity functions. However,

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stroke patients often experience reduced levels of functional independence in their activities of daily living (ADL). There have been a very limited number of DTI studies that focused on ADL as an outcome measure [9-11]. This is partially due to the complexity of ADL, which encompasses ambulatory ability and cognitive functions such as memory.

Owing to the newly developed automated DTI analysis procedure known as XTRACT [12], the assessments of 42 representative neural tracts within the whole brain have become possible within 1 hour per subject. In our previous studies [13-15], we have ensured clinical applicability of this newly developed technique for the assessment of hemiparesis and aphasia [13-15]. This study aimed to further expand this newly developed technology to ADL in addition to extremity functions. Because ADL is evidently influenced by age [11], in this study, we incorporated age in addition to DTI metrics.

METHODS

Patients

The study protocol received approval from the Institutional Review Board of Hyogo Medical University (No. 4546) and informed consent for participation was obtained using the opt-out method. This research utilized a retrospective cohort of medical records. The study database consisted of patients who were admitted to Nishinomiya Kyoritsu Neurosurgical Hospital for the treatment of stroke between April 2022 and September 2023. The diagnosis of stroke was based on conventional computed tomography and/or magnetic resonance imaging scanned in the emergency unit of our hospital [16,17]. The management of stroke aligned with the Japanese Guidelines for the Management of Stroke 2021 [18], including the prescribed rehabilitative regimen.

To mitigate potential confounding factors arising from variations in pre-stroke health status and lesion sites, we restricted our sample to first-ever stroke patients with supratentorial lesions who were functionally independent in ADL prior to the stroke [9,11,19]. We also excluded patients who exhibited subsequent deterioration in neurological manifestations and other medical conditions during acute care [9,11,19]. Moreover, to minimize disparities in the rehabilitative regimen, we specifically collected data from patients exclusively transferred to our affiliated long-term rehabilitation facility, Nishinomiya Kyoritsu Rehabilitation Hospital [9,11,19].

DTI acquisition

DTI scans were typically conducted during the second week following admission to our acute care service [20], utilizing a 3.0-Tesla scanner (MAGNETOM Trio; Siemens AG) equipped with a 32-channel head coil. The acquisition of DTI data employed a single-shot echo-planar imaging sequence in the anterior-to-posterior direction, comprising 30 images with non-collinear diffusion gradients (b=1,500 s/mm^2) and one non-DWI scan (b=0 s/mm^2). For each patient, 80 contiguous axial slices were obtained with a field of view of 256 mm×256 mm, an acquisition matrix of 128×128, and a slice thickness of 2 mm. The echo time was 96 ms, the repetition time was 10,900 ms, and the flip angle was 90°. To address eddy current-induced and echo-planar imaging-induced distortions, two additional non-DWI scans were acquired in the anterior-to-posterior direction and two in the posterior-to-anterior direction. Additionally, for capturing anatomical details of the patients' brains, T1-weighted images were acquired using a three-dimensional fast gradient imaging sequence. For each patient, a total of 176 contiguous sagittal slices were acquired with a field of view of 256 mm×256 mm, an acquisition matrix of 256×256, and a slice thickness of 1 mm. The echo time was 2.52 ms, and the repetition time was 1,900 ms, and the flip angle was 10°.

Image processing

The DTI scan image processing pipeline employed the MRIcron, MRtrix, and FSL software packages [21-23]. The details of image processing were previously published [13-15]. In brief, initial steps involved eliminating the Gibbs ringing artifact, correcting distortions induced by eddy currents and echo-planar imaging, and applying bias field corrections. Brain masks were then derived from the bias field-corrected images. Following the preparatory stage, we utilized the XTRACT function within FSL for fiber tracking [12]. This enabled the generation of tractography for 42 predefined sets of neural bundles. The purpose of the present study was to assess the relationships between neural-fiber damages and outcome measurements among stroke patients. According to our previous studies [9,10,24], the corticospinal tract (CST) was strongly associated with extremity function, whereas association fibers such as the superior longitudinal fasciculus (SLF) and the inferior fronto-occipital fasciculus (IFOF)—partially overlapping with the anterior thalamic radiation (ATR), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF)—were linked to cognitive functions. Our previous studies reported that neural

degeneration was most prominent in these neural tracts among patients following a supratentorial stroke [9,10,24]. To ensure clarity in the statistical procedures, this study focuses on the CST, IFOF, and SLF, as illustrated in Fig. 1. Parameter estimates, including FA values, were then extracted using a threshold set at 0.01, consistent with findings from our prior studies [13-15].

Outcome measurements

In this study, outcomes were assessed using the motor component of the Stroke Impairment Assessment Set (SIAS-motor) [25] and the Functional Independence Measure (FIM) [26]. SIAS-motor comprises five components—arm, finger, hip, knee, and ankle functions—each scored on a scale from null to full (0 to 5). To quantify gross motor function on the paralyzed side for each patient in this study, we calculated the total sum of SIAS-motor scores. This calculation follows the method outlined in our previous studies [13,17]. The FIM, a widely adopted tool for evaluating independence in ADL, consists of two components: motor (13 items) and cognition (5 items). Each item is scored on a 7-point scale (1=total assistance; 7=complete independence). Total scores for both FIM-motor (scale range, 13–91) and FIM-cognition (scale range, 5–35) are commonly used in stroke rehabilitation. SIAS-motor and FIM scores were assessed bi-weekly, with data collection conducted at our affiliated long-term rehabilitation facility upon discharge. Additionally, the total length of hospital stay (LOS) was recorded for each patient.

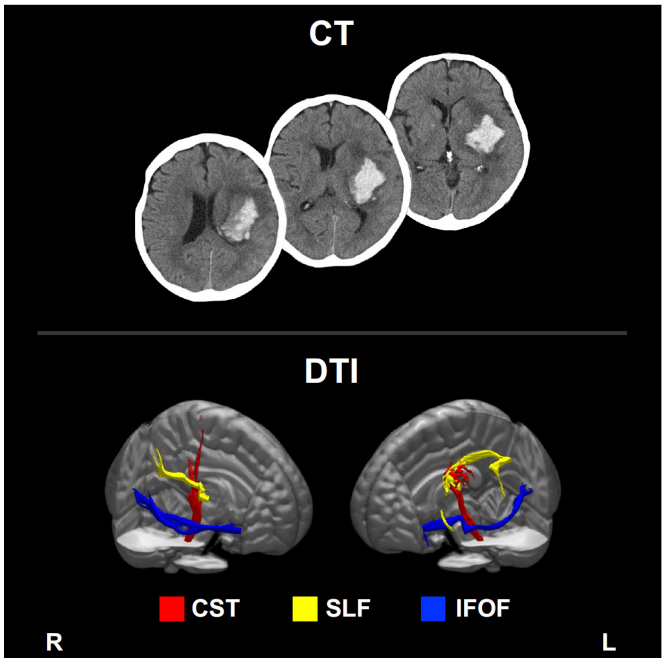

Fig. 1. An example (patient 42 in Table 1) of computed tomography (CT, upper panels) and diffusion-tensor imaging (DTI, lower panels). CST, corticospinal tract; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; R, right; L, left.

Statistical analysis

Multivariate regression was used to analyze the data, with separate assessments conducted for SIAS-motor total, FIM-motor, FIM-cognition, and LOS data. In all analyses, age and lesion-side FA values from the CST, the IFOF, and the SLF were designated as explanatory variables. The final regression models were determined through parameter selection using the Akaike information criterion method. To identify potential multicollinearity, Spearman's correlation test was conducted for all possible pairings of the four explanatory variables. Statistical analyses were performed using the JMP software package (SAS Institute Inc.), and significance was set at a p-value<0.05.

RESULTS

Throughout the study period, a total of 48 patients meeting our inclusion criteria were enrolled. Three patients were excluded due to suboptimal DTI quality, and additional three patients were also excluded because their FIM data were incomplete. Consequently, our final analytical database comprised 42 patients (Table 1). The research cohort comprised 27 cases of ischemic strokes and 15 cases of hemorrhagic strokes, including 28 male and 14 female patients, ranging in age from 42 to 88 years. The calculated FA values within the CST on the lesion side ranged from 0.292 to 0.627. Similarly, the FA values in the IFOF varied from 0.320 to 0.555, while those in the SLF spanned from 0.196 to 0.446. The total score for SIAS-motor ranged from 0 to 25, FIM-motor spanned from 39 to 91, FIM-cognition ranged from 21 to 35, and LOS varied from 36 to 208.

Table 2 presents the outcomes derived from multivariate regression analyses, while Table 3 displays the results of correlation analyses among explanatory variables. For the SIAS-motor total, the CST emerged as the most influential determinant (F=20.340). Although age and the IFOF were identified as statistically significant contributory factors, their impact was comparatively less pronounced. Regarding FIM-motor, three explanatory variables—age, the CST, and the IFOF—were recognized as statistically significant contributory factors. Among these, age emerged as the most prominent determinant factor (F=18.915). In the case of FIM-cognition, age and the IFOF

Table 1. Patient profiles

Pt. No.	Age (yr)	Sex	Lesion site	Stroke type	Lesion-side FA			Non-lesion-side FA			SIAS-motor		FIM		LOS
					CST	IFOF	SLF	CST	IFOF	SLF	Raw	Total	Mot	Cog	
1	80	F	L Frontal	I	0.627	0.530	0.275	0.636	0.522	0.447	5-5-5-5-5	25	89	31	189
2	67	M	L Temporal	I	0.600	0.427	0.399	0.623	0.484	0.425	5-5-5-5-5	25	91	29	42
3	72	M	L PLIC	I	0.589	0.514	0.382	0.632	0.494	0.398	5-5-5-5-5	25	89	28	122
4	50	M	L MCA	I	0.588	0.501	0.406	0.569	0.485	0.410	5-5-5-5-5	25	91	35	50
5	80	F	R Frontal	I	0.586	0.469	0.292	0.594	0.487	0.391	3-3-5-4-5	20	45	30	176
6	64	M	L Frontal	I	0.583	0.504	0.443	0.650	0.487	0.447	4-2-5-5-5	21	91	35	104
7	75	M	L CR	I	0.583	0.532	0.393	0.616	0.514	0.449	4-4-4-4-4	20	78	23	94
8	71	M	R MCA	I	0.580	0.472	0.369	0.553	0.437	0.363	5-5-5-5-4	24	90	35	58
9	61	M	L MCA	I	0.579	0.404	0.313	0.640	0.542	0.486	3-1-4-4-4	16	86	21	171
10	51	M	L Temporal	I	0.579	0.458	0.341	0.574	0.505	0.452	5-5-5-5-5	25	91	34	44
11	75	M	L Frontal	I	0.565	0.454	0.376	0.594	0.453	0.342	4-4-5-5-5	23	87	30	163
12	75	M	L Parietal	H	0.559	0.455	0.359	0.587	0.455	0.414	5-5-5-5-5	25	85	21	83
13	56	M	L PLIC	I	0.555	0.466	0.420	0.626	0.454	0.397	5-5-5-5-5	25	90	35	51
14	82	F	L Parietal	I	0.537	0.453	0.346	0.565	0.451	0.386	4-4-5-5-5	23	79	28	118
15	69	M	R CR	I	0.535	0.555	0.441	0.661	0.586	0.481	4-4-4-4-3	19	86	34	128
16	65	M	R Thalamus	H	0.530	0.455	0.385	0.612	0.491	0.499	5-5-5-5-5	25	91	35	94
17	42	M	R Putamen	H	0.529	0.417	0.388	0.593	0.506	0.374	4-4-4-4-4	20	90	32	78
18	52	M	R Putamen	H	0.501	0.361	0.432	0.568	0.495	0.378	5-4-5-5-5	24	91	33	43
19	62	M	R MCA	I	0.496	0.400	0.218	0.508	0.436	0.329	4-4-4-4-4	20	85	25	126
20	57	F	L PLIC	I	0.496	0.476	0.380	0.569	0.469	0.336	5-5-5-5-5	25	91	35	37
21	63	M	R CR	I	0.491	0.466	0.389	0.557	0.455	0.429	4-5-5-5-4	23	90	35	57
22	67	M	L CR	I	0.485	0.470	0.402	0.603	0.478	0.413	1-0-2-2-3	8	60	28	167
23	75	M	R Putamen	I	0.475	0.465	0.446	0.555	0.486	0.437	1-1-4-4-4	14	68	26	119
24	62	M	L Thalamus	H	0.472	0.471	0.377	0.540	0.468	0.409	5-4-5-4-4	22	90	35	61
25	75	M	R Temporal	I	0.470	0.514	0.293	0.607	0.530	0.387	2-1-3-3-4	13	67	31	117
26	88	F	R CR	I	0.464	0.489	0.382	0.598	0.465	0.373	4-2-3-4-4	17	79	22	95
27	75	F	R CR	I	0.462	0.532	0.398	0.609	0.531	0.419	3-2-4-3-4	16	79	35	157
28	46	M	L PLIC	I	0.461	0.480	0.403	0.599	0.488	0.408	3-2-4-4-4	17	90	35	124
29	55	F	R PLIC	I	0.452	0.497	0.375	0.613	0.498	0.373	4-4-5-5-5	23	89	34	36
30	55	M	R Thalamus	H	0.447	0.442	0.362	0.554	0.407	0.381	5-5-5-5-5	25	91	35	41
31	77	F	L Thalamus	H	0.438	0.467	0.345	0.557	0.483	0.288	5-5-5-5-5	25	89	32	52
32	73	F	L Parietal	H	0.436	0.445	0.299	0.538	0.461	0.335	3-1-4-4-4	16	63	21	208
33	76	M	R Thalamus	H	0.415	0.320	0.363	0.469	0.452	0.370	2-2-3-3-3	13	58	27	199
34	80	M	R Thalamus	H	0.409	0.461	0.396	0.598	0.461	0.383	1-1-2-1-1	6	59	30	176
35	53	F	L Putamen	H	0.397	0.501	0.380	0.615	0.505	0.425	5-4-4-4-4	21	90	35	121
36	59	M	R PLIC	I	0.397	0.504	0.425	0.526	0.526	0.386	4-4-5-5-5	23	90	35	77
37	62	M	L Putamen	H	0.375	0.441	0.303	0.611	0.509	0.462	3-1-3-4-3	14	84	35	102
38	73	F	L Thalamus	H	0.375	0.489	0.384	0.554	0.488	0.391	4-4-5-4-4	21	90	35	55
39	47	F	R MCA	I	0.371	0.382	0.222	0.598	0.521	0.450	2-1-4-4-4	15	86	34	162
40	71	F	L MCA	I	0.365	0.327	0.312	0.558	0.448	0.318	1-0-3-3-3	10	54	21	196
41	61	F	R Putamen	H	0.307	0.344	0.369	0.574	0.521	0.431	0-0-0-0-0	0	39	24	205
42	58	M	L Putamen	H	0.292	0.365	0.196	0.576	0.497	0.405	2-1-2-3-0	8	75	31	202

Patients are ordered according to fractional anisotropy (FA) value of the lesion-side corticospinal tract (CST) (highest to lowest).
Raw SIAS-motor scores are sequenced as arm–finger–hip–knee–ankle.
Pt., patient; SIAS-motor, motor component of the Stroke Impairment Assessment Set; FIM, Functional Independence Measure; LOS, length of hospital stay; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; Mot, motor; Cog, cognition; F, female; M, male, L, left; PLIC, posterior limb of the internal capsule; MCA, middle cerebral artery; R, right; CR, corona radiata; I, ischemic stroke; H, hemorrhagic stroke.

Table 2. Results from multivariate regression analyse

	Estimate	F-value	p-value
SIAS-motor			
Age[a)]	-0.138	4.388	0.043
CST[a)]	42.392	20.340	<0.001
IFOF[a)]	24.907	2.957	0.094
SLF	-	0.011	0.917
Intercept	-3.795	-	-
Adjusted R^2	0.457	-	<0.001
FIM-motor			
Age[a)]	-0.663	18.915	<0.001
CST[a)]	45.858	4.435	0.042
IFOF[a)]	92.914	7.667	0.009
SLF	-	0.050	0.824
Intercept	59.655	-	-
Adjusted R^2	0.421	-	<0.001
FIM-cognition			
Age[a)]	-0.254	21.984	<0.001
CST	-	1.634	0.209
IFOF[a)]	41.719	14.975	<0.001
SLF	-	0.186	0.669
Intercept	28.194	-	-
Adjusted R^2	0.410	-	<0.001
LOS			
Age[a)]	1.932	8.326	0.006
CST	-	1.542	0.222
IFOF[a)]	-283.957	3.851	0.057
SLF[a)]	-303.367	5.268	0.027
Intercept	224.363	-	-
Adjusted R^2	0.314	-	<0.001

SIAS-motor, motor component of the Stroke Impairment Assessment Set; FIM, Functional Independence Measure; LOS, length of hospital stay; CST, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus.
[a)]Parameters that were selected by the Akaike information criterion.

were recognized as statistically significant contributory factors. Consistent with the observations in FIM-motor, age emerged as the most prominent determinant factor (F=21.984). For LOS, age, the IFOF, and the SLF were determined to be statistically significant contributory factors. As similar to the findings for FIM-motor and FIM-cognition, age was recognized as the most powerful determinant (F=8.326). As shown in Table 3, the correlation between the CST and the IFOF (R=0.440) and that between the IFOF and the SLF (R=0.387) were statistically significant.

DISCUSSION

In this study, we investigated the relationships between DTI data and stroke patient outcomes, incorporating age as an additional factor. Regarding extremity function impairment, as indexed by the SIAS-motor total scores, the CST emerged as the most significant determinant, while age played a less prominent role. In contrast, for ADL performance measured by FIM scores, age was the most influential factor, surpassing the impact of damage to neural tracts, as indicated by FA values, including the CST and IFOF. Additionally, LOS was influenced by both age and association fibers, such as the IFOF and SLF.

Table 3. Correlations between explanatory variables

	Age	CST	IFOF
CST	0.135 (p=0.394)	-	-
IFOF	0.216 (p=0.169)	0.440 (p=0.004)[a)]	-
SLF	-0.024 (p=0.880)	0.266 (p=0.088)	0.387 (p=0.011)[a)]

CST, corticospinal tract; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus.
[a)]Statistically significant correlations were show in bold.

The findings of this study emphasize that the primary contributing factors to outcomes vary significantly depending on the modality of assessment, such as ADL and extremity functions. Recent neuroimaging studies focusing on CST integrity often utilized upper extremity function as an outcome measure (e.g., Fugl-Meyer Assessment) [3,27]. Notably, age was rarely incorporated as an explanatory factor in these studies [3], which may be acceptable given the nature of extremity function assessments. In contrast, when ADL was evaluated using the FIM scoring system—comprising motor and cognitive components—age and association fibers, including the IFOF, were more prominently associated with outcome scores. Specifically, age emerged as the most influential determinant for ADL outcomes, possibly due to the inclusion of FIM-motor items, such as dressing, that are closely linked to cognitive function, which is naturally influenced by age. The dissociation between extremity functions and FIM-motor components can likely be attributed to this relationship. As demonstrated, the primary contributing factors exhibit significant variation based on the method of outcome measurements.

Our previous study revealed correlations between stroke outcome scores, including FIM-cognition and FA decrease in broader brain areas, such as the ATR, the UF, and the ILF [24]. Visual inspection on the obtained tractography revealed a partial overlap between the anterior part of the IFOF, the ATR, and the UF [10,15]. Additionally, the posterior part of the IFOF exhibited overlap with the ILF [10,15]. Preliminary correlation analyses among these four neural tracts, similar to those shown in Table 3, demonstrated statistically significant relationships

in four out of six possible pairs. It is true that different neural tracts reflect different aspects of brain function. Among the four neural tracts, however, the IFOF is the largest and is associated with a wider range of cognitive functions [28]. Considering that the FA values derived from these neural tracts are highly correlated and that, given the sample size, we must limit the number of explanatory variables included in the multivariate regression analyses, we selected the IFOF as the representative tract. The XTRACT function implemented in FSL was employed in this study. Concerning the SLF, it generates three parts; the dorsal (part 1), the intermediate (part 2), and the ventral (part 3). Consistent with the aforementioned reasons, we designated part 3 as the representative for the SLF in this study.

The cognitive symptoms in stroke patients vary depending on the side of the lesions; individuals with left hemisphere lesions often experience aphasia and/or apraxia, while those with right hemisphere lesions may suffer from neglect and/or disorientation. Despite these differences in lesion hemisphere and cognitive symptoms, we did not conduct separate analyses for the right and left hemisphere lesion groups in this study. In our previous study, we used tract-based spatial statistics to assess neural damage in relation to clinical symptoms. We employed the FIM-cognition score to evaluate cognitive decline in patients after stroke [24]. The results indicated that the degree of cognitive decline correlated with FA values within some association fibers, including the ATR, the ILF, the SLF, and the UF. The observed patterns were nearly symmetrical between the right hemisphere lesion group and the left hemisphere lesion group [24]. Consequently, for the present study, we did not perform separate analyses for the right hemisphere lesion group and the left hemisphere lesion group.

Results from multivariate regression analyses indicated that, besides age, LOS was influenced by both the SLF and the IFOF (Table 2). In our previous study [11], we assessed the CST integrity using the ipsilesional-to-contralesional ratio of FA within the cerebral peduncles. We then performed multivariate regression for LOS, setting the CST neural integrity, age, and stroke type (ischemic or hemorrhagic) as explanatory variables. The results from our previous study revealed that age and the CST neural integrity accounted for much of the variability in LOS (adjusted R^2=0.420) [11]. Due to technical difficulty, the previous study did not include the IFOF and the SLF data. In this study, as indicated in Table 3, we observed a mild correlation between the CST and the IFOF. Although the results of the LOS analysis did not include the CST as a statistically contributory factor, such an outcome could be expected due to the issue of multicollinearity.

The vast majority of previous DTI studies investigating the association between the CST integrity and motor functions employed the ipsilesional-to-contralesional ratio of FA [3,11,29,30]. This procedure reduces inter-individual differences in the CST-FA. Nevertheless, the application of the ratio FA diminishes the suitability of DTI for individuals experiencing recurrent strokes, as the FA on the non-lesion side is expected to remain undamaged. We have recently investigated the clinical applicability of raw FA values to assess motor functions after a stroke. The findings were promising [13]. Accordingly, in this study, we employed raw FA values to assess the integrity of neural bundles.

In this study, we included both types of ischemic and hemorrhagic strokes in our analytical database. However, we did not include the type of stroke as an explanatory variable in the multivariate regression analysis. In our previous study, we found that the FA decrease in the CST was more evident in hemorrhagic stroke than in ischemic stroke [31]. Nevertheless, the severity of affected extremity functions paralleled the observed FA decreases [31]. In another previous study [11], we investigated the contributions of the type of stroke to the outcome measurements for both the extremity functions and ADL. The obtained results indicated that the contribution of the type of strokes was minimal [11]. Accordingly, in this study, we omitted including the type of stroke as an explanatory variable in the multivariate regression analysis.

Previous studies have indicated that while extremity functions are largely attributed to the integrity of the CST, cognitive functions, such as aphasia and spatial neglect, involve a broader network of associative fibers, including the SLF and the inferior IFOF [9,10,24]. The specific neural substrates responsible for these functions have been partially elucidated through modern neuroimaging techniques. For instance, the SLF is now thought to be associated with phonetic processing, whereas the IFOF is considered to play a role in semantic processing [15,32]. However, in this study, we utilized total scores of FIM-cognition, which provides a general assessment of various cognitive domains, such as memory, expression, and comprehension. Further research is needed to clarify the relationships between specific components of cognitive functions and their associated neural tracts.

In this study, we acquired DTI data during the second week after admission. Ideally, a longer observation period would be preferable to improve the accuracy of detecting FA decreases

[20]. However, under the Japanese health insurance system, stroke patients requiring inpatient rehabilitative treatment are typically transferred to long-term convalescent rehabilitation facilities around the third to fourth week after admission [33]. Unfortunately, our affiliated rehabilitation hospital is not equipped with magnetic resonance scanners. Future studies with longitudinal DTI acquisition settings are desirable [20].

This study has several limitations. First, the FA values are influenced by the threshold setting. In the current study we set the threshold as 0.01 in line with our previous reports in a DTI study series [13-15]. However, there is currently no consensus regarding this setting. Second, the study's population was restricted to first-ever stroke patients who were functionally independent before the onset of stroke. Consequently, the applicability of the study's findings to geriatric patients requiring assistance in ADL before stroke remains uncertain [11]. Third, the sample size for the present study comprised 42 participants, which may be considered relatively small in retrospective research studies. However, it is noteworthy that a recent systematic review [3], examining a wide array of studies, revealed that, among the 71 studies reviewed, interquartile range of the samples was 15 to 50 (median, 28). While a larger sample size could increase statistical power and potentially enhance the generalizability of findings, it is crucial to acknowledge that smaller sample sizes are not uncommon in clinical neuroimaging studies.

Conclusion

This study indicated that, incorporating age, the FA derived from automated tractography is associated with levels of independence in ADL and functional capacity of the affected extremity. However, relative contributions of FA and age were different among the modality of outcomes. These findings suggest that this combination may be useful for predicting outcomes in stroke patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Mochizuki M, Koyama T. Methodology: Koyama T. Formal analysis: Mochizuki M, Koyama T. Funding acquisition: Koyama T. Visualization: Mochizuki M, Koyama T. Writing – original draft: Mochizuki M, Koyama T. Writing – review and editing: Uchiyama Y, Domen K. Approval of final manuscript: all authors.

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Correlation of Sit-to-Stand Test and 6-Minute Walk Test to Illustrate Cardiorespiratory Fitness in Systolic Heart Failure Patients

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Objective: To prove 5-time sit-to-stand (5-STS) and 30-second sit-to-stand (30sSTS) tests in assessing cardiorespiratory fitness in chronic heart failure (HF) patients with systolic dysfunction. Alternative tests, such as 5-STS and 30sSTS, may be used to assess cardiorespiratory fitness in patients with HF but have not been thoroughly evaluated. Thus, this study aimed to prove 5-STS and 30sSTS tests in assessing cardiorespiratory fitness in chronic HF patients with systolic dysfunction.

Methods: A cross-sectional study was done, evaluating chronic HF patients with systolic dysfunction that have received optimal guideline directed medical treatment for at least 3 months. All patients underwent the same intervention on the same day, starting with an initial 5-STS test, followed by a 30sSTS, and a 6-minute walk test (6MWT).

Results: A total of 34 patients were enrolled in this study. The median left ventricular ejection fraction was 44% (interquartile range=34%–48%). Mean values of 5-STS, 30sSTS, and 6MWT were 13.90±4.72, 13.29±3.38, and 463.65±87.04, respectively. 5-STS showed moderate correlation with 6MWT (r=–0.436, p=0.01). However, the 30sSTS revealed strong correlation with 6MWT (r=0.629, p<0.001).

Conclusion: The 30sSTS test had strong correlation with 6MWT. It could be used to illustrate cardiorespiratory fitness in chronic HF patients with systolic dysfunction.

Keywords: Heart failure, Sit-to-stand test, 6-Minute walk test

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INTRODUCTION

Heart failure (HF) occurs due to abnormalities in the heart's structure or function, resulting in a reduced capacity to deliver oxygen throughout the body [1,2]. In 2020, Indonesia ranked as the second-highest country globally in HF-related deaths [3]. Data from the 2018 Basic Health Research indicated that 1.5% of the Indonesian population, approximately 1,017,290 indi-

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viduals, had been diagnosed with congestive HF by healthcare providers [3]. The rising prevalence of this condition highlights the critical need for early detection, prevention, and effective management strategies. Key risk factors include hypertension, diabetes, coronary artery disease, and lifestyle behaviors such as smoking and insufficient physical activity. Symptoms commonly associated with HF are shortness of breath, difficulty breathing while lying flat, episodes of nighttime breathlessness, fatigue, swelling in the ankles, and reduced exercise tolerance [1,4,5]. Severe exercise intolerance is associated with serious long-term effects, including a poor prognosis, higher mortality rates, and a decline in overall quality of life [6-9].

Exercise intolerance refers to a reduced ability to engage in physical activities, often presenting with noticeable symptoms such as fatigue or shortness of breath [5,7,10,11]. This condition may stem from various underlying factors, including compromised heart and lung function, muscle dysfunction, peripheral vascular abnormalities, and disrupted autonomic regulation [7,12]. As a result, assessing exercise capacity has become a key measure in evaluating exercise intolerance in HF patients, particularly in cases of systolic HF. In these patients, a lower left ventricular ejection fraction (LVEF) is often associated with greater limitations in exercise capacity compared to other forms of HF.

Assessing exercise capacity in HF patients often involves measuring VO_2 max, which reflects an individual's maximum oxygen uptake [13]. Although direct testing is considered the gold standard for determining VO_2 levels, many healthcare facilities face challenges in performing cardiopulmonary exercise testing (CPX) due to limited resources and time constraints [7,14]. As an alternative, the 6-minute walk test (6MWT) is commonly used as an indirect measure of exercise tolerance in patients with HFpEF and is regarded as the gold standard among field-based assessments of exercise capacity [15-17]. This test evaluates submaximal functional capacity by recording the distance a person can walk on a flat surface within six minutes [18-21]. However, studies have noted that not all patients are able to complete the 6MWT [22].

The sit-to-stand (STS) test offers an alternative method for assessing lower limb strength and functional performance, which can be performed conveniently in small spaces [16,19,23-25]. Recent research indicates that the STS tests are space-efficient, safe, and a reliable substitute for the 6MWT in evaluating VO_2 levels in patients with HF [15,22,26]. This study, therefore, aimed to examine the correlation between the STS tests (5-time sit-to-stand [5-STS] and 30-second sit-to-stand [30sSTS]) and the 6MWT to provide insights into cardiorespiratory fitness in patients with chronic HF and systolic dysfunction.

METHODS

This cross-sectional study was conducted at the Cardiovascular Outpatient Clinic of Universitas Brawijaya Hospital in Malang between September and November 2023, involving patients with chronic HF and systolic dysfunction. A total of 34 participants meeting the inclusion criteria were enrolled. Eligible participants were stable HF patients aged 21 years or older, classified as HF with mid-range ejection fraction (LVEF 40%–49%) or HF with reduced ejection fraction (LVEF <40%) undergoing at least 3 months of HF treatment, and providing informed consent.

Exclusion criteria included New York Heart Association class IV HF, neurological disorders (e.g., hemiparesis, paraparesis, or peripheral neuropathy in the lower limbs), balance disorders, scores below 26 on the Montreal Cognitive Assessment Indonesian version, musculoskeletal disorders, significant lower limb pain (numeric rating scale≥4), peripheral arterial disease, or inability to complete at least five chair stands or walk.

All participants underwent the same sequence of tests on a single day. Testing began with the 5-STS test, followed by the 30sSTS test, and concluded with the 6MWT. The tests were arranged in order of increasing intensity, with rest intervals of 5 minutes between the two STS tests and 30 minutes between the final STS test and the 6MWT to minimize fatigue. Hemodynamic parameters (blood pressure, heart rate, respiratory rate, and oxygen saturation) and fatigue levels (assessed using the Borg scale) were recorded before and immediately after each test. Both STS tests used a 43 cm chair without armrests, secured against a wall. During the STS tests (Fig. 1), participants began seated with their arms crossed over their chest and feet flat on the ground, performing the 5-STS test, followed by 30sSTS test. The 6MWT was performed in a closed 30-meter corridor, with participants walking as quickly as possible between two marked points for six minutes to assess the distance covered.

Data analysis was carried out using IBM SPSS Statistics 24.0 for Mac (IBM Corp.). The relationship between the STS tests and the 6MWT was analyzed by comparing the correlations of the 30sSTS and 5-STS tests with the 6MWT. Pearson's correlation coefficient was applied for normally distributed data, while

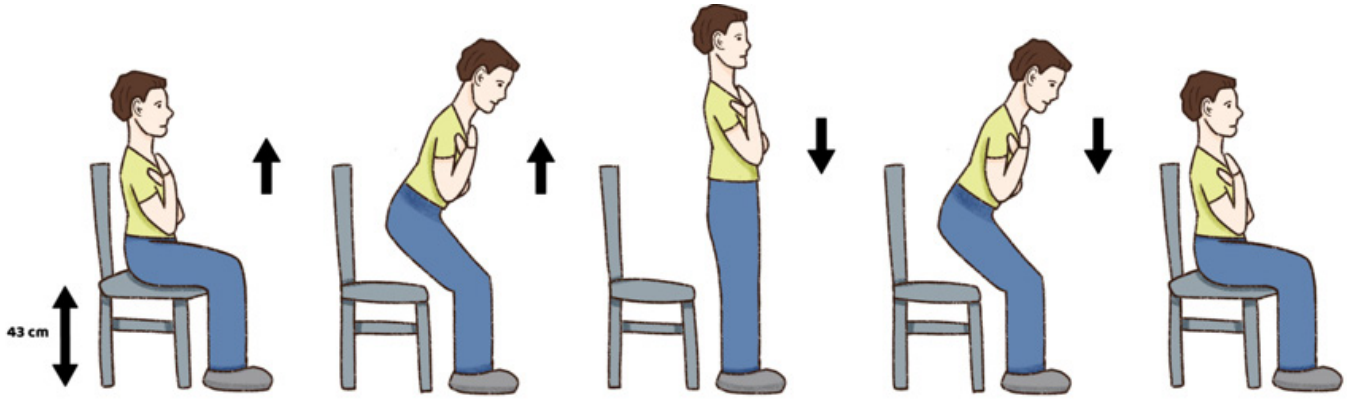

Fig. 1. The 5-time sit-to-stand (5-STS) and 30-second sit-to-stand (30sSTS) tests require specific equipment: a standardized 43.0 cm high chair without armrests and a stopwatch. Instruct participant to sit in a chair with both knees and hips flexed at a 90-degree angle, feet flat on the floor, and arms crossed over their chest. For the 5-STS test, direct participant to stand up and sit down as quickly as possible for 5 repetitions with the option to stop at any time. Meanwhile, for the 30sSTS test, instruct participant to perform the same action for a duration of 30 seconds, also with the option to stop at any point. Scoring involved measuring the time taken to complete 5 repetitions in the 5-STS, while the 30sSTS, each sit-to-stand cycle completed within the 30-second timeframe is counted.

Spearman's correlation coefficient was used for non-normally distributed data.

The study received ethical clearance from the Health Research Ethics Committee of Dr. Saiful Anwar General Hospital Malang (Approval number: 400/207/K.3/302/2023) and obtained a Research Conduct Permit (Approval number: 16/UN10.F08.16.58/PP/2023). Written informed consent was obtained from all participants prior to data collection.

RESULTS

The study included 62 patients with chronic HF, of which 28 were excluded due to conditions such as cognitive, neurological, or musculoskeletal disorders, peripheral arterial disease, and unstable hemodynamics. As a result, 34 patients met the inclusion criteria. Importantly, none of these participants reported significant adverse effects, such as shortness of breath, fatigue, chest pain, fainting, falls, or other symptoms. Baseline characteristics are presented in Table 1.

The mean values recorded for the 5-STS, 30sSTS, and 6MWT were 13.90±4.72, 13.29±3.38, and 463.65±87.04, respectively. Analysis revealed that the 5-STS test had a moderate inverse relationship with the 6MWT (r=-0.436, p=0.01), indicating that shorter completion times in the 5-STS were associated with better 6MWT performance (Fig. 2A). In contrast, the 30sSTS test demonstrated a strong positive correlation with the 6MWT (r=0.629, p<0.001), suggesting that a higher number of repetitions in 30 seconds corresponded to better 6MWT results (Fig. 2B).

Both the 30sSTS and 6MWT showed a negative correlation with LVEF, with r=-0.420 (p=0.013) and r=-0.348 (p=0.044), respectively. However, the 5-STS test did not show a significant correlation with LVEF but exhibited a significant positive correlation with body weight (r=0.402, p=0.019).

DISCUSSION

The current research revealed a significant relationship between the STS tests and the 6MWT, with the 5-STS test showing a moderate inverse correlation (r=-0.436, p=0.01) and the 30sSTS test demonstrating a stronger positive correlation (r=0.629, p<0.001). A prior study by Fuentes-Abolafio et al. [22] found similar results when comparing the 5-STS test to the 6MWT for assessing aerobic capacity (VO_2) in elderly patients with diastolic HF, reporting a moderate inverse correlation with peak VO_2 (r=-0.55, p<0.001). The study concluded that diastolic HF might impair physical function and exercise capacity more severely than systolic HF due to abnormalities in skeletal muscle metabolism, mitochondrial function, and atrophy-related gene expression [12,22,27].

Another study by Adsett et al. [28], involving 49 HF patients undergoing a 12-week rehabilitation program, showed a strong correlation between the 5-STS and 60sSTS tests with the 6MWT (r=-0.70 and 0.76, respectively) and the Timed Up and

Table 1. Participant characteristics

Variable	Value (n=34)
Age (yr)	54.8±8.4
Sex, male	24 (70.6)
Body height (m)	1.6±0.1
Body weight (kg)	71 (61.5–80.9)
Body mass index (kg/m^2)	26.3 (23.6–31.9)
Comorbidities	
Hypertension	17 (50.0)
Diabetes mellitus	14 (41.2)
Hyperlipidemia	24 (70.6)
Active smoker	5 (14.7)
History of stroke/TIA	4 (11.8)
Atrial fibrillation	3 (8.8)
Heart valve disorder	3 (8.8)
Myocardial infarction	22 (64.7)
Percutaneous coronary intervention	9 (26.5)
Echocardiography	
LVEF (%)	44 (34.8–48.0)
LVIDD (mm)	59 (57.0–66.5)
LAD (mm)	39.5±5.0
Functional class	
NYHA I	0 (0)
NYHA II	34 (100)
NYHA III	0 (0)
Cardiovascular medications	
ACEi/ARB/ARNI	33 (97.1)
β-Blocker	31 (91.2)
MRA	29 (85.3)
Loop diuretic	24 (70.6)
Digoxin	14 (41.2)
Statin	27 (79.4)
Antiplatelet	27 (79.4)
Anticoagulants	6 (17.6)
Nitrate	13 (38.2)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; LVIDD, left ventricle internal diameter; LAD, left anterior descending; NYHA, New York Heart Association; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

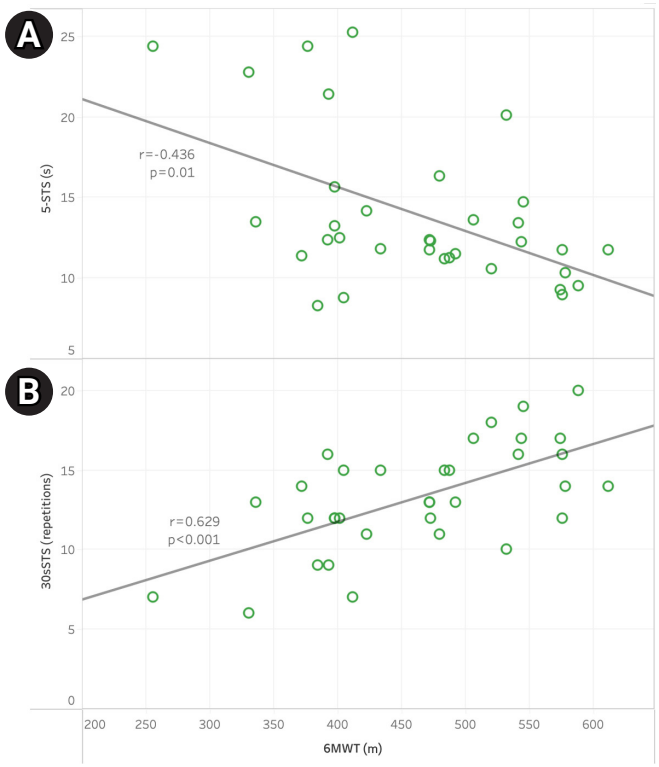

Fig. 2. Scatter plot showing the correlation of (A) 5-time sit-to-stand (5-STS) and (B) 30-second sit-to-stand (30sSTS) with 6-minute walk test (6MWT).

Go test (r=0.79 and -0.77). However, participants performing the 60sSTS reported more fatigue compared to the 5-STS and 6MWT. Previous research has consistently supported the effectiveness of the 30sSTS and 5-STS tests in assessing lower limb strength and endurance [29,30]. Zhang et al. [31] suggested that shorter STS tests evaluate lower limb strength, while longer tests are better for measuring endurance. Similarly, Albalwi and Alharbi [32] concluded that the 5-STS test was better suited for assessing muscle strength and speed, whereas endurance was reflected more accurately in longer STS tests.

Studies by Fuentes-Abolafio et al. [22] and Bohannon et al. [24] emphasized that shorter STS tests may be less reliable in measuring endurance compared to the 10-STS or 30sSTS. Gurses et al. [33] corroborated this finding, demonstrating that the 30sSTS and 60sSTS tests had stronger correlations with the 6MWT (r=0.611 and r=0.647, respectively) than the 10sSTS (r=0.344, p=0.028). The stronger correlation of the 30sSTS and 6MWT with LVEF may stem from hemodynamic changes, which are less pronounced in the 5-STS test. Morita et al. [34] found that STS tests requiring higher repetitions caused greater changes in heart rate and systolic blood pressure due to the increased cardiopulmonary and musculoskeletal effort involved [7].

In patients with HF, particularly systolic dysfunction, reduced cardiac output and impaired oxygen transport to myocytes result in diminished VO_2, reflecting poor exercise capacity [10,24,35,36]. Exercises like the STS test improve VO_2 through enhanced cardiac output, better muscle blood flow, and lower ventilation demand [36,37]. Peripheral muscle adaptations,

including improved mitochondrial density and oxidative function, play a crucial role in increasing VO_2 efficiency, reducing cardiovascular strain during exercise. Such adaptations also enhance central function by improving oxygen transport and gas exchange during physical activity [38-40].

One strength of this study was its ability to assess cardiorespiratory fitness in a time-efficient manner within confined spaces. However, certain limitations must be acknowledged. The absence of a comparison with the gold-standard CPX test restricted the direct assessment of cardiorespiratory fitness using the 30sSTS and 5-STS. The study's limited sample size also precluded a detailed comparison of STS test effects on systolic versus diastolic HF. Additionally, performing all tests on the same day might have induced fatigue in participants, although this was mitigated by monitoring vital signs, subjective feedback, and Borg scale scores.

Future research could enhance validity by incorporating CPX-based VO_2 assessments alongside Borg scale and metabolic equivalents (METs) evaluations to better understand the subjective experience of completing these tests. Increasing the sample size would allow for more robust conclusions regarding the suitability of the 30sSTS as an alternative to the 6MWT for assessing VO_2 and METs in chronic HF patients.

Conclusion

Based on the findings and discussion of this study, both the 30sSTS and 5-STS tests showed a significant correlation with the 6MWT. However, the 30sSTS proved to be a more effective indicator of cardiorespiratory fitness compared to the 5-STS.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Triangto I, Rahmad. Data curation: Triangto I. Methodology: Triangto I, Zuhriyah L, Waranugraha Y. Formal analysis: Triangto I, Rahmad, Waranugraha Y. Funding acquisition: Triangto I. Investigation: Triangto I. Project administration: Triangto I. Resources: Triangto I. Software: Triangto I. Supervision: Triangto I, Witjaksono D, Rahmad, Zuhriyah L, Waranugraha Y. Validation: Triangto I, Dhamayanti AS, Putra MS, Rahmad, Waranugraha Y. Visualization: Triangto I, Dhamayanti AS, Putra MS, Rahmad. Writing – original draft: Triangto I. Writing – review and editing: Triangto I, Zuhriyah L, Waranugraha Y. Approval of final manuscript: all authors.

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Would Integrating Inspiratory Muscle Training Into Pulmonary Rehabilitation of Adults With Burn Injuries Have Any Advantageous Effects? A Randomized, Double-Blind, Sham-Controlled Study

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Objective: To determine the effectiveness of adding inspiratory muscle training (IMT) alongside a pulmonary rehabilitation protocol in terms of inspiratory muscle strength, lung function, and exercise capacity in burned adults.

Methods: A randomized, double-blinded, sham-controlled study. Fifty-two adult patients with burn injuries, more than 20 years old and at least 20% total body surface area, were assigned randomly either to the experimental or the conventional group. The participants in the experimental group were given IMT plus a pulmonary rehabilitation program; the conventional group received only a pulmonary rehabilitation program. The interventions were performed for 8 weeks. At the beginning and after 8 weeks of training, the respiratory muscles' strength, lung function and exercise capacity were all examined.

Results: After 2 months of training, the experimental group demonstrated statistically significant improvements than conventional group in maximum inspiratory pressure, maximum expiratory pressure, 6-minute walk test, forced vital capacity, and forced expiratory volume in 1 second ($p<0.05$).

Conclusion: An 8-week IMT program coupled with pulmonary rehabilitation increases respiratory muscle strength, pulmonary functions, and functional capacity in burn patients. IMT is a beneficial and efficient therapy that can be easily implemented for burn patients.

Keywords: Respiratory muscle training, Pulmonary rehabilitation, Burns, Physical therapy, Rehabilitation

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INTRODUCTION

Burns are life-threatening and devastating injuries that can impair functional exercise capacity, decrease pulmonary function, reduce muscle strength and endurance, and impede normal daily activities [1-6]. As the recovery rates following burn injuries gets higher, serious challenges and significant physical limitations that have a detrimental impact on quality of life and health emerge in the later stages of injury, following the acute stage [2,4,6].

Burned patients have impaired pulmonary function for up to years post burn injury and presented with either restrictive or obstructive pulmonary deficits [1-3]. Respiratory complications are responsible for 41% of mortality and morbidity rates among burned adults [7]. Sixty-nine percent of the burned were later diagnosed with pulmonary deficits, even though none of them experienced pulmonary deficits prior to injury [8].

Burn-injured patients have impaired pulmonary function, lower exercise capacity, and higher desaturation of oxygen during exercise compared to healthy controls. They also stated that these limitations lasted five years following the injury [2]. The hypermetabolic condition linked to major burns, an extended duration of no physical activity during the convalescent stage, and altered pulmonary functions may all contribute to the decrease of respiratory muscle performance and exercise capacity [1,4,5].

Hospital discharge marks the starting point of an important phase in which these individuals reintegrate back to their pre-burn lives. Rehabilitation interventions for sustained recovery in burn patients focus on promoting physical functioning and independence in routine tasks [6,9]. Even though the effect of pulmonary rehabilitation combining resistive and aerobic activities on pulmonary function, aerobic capacity, and muscle strength after burn trauma have been established [1,6,10,11]. Evidence on the effect of inspiratory muscle training (IMT) after acute stage remains scarce.

While research on the reduction of respiratory muscle strength post burns is well recognized [4-6], exercise for respiratory muscle strength is often overlooked. Therefore, a personalized pulmonary rehabilitation, including inspiratory muscle strengthening was recommended [4,5]. Additionally, IMT should be investigated beyond the acute phase of injury. As a result, the main focus of the current investigation was to determine the effectiveness of adding IMT alongside a pulmonary rehabilitation protocol in terms of inspiratory muscle strength, lung function, and exercise capacity in burned adults.

METHODS

Study design

A randomized, double-blinded, sham-controlled, study design was applied. The protocol has been approved by Cairo University's Research Ethics Committee for Physical Therapy (PT. REC/012/004201). The methodologies utilized in this investigation adhered to the Declaration of Helsinki's as well as the CONSORT statement guidelines. The CONSORT statement provided an entire foundation for every aspect of the research procedure, including design of the study, gathering data, and results reporting. Participants received details about the study (i.e., goals, clinical procedures, advantages, and potential difficulties) prior to participation and written informed consent was obtained. The investigation protocol was registered at ClinicalTrials.gov (NCT06315712).

Participants

Fifty-two burn-injured adults who were refered to Cairo University's Faculty of Physical Therapy outpatient clinic for the first time following acute phase therapy from various hospitals in Cairo, Egypt. Participants aged more than 20 years, all of them were healing from injuries that affected at least 20% of their total body surface area (%TBSA). Partial or full thickness burns that either recovered spontaneously or healed by skin grafting. Patients were excluded if they smoked, had open or unhealed wounds, had a known neurological impairment, neuromuscular illnesses, musculoskeletal anomalies, lung, or cardiac diseases, or were unable to exercise regularly.

Sample size

To eliminate type II error, the sample size estimate was performed prior to the initiation of the investigation. G*Power statistical program (version 3.1.9.2) estimated sample size using (F tests- MANOVA: repeated measures, within-between interaction, α=0.05, power=90%, effect size=0.5). The effect size was determined using unpublished findings from a pilot study (5 participants in each group). As a result, the minimum sample size was forty-five participants. To compensate for the drop-off, an extra 15% in the calculated sample size was taken into account, resulting in a study sample size of 52 individuals.

Randomization

Fifty-two burn patients were randomly assigned to either respiratory muscle training combining with pulmonary rehabilitation (experimental group) or pulmonary rehabilitation (conventional group) using a computer-generated block randomization algorithm available at http://www.jerrydallal.com/random/randomize.htm. To eliminate biases and variation between the two groups, participants were randomly assigned to block sizes of 4, 6, and 8, with a 1:1 allocation ratio. The author, who was not involved in recruiting, data collection, or the treatment, oversaw handling the randomization process. Randomization codes were stored in sealed opaque envelopes and consecutively marked to ensure masked allocation. The treating researcher unsealed the envelope and proceeded with therapy based on group allocation. A researcher who was blinded to group randomization collected data at baseline and 8 weeks after the intervention.

Intervention

Everyone who participated in the experimental and conventional groups went through a similar pulmonary rehabilitation program, which consisted of five weekly sessions for eight weeks. Both groups had the same exercise frequency and duration. All exercise sessions were conducted on a case-by-case basis, with supervision. Participants warmed up on the treadmill for five minutes at their own pace, and major muscle groups were stretched at the end of each exercise session. The pulmonary program was: four resistive exercises, aerobic training, and deep breathing exercises. The four primary resisted exercises consisted of four sets of upper- extremity exercises (chest press and biceps curls) and lower-extremity exercises (leg press and knee extension). All exercises were completed with varying resistance equipment. The resistance training equipment has five stages and is conducted at 50%–80% (8–12 repetitions) from the level corresponding to maximum strength [6,12]. Loading intensity was modified biweekly based on maximum strength tests. Aerobic conditioning activities on the treadmill were also included in the schedules. When the participants reported a dyspnea sensation on the Borg scale, the intensity was maintained [6,13]. Resistance training (30 minutes per session) and aerobic exercise (30 minutes per session) were carried out five days a week, each lasting one hour. Participants got instructions to practice deep breathing exercises. Throughout aerobic and resistance training, oral instructions were provided, and deep expiration and inspiration were carried out without urging abdomen retraction [6].

Patients in the experimental group underwent IMT in addition to pulmonary rehabilitation. The POWERbreathe equipment (POWERbreathe International Ltd.) was employed for improving inspiratory muscle strength. It is a respiratory muscle enhancer that employs resistance training principles. Strengthening the inspiratory muscles using POWERbreathe functions similarly to weightlifting in strengthening other muscle groups in the body. The use of this equipment increases the endurance as well as strength of the inspiratory muscles. Initially the participants tried three sets of 30 breaths on the POWERbreathe to adjust the load and become familiar with the device. The training included six 30-breath sets each day, divided into two sessions each. There is a one-minute rest time between each set. Training was scheduled five days a week for eight weeks. In the experimental group, the inspiratory muscle load for training was 50% of maximum inspiratory pressure (MIP), and it was reviewed and changed weekly. The conventional group trained the inspiratory muscles at a set load (5% of MIP), with weekly evaluations but no readjustments [14].

Outcome measures

The MIP was the primary outcome, while the maximum expiratory pressure (MEP), pulmonary function, and 6-minute walk test (6MWT) were the second outcomes. All the outcomes measured before and after eight weeks. To guarantee objective outcome assessment, the assessors were blinded to the intervention allocated to each participant and were not involved in its administration. Before data collection session, each participant received an orientation session to acquire knowledge about the procedures for evaluation and how to conduct appropriate assessments. At baseline, participants' demographics were collected, including age, gender, weight, height, body mass index, TBSA, number of surgeries, cause of burn, depth of burn, number of chests burns and inhalation injuries, and time since burn injury.

MIP and MEP were measured during maximal respiratory effort to determine respiratory muscle strength. The assessment was conducted using an electronic respiratory pressure meter (Micro RPM; Micro Medical) in accordance with the American Thoracic Society (ATS) and European Respiratory Society (ERS) regulations. The subjects repeated the respiratory muscular strength test 3–5 times until there was at least a 10% difference between the values. The highest value was recorded and analyzed. The MIP and MEP values are reported in cmH_2O [15].

Pulmonary function assessment was performed with a mobile spirometer following ATS and ERS recommendations. At the completion of the pulmonary function test, the forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio were calculated. The spirometer reports the results of the pulmonary function test in liters [16].

The 6MWT assessed participants' functional exercise capacity. The 6MWT was performed using standard instructions based on the ATS recommendations. The individuals were instructed to walk as quickly as they could for 6 minutes along a straight hallway of 30 meters. At the end of the test, the 6MWT distance was measured [17].

Statistical analysis

The statistical analysis was carried out using IBM SPSS software for Windows, version 25.0 (IBM Corp.). It was carried out with the intention to treat analysis, the data missed from the eighth-week measurements using the multiple imputation approach. Descriptive statistics were computed for each group at baseline and after 8 weeks. The Shapiro–Wilk test is used to determine the normal distribution of data. Two-way mixed model of multivariate analyses of variance, with the time is within subject factor, were utilized to determine any differences between the mean change scores of each group regarding MIP, MEP, 6MWT, FVC, FEV1, and the FEV1/FVC ratio at each time interval. The F-value was calculated using Wilks' lambda. If the MANOVA showed a significant effect ($p<0.05$), a follow-up univariate ANOVAs were conducted. To avoid the risk of a type I error, multiple comparisons were done with Bonferroni correction. All statistical tests had a level of significance of $p<0.05$.

RESULTS

Fig. 1 depicts the patient flow diagram used throughout the trial. Table 1 shows the baseline demographic and clinical data for all participants in the experimental and conventional groups. A two-way mixed design multivariate analysis was used to compare the magnitude of variation in values on all outcome measures between experimental participants and conventional participants. Significant multivariate effects were identified for the impact of therapy, Wilk's $\lambda=0.48$; $F_{(6, 45)}=8.12$, $p<0.001$, $\eta^2=0.52$, for time, Wilk's $\lambda=0.05$; $F_{(6, 45)}=144.17$, $p<0.001$, $\eta^2=0.95$; and the

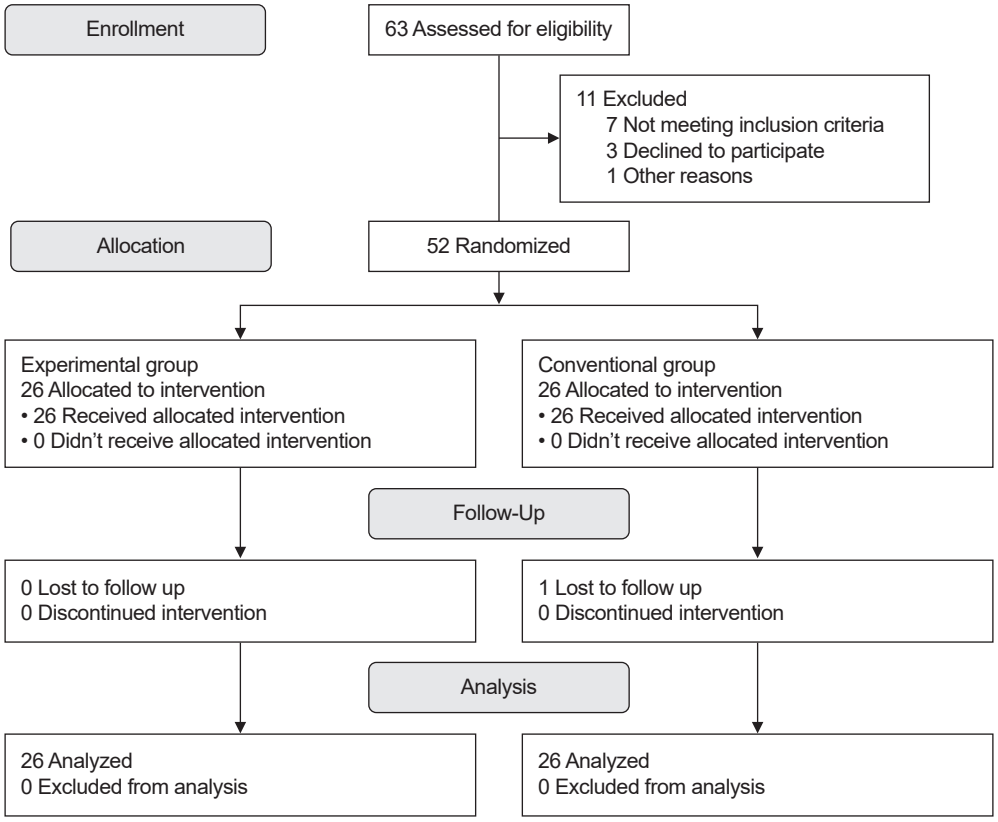

Fig. 1. CONSORT 2010 flow diagram.

Table 1. Baseline demographic and clinical characteristics of subjects (N=52)*

Characteristic	Experimental group (n=26)	Conventional group (n=26)	p-value
Age (yr)	36.27±9.48	38.12±9.17	0.48
Height (cm)	174.32±9.66	171.42±8.65	0.26
Weight (kg)	79.38±9.37	77.61±8.99	0.49
Body mass index (kg/m^2)	26.08±1.71	26.34±1.37	0.55
TBSA (%)	37.31±6.57	35.96±5.88	0.44
Time since burn (day)	88.38±15.80	84.46±15.07	0.36
Sex			
Male	20 (76.9)	17 (65.4)	0.36
Female	6 (23.1)	9 (34.6)	
No. of operations			
None	4 (15.38)	4 (15.38)	0.93
1	9 (34.62)	11 (42.31)	
2	10 (38.46)	9 (34.62)	
3	3 (11.54)	2 (7.69)	
Cause of burn			
Flame	18 (69.23)	20 (76.92)	0.75
Scald	6 (23.07)	5 (19.23)	
Electrical	1 (3.85)	0 (0)	
Chemical	1 (3.85)	1 (3.85)	
Depth of burn			
1st and 2nd degree	9 (34.62)	7 (26.92)	0.55
2nd and 3rd degree	17 (65.38)	19 (73.08)	
Chest burn			
Yes	9 (34.62)	12 (46.15)	0.4
No	17 (65.38)	14 (53.85)	
Inhalation injury			
Yes	14 (53.85)	13 (50.0)	0.78
No	12 (46.15)	13 (50.0)	
MIP (cmH_2O)	75.62±16.47	72.69±11.67	0.46
MEP (cmH_2O)	82.88±16.98	79.19±8.63	0.33
6MWT (m)	462.20±89.19	425.20±54.39	0.08
FVC (L)	3.86±0.23	3.77±0.25	0.15
FEV1 (L)	3.13±0.30	3.00±0.25	0.08
FEV1/FVC	81.16±6.95	79.66±6.23	0.42

Values are presented as mean±standard deviation or number (%).
TBSA, total body surface area; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; 6MWT, 6-minute walk test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.
*p<0.05 indicate statistical significance.

Table 2. Clinical characteristics of subjects in both groups after 8 weeks (N=52)*

Characteristic	Experimental group (n=26)	Conventional group (n=26)	MD (95% CI)	p-value
MIP (cmH_2O)	95.46±16.56	82.50±13.79	12.96 (4.47, 21.45)	0.003
MEP (cmH_2O)	99.77±13.22	87.77±12.40	12.00 (4.86, 19.14)	0.001
6MWT (m)	538.40±93.78	453.20±64.13	85.19 (40.44, 129.95)	0.0004
FVC (L)	4.66±0.37	4.14±0.31	0.52 (0.33, 0.71)	0.0001
FEV1 (L)	3.89±0.27	3.31±0.30	0.58 (0.42, 0.73)	0.0001
FEV1/FVC	83.48±4.75	80.03±6.51	3.45 (0.27, 6.62)	0.03

Values are presented as mean±standard deviation.
MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; 6MWT, 6-minute walk test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; MD, mean difference; CI, confidence interval.
*p<0.05 indicate statistical significance.

interaction of treatment and time Wilk's λ=0.25; $F_{(6, 45)}$=23.15, p<0.001, η^2=0.76.

Follow-up univariate ANOVAs showed significant change for MIP, $F_{(1,50)}$=9.4, p=0.003, η^2=0.16; for MEP, $F_{(1,50)}$=11.4, p=0.001, η^2=0.19; for 6MWT, $F_{(1,50)}$=14.62, p=0.001, η^2=0.23; for FVC, $F_{(1,50)}$=30.42, p<0.001, η^2=0.38; for FEV1, $F_{(1,50)}$=53.23, p<0.001, η^2=0.52; and for FEV1/FVC ratio, $F_{(1,50)}$=4.76, p=0.03, η^2=0.09.

The results revealed no statistically significant variations between groups in terms of MIP, MEP, 6MWT, FVC, FEV1, and FEV1/FVC ratio at baseline (p>0.05). Table 2 and Fig. 2 demonstrate statistically significant changes between groups following 8 weeks of the intervention for all outcome measures (p<0.05). Table 3 shows that after 8 weeks of treatment, there were statistically significant differences in all outcome measures (p<0.05)

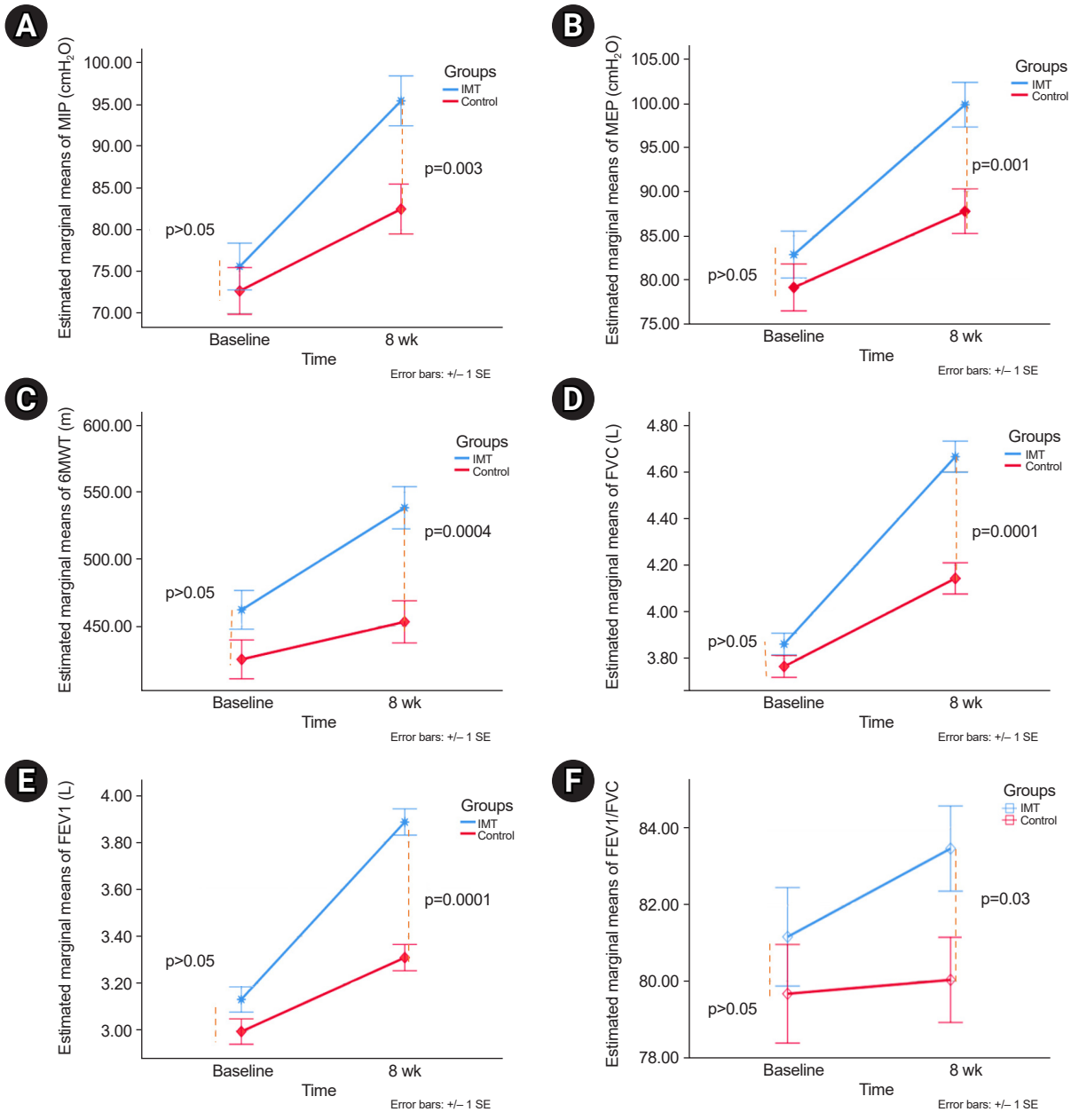

Fig. 2. Clinical characteristics of subjects in both groups after 8 weeks. (A) Maximum inspiratory pressure (MIP). (B) Maximum expiratory pressure (MEP). (C) Six-minute walk test (6MWT). (D) Forced vital capacity (FVC). (E) Forced expiratory volume in 1 second (FEV1). (F) FEV1/FVC.

Table 3. Within group comparisons for the two groups at baseline and after 8 weeks*

Outcome	Experimental group (n=26)		Conventional group (n=26)	
	Change from baseline to 8 weeks		Change from baseline to 8 weeks	
	MD (99% CI)	p-value	MD (99% CI)	p-value
MIP (cmH_2O)	19.85 (17.05, 22.64)	0.0001	9.81 (7.01, 12.61)	0.0001
MEP (cmH_2O)	16.89 (14.47, 19.30)	0.0001	8.58 (6.17, 10.99)	0.0001
6MWT (m)	76.19 (69.31, 83.07)	0.0001	28.00 (21.12, 34.88)	0.0001
FVC (L)	0.80 (0.65, 0.95)	0.0001	0.38 (0.23, 0.53)	0.0001
FEV1 (L)	0.75 (0.65, 0.86)	0.0001	0.31 (0.21, 0.42)	0.0001
FEV1/FVC	2.32 (-1.16, 5.79)	0.19	0.37 (-3.11, 3.84)	0.83

MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; 6MWT, 6-minute walk test; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second, MD, mean difference; CI, confidence interval.
*p<0.05 indicate statistical significance.

in each group, except for the FEV1/FVC ratio (p>0.05).

DISCUSSION

The current research has demonstrated that IMT combined with pulmonary rehabilitation is more successful than pulmonary rehabilitation alone in increasing pulmonary function, respiratory muscle strength, and exercise capacity in adult burned patients following hospitalization stage of injury. These findings agreed with previously published studies on burned patient in acute stage, burned children and inhalation injuries [5,18,19], or populations with different conditions for increasing inspiratory muscle strength and improvement in exercise capacity [14,20-24]. Although the impacts of IMT have been tested in several studies, [14,20-24], there remains a lot of curiosity in the effects of such a therapy strategy on adult burned patients following the hospitalization stage of injury. As a result, the findings presented herein may add to the body of evidence supporting the efficacy of IMT in burn trauma.

The American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation Committee has supported IMT as a component of pulmonary rehabilitation [21]. Furthermore, the ERS agreement advises IMT in conjunction with a standard pulmonary rehabilitation program for individuals with inspiratory muscle weakness. This advice depends on the findings from multiple meta-analyses [22,23], which indicated that IMT improved inspiratory muscle strength and endurance, as well as exercise capacity in the 6MWT.

The experimental group had a mean MIP of 75.62±16.47, while the conventional group had a mean MIP of 72.69±11.67. At baseline, adult burn injured participants had significantly reduced respiratory muscle strength than healthy controls [4]. This contradicts the ATS and ERS, which state that MIP below 80 cmH_2O indicates inspiratory muscle weakness [15]. In our investigation, patients attained a statistically significant improvement in MIP of 20 cmH_2O in the experimental group, which is greater than the minimal clinically important difference value of 13 cmH_2O [23]. This result demonstrated an improvement in inspiratory muscular strength, which was consistent with findings from earlier research on older subjects [20], chronic obstructive pulmonary disease [21-23] and asthmatic patients [24].

In addition to MIP, MEP levels increased in the experimental group. The latter finding can be clarified through neural conditioning caused by repeated exposures to the same task (learning effect), which is a mechanism that increases respiratory muscle strength by enhancing neuromuscular recruitment patterns [20]. These findings can be attributed to the fact that the process of adaptation to training is dependent on an increase in the ratio of type I fibres and the size of type II fibres, which directly alters the length-tension relationship that governs the respiratory system's force-generating mechanics [25]. Furthermore, a training regimen like the one presented here results in increased diaphragm neural activation and chest wall muscle recruitment [26]. According to Komi [27], increases in muscle strength after brief bouts of training with progressive loads seem to be caused by improved intra- and intermuscular neural adjustment. These methods improve synchronization in the frequency of neuromuscular firing, resulting in higher motor unit activation. Whatever of the cause, it is believed that increasing the strength of the respiratory muscles may help enhance exercise capacity and reduce the incidence of respiratory infections and hospitalization due to increased expiratory force, which leads to more efficient coughing [20].

In line with our results, previous research suggests that IMT in combination with other exercise trainings improves function-

al exercise capacity more than exercise training alone in patients with chronic obstructive pulmonary disease [21,22]. In our investigation, a rise of 55 m in the 6-minute walking distance exceeds the literature's minimal clinically important difference [23]. The consequences are partly attributed to the reduction of the respiratory metaboreflex caused by IMT. The metaboreflex hypothesis has been developed to explain respiratory muscle training ergogenic effects. In brief, the metaboreflex theory proposes that fatigued respiratory muscle contractions during high-intensity exercise increase sympathetic output, restricting leg blood flow and performance during exercise. higher tolerance to respiratory muscle fatigue would thus attenuate the response, resulting in decreased sympathetic output, higher leg blood flow, and improved endurance performance [28,29].

A number of studies have found that patients with burns have lower FVC and FEV1 values than healthy people [1-4]. In our research, patients accomplished a statistically significant rise of 21.74% in FVC and 23.96% in FEV1, which additionally ended in a better FEV1/FVC ratio. It is probable that IMT enabled the diaphragm and respiratory muscles to perform more work, resulting in an improvement in respiratory capacity and an increase in thoracic expansion, which had a role in raising static and dynamic lung volumes [30].

The conventional group (sham IMT) was designed to meet the real placebo criteria described by Ojanen [31], which state that placebo therapy should be relevant to participants, inactive, and generate expectations, participation, and subjective utility. For this investigation, we used the lowest possible training load (5% of MIP). As a result, it is possible that our procedure met the previously stated placebo criterion. The placebo group showed considerable post-treatment improvement in exercise capacity, respiratory muscle strength, and pulmonary function. The resulting improvements could be attributable to the effects of respiratory exercises, that may have encouraged a better controlled respiration pattern, better thoracic mobility, higher diaphragmatic strength, and improved respiratory efficiency. Another potential cause is the psychological impact of placebo IMT. Preparation as well as expectations may have served an important role in enhancing outcomes, particularly since the participating youngsters had been receiving regular placebo training for two months [31].

Unfortunately, we did not evaluate the subjects' physical activity levels, which may have influence on the improvements of all measurement's; this parameter should be included as an outcome in further studies. Inability of follow-up with volunteers in the months following the training prevented evaluation of IMT's long-term efficacy. Future research should investigate burn trauma factors (degree of burn, location, TBSA and inhalation injury, etc.) that may influence respiratory muscle strength and pulmonary function in burn patients.

Conclusion

In this study, we demonstrated that eight weeks of IMT in addition to pulmonary rehabilitation increases respiratory muscle strength, pulmonary function, and functional capacity in burn patients. IMT is a safe and efficient therapy that can be easily implemented in the rehabilitation program for burn victims. However, more evidence is needed to draw more consistent results.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Abdel-Aal NM, Kamel FH. Data curation: Basha MA, Aloraini SM, Kamel FH. Formal analysis: Abdel-Aal NM. Investigation: Abdel-Aal NM, Basha MA, Kamel FH. Methodology: Abdel-Aal NM, Azab AR, Kamel FH. Project administration: Basha MA, Resources: Basha MA, Aloraini SM, Azab AR. Software: Basha MA, Aloraini SM. Supervision: Abdel-Aal NM, Kamel FH. Validation: Abdel-Aal NM, Azab AR. Visualization: Basha MA, Aloraini SM. Writing – original draft: Abdel-Aal NM, Basha MA, Kamel FH. Writing – review & editing: Abdel-Aal NM, Basha MA, Aloraini SM, Azab AR, Kamel FH. Approval of final manuscript: all authors.

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Nerve Conduction Study, Sympathetic Skin Response Test, and Demographic Correlates in Type 2 Diabetes Mellitus Patients

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Objective: To comprehensively assess the relationship between nerve conduction study (NCS), sympathetic skin response (SSR), and demographic factors in patients with diabetic neuropathy, exploring potential risk factors and mechanisms.
Methods: A retrospective study (N=184) included patients diagnosed with type 2 diabetes mellitus undergoing NCS and SSR. Demographic, clinical, and laboratory data were analyzed. Patients were categorized by diabetic peripheral neuropathy (DPN) and SSR stages for comparative analysis.
Results: HbA1c levels correlated with DPN progression. SSR stages exhibited age-related differences. Height correlated with DPN but not SSR stages. Body mass index showed no significant differences.
Conclusion: While DPN progression correlated with glycemic control and duration of diabetes, SSR was influenced by age. Unexpectedly, cholesterol levels remained within the normal range, challenging established concepts. Understanding these relationships is crucial for interpreting test results and developing targeted interventions for diabetic neuropathy.

Keywords: Diabetic neuropathies, Nerve conduction studies, Sympathetic nervous system, Physiology

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common and debilitating complication of diabetes mellitus (DM), affecting a significant proportion of individuals with the disease. It is characterized by peripheral nerve dysfunction, leading to sensory disturbances, motor deficits, and autonomic dysfunction. Understanding the pathophysiology and clinical manifestations of diabetic neuropathy is essential for early diagnosis, appropriate management, and the prevention of further complications.

Nerve conduction study (NCS) and sympathetic skin response (SSR) studies are valuable diagnostic tools for evaluating diabetic neuropathy. NCS measures the speed and amplitude of nerve signals, providing objective assessments of large myelinated nerve function and detecting abnormalities in sensory or motor nerve responses [1,2]. SSR, on the other hand, assesses the sympathetic autonomic response by measuring changes in skin electrical conductivity following a stimulus [3,4]. SSR is influenced by both large-diameter sensory fibers in the afferent pathway and small unmyelinated fibers in the efferent pathway. Together, these studies offer complementary information about

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the involvement of both sensory and autonomic nerves in diabetic neuropathy. SSR examinations in diabetics with no or only slight clinical signs of neuropathy may detect autonomic disturbances at an early stage [5,6]. Therefore, SSR is a valuable method for assessing unmyelinated axonal damage (small unmyelinated C-fibers) and autonomic involvement, in conjunction with other autonomic function tests, in diabetic neuropathy patients [7].

While NCS and SSR have been extensively studied in diabetic neuropathy, few investigations have explored their relationship with demographic factors and other clinical test results. Demographic factors, including age, sex, duration of diabetes, and glycemic control, have been shown to influence the development and progression of diabetic neuropathy [8,9]. Examining the association between these factors and nerve conduction abnormalities or altered SSR may provide valuable insights into the underlying mechanisms and potential risk factors for diabetic neuropathy.

Therefore, the aim of this study is to assess the relationship between NCS, SSR studies, demographic factors, and other clinical test results in patients with diabetic neuropathy. By comprehensively exploring these factors and their interactions, we hope to deepen our understanding of the multifaceted nature of diabetic neuropathy. Specifically, this study will investigate the progression of DPN, primarily focusing on larger fiber disorders, as well as the progression of sensory-autonomic fiber dysfunction represented by SSR [10].

METHODS

Participants

This retrospective study was conducted at a tertiary medical institution (Inha University Hospital). We included patients previously diagnosed with type 2 DM or those newly diagnosed who underwent NCS and SSR tests between 2020 and 2022. Patients with potential causes of neuropathy other than diabetes, such as radiculopathy (n=38), chemotherapy (n=18), or systemic diseases affecting the peripheral nerves (n=25), were excluded.

A comprehensive analysis of NCS and SSR results was conducted on 184 patients, incorporating demographic, clinical, and laboratory data. All participants were informed about the research, and informed consent was obtained. The study protocol was approved by the Inha University Hospital Research Ethics Committee (IRB No: 2022-11-016).

Methods

For the NCS, Keypoint equipment (Dantec) was used. The patients' skin temperature was maintained above 32°C. Sensory nerve conduction tests were performed using the antidromic technique on the median, ulnar, superficial peroneal, and sural nerves. Motor NCS included assessments of the median, ulnar, deep peroneal, and tibial nerves. Amplitude was measured from baseline to peak, with filtering frequencies ranging from 20 Hz to 10 kHz for motor nerves and 20 Hz to 2 kHz for sensory nerves.

The mean values of 10 recordings were obtained for both sensory and motor NCS, and minimal F-M latencies were determined using supramaximal stimulation. F-waves were recorded by stimulating each motor nerve (median, ulnar, peroneal, and tibial) with more than 10 supramaximal stimuli, documenting the minimal F-M latency. The diagnosis of DPN was based on electrodiagnostic values of the median, ulnar, peroneal, sural, and tibial nerves, following our laboratory's standards, which were adapted from a diabetes control and complications study group [11]. The presence of more than three abnormal values in at least two different nerves was the minimum requirement for diagnosing DPN. If any abnormal values were observed but did not meet the full diagnostic criteria, the condition was classified as early-stage diabetic neuropathy. We aimed to identify patients with early-stage DPN, characterized by fewer than three abnormal values in at least two nerves. No cases of cubital tunnel syndrome were found in this patient group. In some patients with carpal tunnel syndrome, the neurophysiological examination showed only mild conduction velocity reduction in the wrist area during segmental studies, but they did not present any clinical symptoms of carpal tunnel syndrome.

The SSR was recorded using standard electromyograph equipment. Active surface electrodes were placed on the palms and soles, with reference electrodes on the dorsum of the respective body parts. Before electrode placement, the skin was cleaned, and electrolyte gel was applied. Recordings were made in a quiet, dimly lit room maintained at 22°C–24°C, with a filtering frequency range of 0.5 Hz to 500 Hz. Electrical stimulation was applied to the median nerve at both wrists using a single 20 mA stimulus, with sessions conducted at intervals of at least 30 seconds.

Patients were divided into groups based on DPN stage and SSR progression. For NCS, patients with normal values for all criteria were categorized as Group 1 [8]. Patients with abnormal values who did not meet the diagnostic criteria for DPN were categorized as Group 2, while those meeting the diagnostic

criteria were classified as Group 3. In the SSR test, participants were classified as Group 1 if they showed an evoked response in both upper and lower extremities, Group 2 if they had responses only in the upper extremities, and Group 3 if no evoked response was present in either upper extremity.

We analyzed the contrast between the DPN stage, assessing large fiber neuropathy, and the SSR stage, which includes both large and small fiber neuropathy.

Statistical analysis

SPSS software version 26.0 (IBM Corp.) was used for the statistical analysis. Null hypotheses of no difference were rejected if p-values were less than 0.05.

T-tests were employed to assess differences between two independent groups, ANOVA was used to examine variations among multiple independent groups, and ANCOVA was applied to control for covariates and evaluate group differences. These statistical methods were selected to explore various aspects of the data, ensuring a comprehensive analysis of the relationships and differences among the studied variables.

RESULTS

A total of 184 patients were included in the study, comprising 84 males and 100 females. The respective values for males and females are recorded in the Table 1.

The initial phase of the study involved categorizing groups based on DPN Group 1, 2, 3, and SSR Group 1, 2, 3 for comparative analysis. The second phase of the study involved dividing participants into four groups based on DPN Group and SSR Group for subsequent analysis. Based on the results of NCS and SSR tests (Table 2), we classified the patients into different groups to examine the significance between them. Group A consisted of patients who belonged to SSR Group 1 and DPN Group 1. Group B included patients who were categorized as SSR Group 2 or 3 and DPN Group 1. Group C consisted of patients who were SSR Group 1 and DPN Group 2 or 3. Finally, Group D comprised patients who fell under SSR Group 2 or 3 and DPN Group 2 or 3.

The rationale behind consolidating the original nine groups into four categories in the table was to facilitate statistical analysis. This grouping strategy was employed to enhance the feasibility and interpretability of the statistical analyses conducted on the data.

DPN groups

We first performed an ANOVA by dividing the participants into DPN groups (Table 3). Significant differences were found between DPN Groups 1 and 3. DPN Group 1 had higher total

Table 2. Classification of patients based on NCS and SSR test results

		SSR Group			Total
		1	2	3	
DPN Group	1	49[a]	10[b]	12[b]	71
	2	15[c]	4[d]	5[d]	24
	3	33[c]	20[d]	36[d]	89
Total		97	34	53	184

NCS, nerve conduction study; SSR, sympathetic skin response; DPN, diabetic peripheral neuropathy.
[a]Group A (both normal NCS, SSR), [b]Group B (SSR abnormal only), [c]Group C (NCS abnormal only), [d]Group D (both abnormal NCS, SSR).

Table 1. Physiological and demographic factors of participants

	Total	Male	Female	p-value
No. of participants	184	84	100	-
Age (yr)	62.9±13.6	61.0±13.7	64.5±13.4	0.078
TC (mg/dL)	151.1±53.7	146.8±57.4	154.6±50.6	0.334
TG (mg/dL)	138.0±65.8	134.5±61.5	141.7±70.5	0.539
HDL-cholesterol (mg/dL)	45.0±13.0	42.7±12.1	47.5±13.5	0.038*
LDL-cholesterol (mg/dL)	85.9±41.3	80.7±41.8	91.5±40.4	0.149
HbA1c (%)	8.2±2.6	8.6±2.9	7.9±2.3	0.064
DurDM (yr)	10.9±10.2	11.7±10.5	10.2±10.0	0.378
Height (m)	1.61±0.09	1.68±0.06	1.55±0.07	<0.001***
Weight (kg)	66.1±13.9	70.8±12.9	62.0±13.4	<0.001***
Body mass index (kg/m^2)	25.5±4.5	25.0±3.6	25.8±5.2	0.205

Values are presented as mean±standard deviation.
TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; DurDM, duration of diabetes.
*p<0.05, ***p<0.001.

cholesterol and low density lipoprotein (LDL)-cholesterol levels (p<0.05), while HbA1c levels and the duration of diabetes were significantly higher in DPN Group 3 (p<0.05). Additionally, DPN Group 3 had a greater height compared to DPN Group 1 (p<0.05). After adjusting for sex, age, and duration of diabetes, no significant differences were observed in total cholesterol levels (p>0.05). However, triglyceride levels were higher in DPN Group 1 than in DPN Group 3, although still within the normal range (p<0.05). No significant differences were noted in age, high density lipoprotein (HDL)-cholesterol, weight, or body mass index (BMI) among the groups (p>0.05).

SSR groups

Next, we conducted an ANOVA by dividing the groups based on SSR classifications (Table 4). SSR Groups 2 and 3 were significantly older than Group 1 (p<0.05). Total cholesterol and

Table 3. Physiological and demographic factors of participants by DPN stage group

	DPN Group						p-value
	1		2		3		
	n	Mean±SD	n	Mean±SD	n	Mean±SD	
Sex (male/female)	71 (23/48)	-	24 (9/15)	-	89 (52/37)	-	0.003**
Age (yr)	71	60.4±13.5	24	63.3±13.9	89	64.8±13.5	0.121
TC (mg/dL)	70	166.5±55.7[a)]	23	146.4±50.7[a),b)]	88	140.1±50.4[b)]	0.008**
TG (mg/dL)	40	156.2±80.9	16	134.9±61.7	69	128.1±54.8	0.096
HDL-cholesterol (mg/dL)	40	48.0±12.6	16	44.7±11.1	69	43.4±13.5	0.205
LDL-cholesterol (mg/dL)	40	102.3±42.4[a)]	16	80.6±40.7[a),b)]	69	77.6±38.6[b)]	0.009**
HbA1c (%)	61	6.9±1.4[a)]	24	8.1±2.2[a),b)]	88	9.2±2.9[b)]	<0.001***
DurDM (yr)	48	7.2±7.7[a)]	23	10.0±10.0[a),b)]	86	13.3±10.9[b)]	0.003**
Height (m)	67	1.58±0.09[a)]	22	1.60±0.08[a),b)]	88	1.63±0.09[b)]	0.005**
Weight (kg)	67	64.5±14.1	22	67.0±10.8	88	67.1±14.4	0.475
Body mass index (kg/m^2)	67	25.7±5.0	22	26.1±3.7	88	25.1±4.3	0.609

Groups sharing the same letter (e.g., [a)] or [b)]) do not differ significantly from each other according to the Tukey post hoc test (p>0.05). Groups with different letters indicate statistically significant differences (p<0.05).
DPN, diabetic peripheral neuropathy; SD, standard deviation; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; DurDM, duration of diabetes.
[a)]Tukey post hoc test.
[b)]Tukey post hoc test.
**p<0.01, ***p<0.001.

Table 4. Physiological and demographic factors of participants by SSR stage group

	SSR Group						p-value
	1		2		3		
	n	Mean±SD	n	Mean±SD	n	Mean±SD	
Sex (male/female)	97 (44/53)	-	34 (15/19)	-	53 (25/28)	-	0.958
Age (yr)	97	58.3±13.2[a)]	34	68.8±9.2[b)]	53	67.6±13.9[b)]	<0.001***
TC (mg/dL)	95	159.9±56.0[a)]	34	147.0±59.8[a),b)]	52	137.6±41.7[b)]	0.048
TG (mg/dL)	62	140.5±73.1	26	133.3±55.9	37	136.9±60.6	0.892
HDL-cholesterol (mg/dL)	62	46.1±12.2	26	44.6±14.5	37	43.5±13.4	0.622
LDL-cholesterol (mg/dL)	62	96.1±44.3[a)]	26	80.2±42.5[a),b)]	37	72.8±30.5[b)]	0.017*
HbA1c (%)	88	8.2±2.7	34	8.7±2.7	51	8.0±2.4	0.410
DurDM (yr)	74	9.2±9.8	31	10.6±9.8	52	13.6±10.7	0.053
Height (m)	92	1.62±0.09	33	1.59±0.08	52	1.60±0.10	0.217
Weight (kg)	92	67.1±13.9	33	64.2±12.8	52	65.6±14.5	0.554
Body mass index (kg/m^2)	92	25.5±4.7	33	25.4±4.9	52	25.4±4.0	0.990

Groups sharing the same letter (e.g., [a)] or [b)]) do not differ significantly from each other according to the Tukey post hoc test (p>0.05). Groups with different letters indicate statistically significant differences (p<0.05).
SSR, sympathetic skin response; SD, standard deviation; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; DurDM, duration of diabetes.
[a)]Tukey post hoc test.
[b)]Tukey post hoc test.
*p<0.05, ***p<0.001.

LDL-cholesterol levels were higher in SSR Group 1 compared to Group 3 (p<0.05), although all values remained within the normal range. The duration of diabetes tended to be longer in groups with advanced SSR, but this was not statistically significant (p=0.053). No significant differences were found in triglyceride, HDL-cholesterol, HbA1c, height, weight, or BMI (p>0.05). After adjusting for sex, age, and duration of diabetes, no significant differences were observed in total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, or HbA1c levels (p>0.05).

Grouped by DPN, SSR groups

We performed an ANOVA after dividing the patients into four groups: Group A (both NCS and SSR normal), Group B (SSR abnormal only), Group C (NCS abnormal only), and Group D (both NCS and SSR abnormal) (Table 5).

Significant differences were found between the groups: Group D had lower total cholesterol and LDL-cholesterol levels compared to Group A (p<0.05), although all values were within the normal range. HbA1c levels were higher in Groups C and D than in Groups A and B (p<0.05), and Group D had a longer duration of diabetes compared to Group A (p<0.05). Additionally, Group B was shorter in height than Groups A, C, and D (p<0.05). No significant differences were observed in triglyceride, HDL-cholesterol, weight, or BMI among the groups (p>0.05).

ANCOVA analysis

We performed an ANCOVA on Tables 3, 4, and 5 to assess the influence of sex, age, and duration of diabetes as covariates. When comparing the DPN groups, total cholesterol showed no significant differences after adjustment (p>0.05). Triglyceride levels were significantly higher in DPN Group 1 compared to DPN Group 3 (p<0.05), although the values remained within the normal range (50–200 mg/dL). HbA1c levels were significantly higher in DPN Group 3 compared to Groups 1 and 2 (Group 1: 7.2±0.4, Group 2: 8.0±0.5, Group 3: 9.3±0.3; p<0.05). No significant differences were observed in HDL-cholesterol and LDL-cholesterol levels among the DPN groups (p>0.05). For the SSR groups, there were no significant differences in total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, or HbA1c levels after adjustment (p>0.05).

Additionally, using the least significant difference post hoc test, we examined Groups A–D after adjusting for age, duration of diabetes, and sex. Significant differences were observed in triglyceride and HbA1c levels (p<0.05). HbA1c was better controlled in Groups A and B compared to Groups C and D (Group A: 7.3±0.5, Group B: 7.1±0.6, Group C: 9.1±0.4, Group D: 9.0±0.3; p<0.05). While triglyceride levels showed significant differences, the values within each group remained within the normal range. No significant differences were found in total cholesterol, HDL-cholesterol, or LDL-cholesterol levels after adjustment (p>0.05), indicating minimal variation in these parameters.

Table 5. Physiological and demographic factors of participants by group

	Group A		Group B		Group C		Group D		p-value
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	
Sex (male/female)	49 (19/30)	-	22 (4/18)	-	48 (25/23)	-	65 (36/29)	-	0.012
Age (yr)	49	57.0±13.2[a)]	22	67.9±11.3[b)]	48	59.6±13.2[a)]	65	68.2±12.6[b)]	<0.001***
TC (mg/dL)	48	171.9±60.1[a)]	22	154.6±43.4[a),b)]	47	147.7±49.2[a),b)]	64	136.8±50.9[b)]	0.006**
TG (mg/dL)	27	162.0±83.6	13	144.2±76.8	35	123.9±59.9	50	133.1±53.2	0.133
HDL-cholesterol (mg/dL)	27	49.0±11.6	13	45.9±14.7	35	43.9±12.3	50	43.4±13.6	0.314
LDL-cholesterol (mg/dL)	27	105.0±47.2[a)]	13	96.6±30.9[a),b)]	35	89.2±41.2[a),b)]	50	70.4±35.3[b)]	0.002**
HbA1c (%)	40	7.0±1.7[a)]	21	6.8±0.9[a)]	48	9.2±3.0[b)]	64	8.8±2.7[b)]	<0.001***
DurDM (yrs)	28	6.5±7.7[a)]	20	8.1±7.6[a),b)]	46	10.8±10.6[a),b)]	63	13.9±10.8[b)]	0.006**
Height (m)	46	1.61±0.08[a)]	21	1.54±0.08[b)]	46	1.64±0.09[a)]	64	1.62±0.09[a)]	<0.001***
Weight (kg)	46	66.5±15.1	21	60.1±10.7	46	67.7±12.8	64	66.7±14.4	0.188
Body mass index (kg/m^2)	46	25.8±5.5	21	25.5±4.0	46	25.2±3.8	64	25.4±4.5	0.955

Groups sharing the same letter (e.g., [a)] or [b)]) do not differ significantly from each other according to the Tukey post hoc test (p>0.05). Groups with different letters indicate statistically significant differences (p<0.05).
SD, standard deviation; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; DurDM, duration of diabetes.
[a)]Tukey post hoc test.
[b)]Tukey post hoc test.
**p<0.01, ***p<0.001.

DISCUSSION

Demographic factors

When comparing age among the groups, we observed that Groups B and D were significantly older than Groups A and C. This suggests a tendency for decreased SSR in relatively older diabetic patients.

Some studies have indicated that taller height may be associated with increased vulnerability to diabetic neuropathy in diabetic patients [12,13]. Although research on the relationship between SSR and height is limited, Levy et al. [14] reported no significant correlation between height and SSR latency or amplitude in their study on quantitative measures of SSR in diabetes. Additionally, while not specifically focusing on diabetic patients, Emad et al. [15] found that individuals with a height of 1.7 m or more exhibited significantly longer SSR latency compared to those shorter than 1.7 m. Given that diabetic neuropathy is often related to nerve length, it can be speculated that individuals with shorter limb lengths might experience slower neuropathy progression. In Table 3, DPN groups showed significant progression in individuals with taller heights. However, there was no significant difference observed among the SSR groups in Table 5.

The finding that Group B has a significantly lower height than Groups A, C, and D suggests that further research is needed to draw meaningful conclusions. This difference, along with the fact that Groups C and D had greater heights, could imply that taller individuals might be more susceptible to typical diabetic neuropathy risk factors. On the other hand, when considering the relationship with Group A, we noticed that individuals with shorter height did not show diabetic neuropathy progression but did exhibit a decrease in SSR. This raises the possibility that other factors may be influencing these outcomes. The lower height observed in Group B could be due to the higher proportion of females in this group compared to the others, as gender differences likely have a significant impact on height. Future research with balanced gender ratios is necessary to validate these findings. Additionally, studies exploring the relationship between height and latency/amplitude values could provide valuable insights into the complex interactions among height, diabetic neuropathy, and SSR.

In a study by Oh et al. [16], higher BMI values, which are associated with obesity and insulin resistance, were reported to influence the progression of DPN. However, Smith and Singleton [17] found no significant correlation between BMI and the progression of DPN, highlighting conflicting results that suggest multiple factors influence DPN. In our study, BMI was not used as a covariate in the adjusted analysis (which included age, sex, and duration of diabetes), and no significant differences in BMI were observed between the DPN or SSR groups in the crude analysis. These findings suggest that BMI may not be a key factor in the development or progression of DPN, including both large and small fiber neuropathy, in the population studied. Understanding the relationship between body weight, BMI, and their influence on DPN and SSR groups could provide valuable insights for developing effective diabetes prevention and management strategies. Our study population aligns with other studies that did not include BMI as a control variable, suggesting that the lack of BMI adjustment may contribute to population bias, potentially leading to divergent outcomes across different studies.

In our analysis of differences among SSR groups within DPN Group 1, aside from age, we found that age appears to influence SSR progression in well-controlled DM groups. We observed a tendency for increased age in SSR-deteriorated Groups 2 and 3 compared to Group 1. The limited sample size of this study suggests a need for further research to validate these findings.

The other factors

In previous studies, the relationship between type 2 diabetic neuropathy and total cholesterol or LDL-cholesterol levels has shown conflicting results, with some highlighting the importance of lipid control through medication or therapeutic exercise. While some studies reported a lack of significant association between diabetic neuropathy and total cholesterol or LDL-cholesterol levels [18,19], others suggested that increasing LDL-cholesterol levels may contribute to the progression of diabetic neuropathy [20]. In our study, we observed that total cholesterol and LDL-cholesterol levels in Group D were significantly lower compared to Group A. This significant decrease in cholesterol levels in the group showing neuropathy progression aligns with another study that visualized in vivo findings, demonstrating that lower LDL-cholesterol levels in type 2 diabetic neuropathy patients were associated with peripheral nerve enlargement and a higher lipid-equivalent lesion burden [21]. This finding supports the notion that lower total cholesterol and LDL-cholesterol levels may adversely affect nerve enlargement and regeneration, possibly contributing to peripheral nerve damage.

Although we did not investigate this specifically, it is possible

that patients in Group D had better compliance with dyslipidemia medication, which could explain their lower cholesterol levels. However, the ANCOVA results, which adjusted for sex, age, and duration of the disease, did not show significant differences between Groups A to D.

Our study also found that both the progression of DPN stages and the deterioration of SSR were associated with a longer duration of diabetes. Group D, in particular, had a significantly longer duration of diabetes compared to Group A, indicating a link between prolonged diabetes and more advanced neuropathy. This suggests that a longer duration of diabetes may be associated with the simultaneous progression of both DPN and SSR, implying a higher likelihood of neuropathy as the disease persists over time.

Previous studies have demonstrated an association between elevated HbA1c levels and the progression and severity of diabetic neuropathy in type 2 diabetes [22-24]. Ashar et al. [25] also observed a positive correlation between HbA1c and SSR latency. Although not statistically significant, their study reported a trend where decreasing SSR amplitude was associated with higher HbA1c levels. However, research exploring the relationship between SSR testing, small fiber neuropathy, and HbA1c levels remains limited. Therefore, further investigations are needed to clarify this connection, which could provide valuable insights for preventing and managing diabetic neuropathy in individuals with type 2 diabetes.

Our findings suggest that age had a more substantial effect on SSR results than HbA1c levels, as observed in the analysis comparing Groups A–D, where the progression of diabetic neuropathy was more pronounced in groups with higher HbA1c levels, aligning with our DPN classification [26]. When comparing based on DPN groups, we found that higher HbA1c levels had a significant impact on the progression of neuropathy. However, when comparing based on SSR groups, HbA1c levels did not show statistical significance. Additionally, HbA1c levels in Groups C and D were significantly higher than in Groups A and B, suggesting that elevated HbA1c levels may contribute to the worsening of DPN. However, HbA1c levels may not have a substantial impact on the results of the SSR group.

This implies that controlling and managing HbA1c levels may play a crucial role in preventing or mitigating the progression of DPN but might not significantly influence the progression of SSR. Therefore, our study confirms that changes in HbA1c have a significant impact on the progression of DPN. In contrast, no significant differences in HbA1c levels were observed among the SSR groups. Previous studies comparing SSR between healthy individuals and diabetic patients showed changes according to the duration of the disease in uncontrolled DM patients (HbA1c: 11.3±2.8) [14], which differs from our study participants. This suggests that small unmyelinated nerve fibers may be functionally less affected by glucose control than myelinated fibers.

Limitation

Given that our study is cross-sectional, it is important to acknowledge that it does not capture changes in the diabetic condition over time, as a longitudinal study would. Additionally, our study is limited to patients who underwent NCS and SSR testing, introducing the potential for population bias. Demographic factors such as age and gender distribution may slightly differ from the overall diabetic population in Korea.

It is also essential to consider the influence of other physiological factors on the test results, making the establishment of definitive normal ranges challenging. Therefore, fully replacing tests such as the thermoregulatory sweat test and the quantitative sudomotor axon reflex test remains difficult due to these limitations.

Since there were no cases where the SSR response originated exclusively from both upper limbs while being absent in the lower limbs, we did not create a separate category based on this criterion. Additionally, the presence or absence of evoked responses was not asymmetric in either limb.

While the SSR test is a valuable tool for autonomic nervous system evaluation, its results can be influenced by factors such as electrode placement, individual sensitivity, body temperature, and emotional states. Similarly, the use of lipid-lowering medications (67.4% of patients) could have confounded our results. Further research would be needed to control these variables and understand their impact more clearly.

The limited number of studies investigating the correlation between BMI and SSR highlights the need for further research in this area. Future studies should explore this correlation in larger, more diverse populations to better understand how BMI influences SSR.

Additional investigations are warranted to clarify the relationship between HbA1c levels and the progression of DPN and SSR groups. The differential impact of glucose control on small unmyelinated nerve fibers versus myelinated fibers should be explored through histological studies.

Furthermore, including patients who were randomly select-

ed and had undergone treatment for several years, rather than focusing on the onset of type 2 diabetes, may limit the significance of the findings. Including patients at various stages of diabetes management could introduce confounding variables that affect the results. Therefore, caution is necessary when interpreting the outcomes. Future research should target patients in the early stages of type 2 diabetes and conduct long-term follow-up to gain a better understanding of disease progression and treatment effects over time.

Conclusions

In this study, we established correlations between various demographic characteristics among patient groups classified based on DPN and SSR. For NCS, factors such as glycemic control and duration of diabetes played a significant role in neuropathy, particularly in large fiber nerves. In the assessment of SSR, age emerged as the most significant factor in the combined evaluation of both large and small fiber types, while the duration of diabetes also had a notable impact.

Among the various known factors, including age, sex, height, weight, and exercise indicators (cholesterol), only age-related factors showed a significant influence in this study. These findings suggest that multicenter studies or longitudinal follow-up research may be necessary.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Kim CH. Data curation: Lee Y. Formal analysis: Lee Y. Investigation: Lee Y, Kim CH. Methodology: Lee Y, Kim CH. Visualization: Lee Y. Supervision: Kim CH. Validation: Kim CH. Writing – original draft: Lee Y, Kim CH. Writing – review & editing: Lee Y, Kim SH, Kim CH. Approval of final manuscript: all authors.

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Early Rehabilitation Interventions by Physical Therapists for Severe COVID-19 Patients Were Associated With Decreased Incidence of Post-ICU Physical Impairment

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Objective: To implement early rehabilitation interventions by physical therapists is recommended. However, the effectiveness of early rehabilitation for severe coronavirus disease 2019 (COVID-19) patients in the prevention of post-intensive care syndrome (PICS) is unclear. We analyzed a multicenter prospective observational study (Post-Intensive Care outcomeS in patients with COronaVIrus Disease 2019) to examine the association between early rehabilitation interventions and PICS physical impairment.

Methods: An analysis was performed on COVID-19 patients who were admitted to intensive care units (ICUs) between March 2020 and March 2021, and required mechanical ventilation. The primary outcome was the incidence of PICS physical impairment (Barthel Index≤90) after one year. Multivariate logistic regression analysis was used to estimate the association between early rehabilitation interventions and PICS physical impairment by adjusting ICU mobility scale (IMS) during seven-day following ICU admission, and clinically relevant risk factors.

Results: The analysis included 259 patients, 54 of whom developed PICS physical impairment one year later. In 81 patients, physical therapists intervened within seven days of ICU admission. There was no significant difference in mean IMS by day seven of admission between the early and non-early rehabilitation patients (0.70 and 0.61, respectively). Multivariate logistic regression analysis showed that early rehabilitation interventions were significantly associated with a low incidence of PICS physical impairment (odds ratio, 0.294; 95% confidence interval, 0.123–0.706; p=0.006).

Conclusion: Early rehabilitation interventions by physical therapists were an independent factor associated with the decreased development of PICS physical impairment at one year, even though early rehabilitation had no significant effect on IMS.

Keywords: Critical illness, Rehabilitation, Post-intensive care syndrome, COVID-19

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INTRODUCTION

Post-intensive care syndrome (PICS) is a syndrome consisting of impairment of physical, mental, and cognitive function that occurs during or after intensive care unit (ICU) stay and affects the patient's prognosis after discharge [1,2]. It has been reported that 40%–60% of patients admitted to an ICU develop PICS [1]. PICS decreases quality of life (QOL) of patients after discharge and makes it challenging for them to return to society. The prevention of PICS is a critical issue for medical staff in ICUs [1-3].

Early rehabilitation interventions to prevent PICS have been recommended [4-6]. It has been reported to decrease ICU-acquired weakness [7] and improve ICU Medical Council Scores within 48 hours after ICU discharge [7,8]. While early rehabilitation improves early PICS physical impairment in the short term after ICU discharge [8-10], the recent large randomized controlled trials (RCTs) showed that early rehabilitation did not improve PICS physical impairment in the late term after ICU discharge [9,11-13]. However, the effectiveness of early rehabilitation is controversial for long-term PICS physical impairment because of differing definitions of rehabilitation, target populations, and outcome assessments. Furthermore, the efficacy of early rehabilitation interventions for long-term PICS physical impairment may vary depending on the contents of the rehabilitation program and the professional composition of the healthcare providers involved. In Japan, numerous hospitals have integrated physical therapists specializing in critical care into the early rehabilitation process. Nevertheless, the association between the participation of physical therapists specializing in critical care in early rehabilitation interventions and the resultant long-term PICS physical impairment attributed to PICS remains unclear.

It had been difficult for physical therapists to provide rehabilitation interventions for severe coronavirus disease 2019 (COVID-19) patients. Severe COVID-19 patients were also isolated due to the risk of spreading COVID-19, limiting the quality and quantity of rehabilitation interventions by physical therapists [14-16] .Many patients required mechanical ventilation and extracorporeal membrane oxygenation (ECMO) during COVID-19 pandemic, which had overwhelmed medical resources. These factors may have made effective rehabilitation interventions difficult. Therefore, it is also unclear for severe COVID-19 patients whether early rehabilitation interventions by physical therapists are associated with improved long-term prognosis related to PICS physical impairment.

In this study, we analyzed part of a multicenter prospective observational study (Post-Intensive Care outcomeS in patients with COronaVIrus Disease 2019, PICSCOVID) [17,18] to determine whether early rehabilitation interventions by physical therapists of severe COVID-19 patients were associated with PICS physical impairment at one year.

METHODS

Study design and settings

This study was conducted as part of the PICSCOVID [17,18] study, an exploratory prospective multicenter observational study that investigated the long-term outcomes of patients with severe COVID-19 infection. Thirty-two Japanese ICUs participated in this study. The study was approved by the Ethics Committees of the Tokyo Medical Center (approval number: R20-133, approval date: November 26, 2020) and each participating institution. The study protocol was registered in the UMIN network (UMIN000041276). The study complied with the Helsinki guidelines.

Study participants

Participants in this study were COVID-19 patients aged 20 years or older who required mechanical ventilation and were admitted to an ICU between March 2020 and March 2021. The PICSCOVID study initially planned to recruit patients between March and December 2020. However, owing to the increase in the number of patients following the spread of COVID-19 in Japan, the recruitment period was extended to March 2021. The decision regarding the indication for mechanical ventilation induction was made at the discretion of each institution. Participants were treated in isolated units in ICUs. Confirmation of infection by COVID-19 was made by polymerase chain reaction test. Patients who did not give consent for the study or who were unable to walk unaccompanied with or without assistive devices at the time of admission were excluded. Patients with COVID-19 requiring mechanical ventilation are promptly registered in the CRoss Icu Searchable Information System (CRISIS) registry upon admission to the ICUs of each participating institution, following national policy. Those patients included in the CRISIS registry were enrolled in PICSCOVID if they met the specified inclusion criteria. Written informed consent was obtained from all patients in the analysis.

Patients were divided into two groups. In the early rehabilitation intervention (ERI) group, patients received therapeutic in-

tervention by a physical therapist within 7 days; in the non-early rehabilitation intervention (NERI) group, patients received no therapy within 7 days. The physical therapists were dedicated to the ICU with at least five years of experience in acute care. The rehabilitation intervention by physical therapists was defined as the development of a plan with both physicians and nurses, after understanding and evaluating the patients' situation, of specific support measures to maintain, improve, or reacquire various functions, including motor, respiratory, feeding and swallowing, digestion and absorption, and excretory functions. In addition, the efforts made based on the plan were periodically evaluated and revised based on the patients' condition.

Procedures

To evaluate PICS, questionnaires were sent to consenting patients between 10 and 15 months after discharge from the ICU. We included patients who returned the questionnaire. The questionnaire consisted of simple questions on PICS. The Barthel Index (BI) score was used to assess physical function, the Short-Memory Questionnaire (SMQ) to assess cognitive function, the Hospital Anxiety and Depression Scale (HADS) to assess mental health, anxiety, and depression, and the EuroQol 5 Dimension 5 Level (EQ-5D-5L) to assess QOL. Patients completed the questionnaires alone or were assisted by a family member or acquaintance. Patients who returned the questionnaires were eligible to receive a gift of JPY 1,000.

Outcomes

The primary outcome was the incidence of PICS physical impairment one year after discharge from the ICU. PICS physical impairment was defined as 90 points or less based on BI score [19]. The secondary outcomes were other items of the questionnaire, particularly the incidence of PICS, cognitive impairment, mental disorder, and QOL. Cognitive impairment was defined as a SMQ score of 40 or less [20,21], and HADS score of eight or more on the mental disorder as an anxiety or depression scale [22-24]. PICS onset was defined by PICS physical, cognitive, or mental impairment onset. QOL was evaluated using EQ-5D-5L [25].

Statistical analysis

Patient demographic characteristics and long-term health outcomes were presented as medians (interquartile range) for continuous variables and as absolute values and percentages for categorical variables. Continuous patient characteristic variables were compared using the Mann–Whitney U-test, and categorical variables were compared using the chi-square test. Univariate logistic regression analysis was used to evaluate the associations among early rehabilitation interventions by physical therapists and mean ICU mobility scale (IMS) within seven days of ICU admission and outcomes related to PICS at one year later. Multivariate logistic regression analysis was used to estimate the association of early rehabilitation by physical therapists on the incidence of PICS physical impairment by adjusting by the mean IMS during ICU admission for seven days and clinically relevant factors. The following clinically relevant factors were incorporated: age [26], sex [26,27], body mass index (BMI) [28], Clinical Frailty Scale before hospitalization [29], Sequential Organ Failure Assessment (SOFA) score [27], delirium [30], mechanical ventilation duration [27], ECMO [29], continuous muscle relaxant administration [27], maximum daily steroid dose (prednisolone equivalent dose) [31], and prone position [32]. The mean IMS within seven days of ICU admission was analyzed by calculating mean IMS on days 3, 5, and 7 after ICU admission. Mean IMS was redefined as an ordinal variable, with a score of zero for zero, two for four or more, and one for others. Odds ratios (ORs) were presented as means and 95% confidence intervals (CIs). Missing values were excluded from the analysis. Significance was set at p-values<0.05 (two-tailed) using Python, version 3.10.9.

RESULTS

An outline of the study is shown in Fig. 1. Between March 2020 and March 2021, 673 severe COVID-19 patients required mechanical ventilation in participating ICUs. Of these, 508 patients were enrolled in the study. Of 401 patients who were discharged, 270 responded to the questionnaire. Eleven patients were excluded due to missing clinical information. Finally, 259 patients were evaluated for PICS outcomes. Eighty-one patients received early rehabilitation by physical therapists and 178 patients did not.

Patient backgrounds are shown in Table 1. Patients in ERI group had higher SOFA scores than those in NERI group (p=0.01). There were no patients with malignancy complications in ERI group, but there were 13 (7.3%) patients in the NERI group (p=0.03). Both ERI and NERI groups also had lower IMS on days three, five, and seven after ICU admission (Fig. 2). There was no significant difference in IMS on days three and seven; however, it was significantly higher in ERI group on day

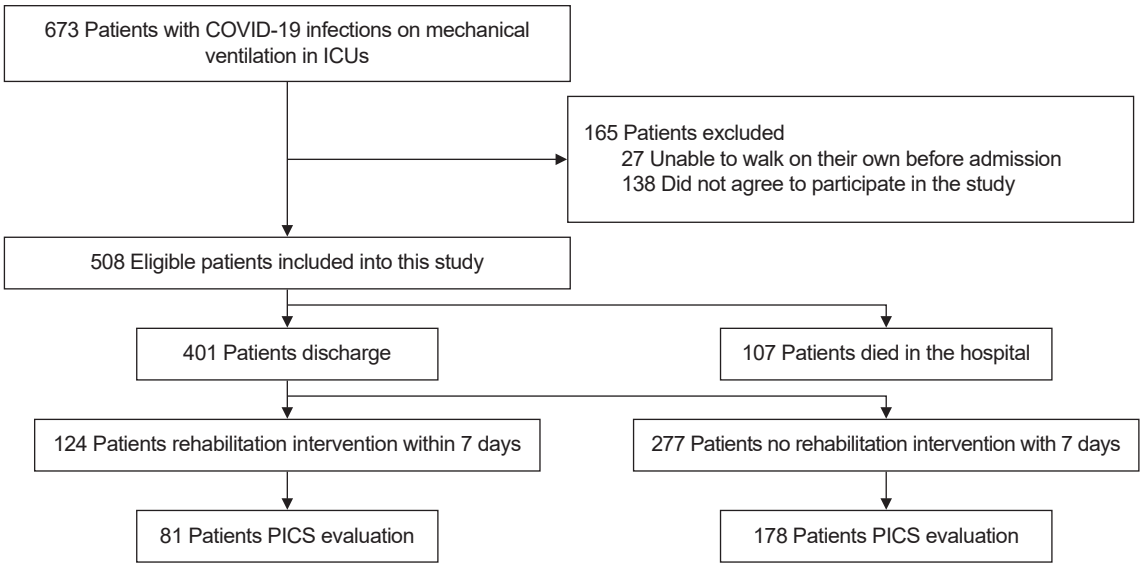

Fig. 1. Outline of the study. COVID-19, coronavirus disease 2019; ICUs, intensive care units; PICS, post-intensive care syndrome.

Table 1. Overall information

	Rehabilitation interventions within 7 days of ICU admission (n=81)	No rehabilitation interventions within 7 days of ICU admission (n=178)	p-value
Age (yr)	64.5±12.3	65.7±11.3	0.66
Sex			0.9
Male	65 (80.2)	140 (78.7)	
Female	16 (19.8)	38 (21.3)	
Body mass index (kg/m^2)	25.7±4.6	25.7±4.2	0.98
SOFA score on the day of ventilation start	6.0 (4.0, 8.0)	5.0 (3.0, 7.0)	0.01
Clinical Frailty Scale before hospitalization	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	0.09
Delirium	19 (23.5)	35 (19.7)	0.6
Duration of delirium within 1 week of ICU admission (day)	0.8±1.7	0.5±1.3	0.31
Duration of invasive mechanical ventilation (day)	15.2±18.0	12.3±10.0	0.19
Length of ICU stay (day)	16.1±16.9	16.0±10.8	0.97
Length of hospital stay (day)	38.3±42.6	30.1±26.0	0.11
Length of hospital stay after ICU discharge (day)	22.2±29.0	14.1±21.1	0.03
Rehabilitation interventions by physical therapists in ICU	81 (100)	58 (32.6)	<0.01
Comorbidity			
Hypertension	40 (49.4)	87 (48.9)	>0.99
Diabetes	34 (42.0)	56 (31.5)	0.13
Cardiac disease	12 (14.8)	21 (11.8)	0.64
Chronic kidney disease	2 (2.5)	5 (2.8)	>0.99
Autoimmune diseases	1 (1.2)	7 (3.9)	0.44
Malignant tumors	0 (0)	13 (7.3)	0.03
COPD	7 (8.6)	14 (7.9)	>0.99
Immunodeficiency	0 (0)	8 (4.5)	0.12
Maximum prednisolone dose (mg/day)	40.0 (20.0, 82.5)	44.0 (30.0, 100.0)	0.34

Values are presented as mean±standard deviation for normally distributed continuous variables or median (interquartile range) for non-normally distributed continuous variables. Categorical variables are presented as number (%).
ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

five (p=0.004).

In Table 2, the PICS outcomes for the ERI and NERI patient groups are summarized. On the other hand, looking at the continuous variables, there was no significant difference because many people had high BI scores, but the incidence of PICS physical impairment after 1 year, which was the primary endpoint, was significantly lower in the ERI group (10 cases [12.3%] vs. 44 cases [24.7%], p=0.04). In contrast, there were no significant differences in the incidences of PICS cognitive impairment (38 [46.9%] vs. 87 [50.3%]), mental impairment (21 [25.9%] vs. 49 [27.7%]), and PICS (42 [51.9%] vs. 110 [62.5%]) between ERI and NERI groups. There was no significant difference in EQ-5D-5L between ERI (0.87 [0.76, 1.00]) and NERI group (0.85 [0.77, 1.00]).

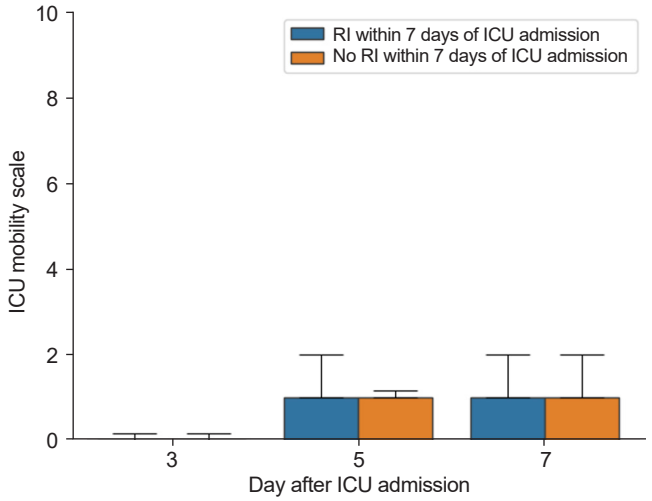

Fig. 2. Intensive care unit (ICU) mobility scale up to 7 days after ICU admission for patients with and without rehabilitation interventions (RIs) by physical therapists within 7 days. The bars show median values, and the error bars show quartile ranges.

Table 3 shows the scores for each item of the BI for the patients in ERI and NERI groups. The score for the transfer item is significantly higher in the ERI group (14.8±1.0) compared to the NERI group (14.3±2.9), with a p-value of 0.04.

The results of the univariate and multivariate logistic regression analyses of PICS outcomes are shown in Tables 4 and 5, respectively. Univariate logistic regression analysis showed that early rehabilitation interventions by physical therapists within seven days of ICU admission was significantly correlated with a low incidence of PICS physical impairment one year later (OR, 0.429; 95% CI, 0.204–0.903; p=0.03). Adjusted for age, sex, BMI, CFS, SOFA score, delirium, duration of mechanical ventilation, ECMO, continuous muscle relaxant administration, maximum

Table 2. Outcomes one year after ICU admission of patients

	Rehabilitation interventions within 7 days of ICU admission (n=81)	No rehabilitation interventions within 7 days of ICU admission (n=176)	p-value
Barthel Index	100 (100.0, 100.0)	100 (95.0, 100.0)	0.08
Short-Memory Questionnaire	40.0 (34.0, 43.0)	39.0 (36.0, 43.0)	0.96
Hospital Anxiety and Depression Scale	7.0 (2.0, 12.0)	7.0 (3.0, 12.0)	0.82
EuroQol 5 Dimension 5-level	0.87 (0.76, 1.00)	0.85 (0.77, 1.00)	0.87
PICS	42 (51.9)	110 (62.5)	0.14
PICS-physical	10 (12.3)	44 (25.0)	0.04
PICS-cognitive	38 (46.9)	87 (49.4)	0.71
PICS-mental	21 (25.9)	49 (27.8)	0.89
Visual analog scale			
Physical condition	7.5 (5.5, 8.6)	7.5 (6.2, 8.7)	0.32
Cognitive condition	8.3 (6.7, 9.9)	8.9 (7.4, 9.9)	0.19
Mental condition	8.0 (5.9, 9.2)	8.2 (6.7, 9.3)	0.55
Dyspnea	41 (50.6)	74 (42.0)	0.2
Walking difficulty	20 (24.7)	50 (28.4)	0.66
Weight loss	24 (29.6)	59 (33.5)	0.7
Memory impairment	23 (28.4)	51 (29.0)	>0.99
Execution disability	38 (46.9)	77 (43.8)	0.74
Depression	35 (43.2)	71 (40.3)	0.66
Anxiety	36 (44.4)	94 (53.4)	0.27
Sleeping disorder	36 (44.4)	75 (42.6)	0.83

Values are presented as median (interquartile range) for non-normally distributed continuous variables. Categorical variables are presented as number (%).
ICU, intensive care unit; PICS, post-intensive care syndrome.

Table 3. Differences in Barthel Index

	Rehabilitation interventions within 7 days of ICU admission	No rehabilitation interventions within 7 days of ICU admission	p-value
Feeding	9.9±0.6	9.8±1.4	0.17
Transfers	14.8±1.0	14.3±2.9	0.04
Grooming	4.9±0.6	4.8±0.9	0.24
Toilet use	9.8±1.1	9.5±2.1	0.19
Bathing	4.6±1.4	4.6±1.4	0.86
Mobility	14.4±2.3	14.2±3.1	0.46
Stairs	9.3±2.3	9.3±2.2	0.91
Dressing	9.7±1.2	9.4±2.2	0.13
Bowels	9.4±1.8	9.2±2.5	0.31
Bladder	9.3±2.1	9.1±2.6	0.44

Values are presented as mean±standard deviation for normally distributed continuous variables.
ICU, intensive care unit.

Table 4. Univariable logistic regression analyses of PICS and each element in patients

	Physical impairment			Cognitive impairment			Mental impairment			PICS		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Rehabilitation interventions within 7 days of ICU admission	0.429	0.204–0.903	0.03	0.858	0.515–1.481	0.62	0.914	0.504–1.660	0.77	0.646	0.379–1.100	0.11
Mean IMS for 7 days	0.616	0.344–1.101	0.1	1.008	0.628–1.619	0.97	1.083	0.598–1.699	0.98	0.98	0.611–1.573	0.93

PICS, post-intensive care syndrome; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IMS, ICU Mobility Scale.

Table 5. Multivariable logistic regression analyses of PICS and each element in patients

	Physical impairment			Cognitive impairment			Mental impairment			PICS		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Rehabilitation interventions within 7 days of ICU admission	0.294	0.123–0.706	0.006	0.809	0.454–1.441	0.47	0.731	0.380–1.404	0.34	0.542	0.301–0.979	0.04
Mean IMS for 7 days	0.691	0.337–1.419	0.31	1.166	0.593–1.738	0.96	1.155	0.633–2.168	0.64	1.156	0.672–1.990	0.52

Adjusted by age, BMI, CSF, SOFA, delirium, duration of ventilation, presence, or absence of ECMO, continuous muscle relaxant administration, maximum daily steroid dose, prone position, and IMS.
PICS, post-intensive care syndrome; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; IMS, ICU Mobility Scale; BMI, body mass index; CFS, Clinical Frailty Scale; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation.

daily steroid dose, prone position, and mean IMS within seven days of ICU admission, early rehabilitation was significantly correlated with a low incidence of PICS physical impairment one year later (OR, 0.294; 95% CI, 0.123–0.706; p=0.006). It was significantly correlated with a low incidence of PICS (OR, 0.542; 95% CI, 0.301–0.979; p=0.04), but not significantly correlated with the incidence of PICS cognitive impairment (OR, 0.809; 95% CI, 0.454–1.441) or PICS mental impairment (OR, 0.731; 95% CI, 0.380–1.404). Mean IMS within seven days of ICU admission was not significantly correlated with the incidence of PICS physical impairment (OR, 0.691; 95% CI, 0.337–1.419) by multivariate logistic regression analysis.

DISCUSSION

In this post-hoc analysis of the PICSCOVID study, we found that early rehabilitation interventions by physical therapists in severe COVID-19 patients associated with a decreased incidence of PICS physical impairment after one year, even after adjustment for confounding factors. IMS during the first seven days of ICU stay in patients with severe COVID-19 that required mechanical ventilation was low, and there was no clinical difference between ERI and NERI group.

Our results showed early rehabilitation intervention by physical therapists may be associated with a decreased incidence of

PICS physical impairment after one year despite the low level of patient activity in ICU. Surprisingly, our logistic regression multivariate analysis showed that early rehabilitation intervention by physical therapists was significantly associated with a decreased incidence of PICS physical impairment after one year, even after adjusting IMS score within first ICU admission seven days. This may suggest that rehabilitation interventions planned by physical therapists within the first seven ICU admission days may improve incidence of PICS physical impairment beyond improvement in physical activity level in ICUs. Electric muscle stimulation (EMS) has been reported to maintain muscle strength in patients with low activity levels [33-35], although EMS is not considered for IMS. Respiratory rehabilitation has been also reported to be associated with a better score of BI scores in long term in mild COVID-19 patients, and it may be effective in severe COVID-19 patients. Early involvement of the physical therapist with the patient may have made it possible to provide various treatments such as EMS and respiratory rehabilitation other than increasing the patient's activity in ICU.

The recent large RCTs showed that early rehabilitation improved PICS physical impairment in short term after ICU discharge, but did not in late term [9,11-13]. The TEAM Study Investigators and the ANZICS Clinical Trials Group reported that there is no difference between the early rehabilitation and usual care groups in 6-month BI scores, which used in our definition of PICS physical impairment. There are several possible reasons why the results of our study and the previous RCTs differed. First, it was difficult for the control group in our study to receive rehabilitation interventions from other medical staff such as nurses, because of the isolation ward. The usual care group in previous RCTs received standard-protocol [9,11-13]. Our study suggests that the lack of intervention by physical therapists in the early phase of treatment might be associated with the increased incidence of PICS physical impairment [9,11-13]. Second, the population of our study was older and had a longer duration of ventilator use than previous RCTs [9,11-13]. The population in our study was at high risk of PICS physical impairment due to these factors. Therefore, it is possible that this high-risk population was more likely to benefit from early rehabilitation [9,11-13,36]. Third, the pathophysiology of COVID-19 and non-COVID-19 patients is different, which may explain the difference in effectiveness. Although some reports indicate that early rehabilitation in COVID-19 patients improves physical impairment at discharge from the hospital [37,38], no reports within the scope of our study were reported in the late term. Early rehabilitation may reduce PICS physical impairment in the long term by selecting an appropriate population and rehabilitation methods. However, the mechanism by which early rehabilitation reduces PICS physical impairment is unknown. Further research is needed to elucidate its effectiveness and mechanism.

Both ERI and NERI groups in our study had low IMS for up to 7 days after ICU admission. Furthermore, both ERI and NERI groups had clinically similar IMS courses for up to 7 days after ICU admission, because the difference of IMS on day 5 was lower than the clinically meaningful IMS difference of 1.4 to 3 reported in previous studies [39]. Hodgson et al. [7] reported that non-COVID-19 patients requiring mechanical ventilation who received early rehabilitation had a higher incidence of IMS after ICU admission than those who received usual care. These results suggest that early rehabilitation interventions with physical therapists in COVID-19 patients did not have improved physical activity level in early phase in ICUs. One possible reason for the very low IMS in our study was the influence of the COVID-19 pandemic, which limited human health care resources and staff due to the high levels of critically ill patients. Inadequate staffing levels have been reported as a factor preventing adequate rehabilitation [40]. Furthermore, the quality and quantity of rehabilitation that could be provided were limited due to patients being in an isolated environment to prevent the spread of the virus to medical staff [14-16]. Therefore, early rehabilitation interventions may fail to increase ICU activity in patients during the early phase.

There are several limitations to this study. First, there are some potential biases due to observational study. The delay in the initiation of rehabilitation in the NERI group could not be fully clarified, this potential factor may have affected the outcome. Second, rehabilitation protocols were not standardized and were conducted on a facility-specific basis. Especially, it has not been observed whether EMS or respiratory rehabilitation was performed. Furthermore, we did not measure rehabilitation interventions after ICU discharge. As the length of hospital after ICU discharge was longer in early rehabilitation group, there was possibility that they were given more rehabilitation in longer hospital days after ICU discharge. However, it was likely challenging for physical therapists to be involved in rehabilitation on general wards. Previous reports indicate that only 19% of ICUs had physical therapist involvement during the ICU stay [14], suggesting limited availability. After ICU discharge, it is probable that even fewer patients had access to physical

therapist-led rehabilitation in general wards. Additionally, no physical therapist involvement occurred following discharge from each facility. Therefore, the presence or absence of post-ICU physical therapy likely had minimal impact on the results of this study. Third, PICS physical impairment was assessed by BI scores. No assessment was made using objective measures such as the 6-minute walk. Fourth, IMS was assessed only up to the seventh day of admission to ICU. The approach of averaging IMS scores across 7 days might not be a clinically meaningful measure of patient mobility. It is possible that there were differences regarding the physical activities not evaluated by IMS. Fifth, this study is based on COVID-19 patients who require mechanical ventilation. These results may not be applicable to COVID-19 patients who do not require ventilation or to non-COVID patients.

Conclusions

In this analysis, we found that early rehabilitation interventions by physical therapists were associated with a decreased incidence of PICS physical impairment after one year in severe COVID-19 patients with low physical activity. Our results may indicate that early rehabilitation interventions by physical therapists are possible to prevent PICS physical impairment when the patients' activities cannot be adequately increased in ICU.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Nakamura K, Hatakeyama J. Methodology: Nakamura K, Oku S. Formal analysis: Oku S. Investigation: Hatakeyama J, Liu K, Inoue S, Yamakawa K, Nishida T, Ohshimo S, Hashimoto S, Maruyama S, Ogata Y, Kawakami D, Shimizu H, Hayakawa K, Fujino Y, Oshima T, Fuchigami T, Yawata H, Oe K, Kawauchi A, Yamagata H, Harada M, Sato Y, Nakamura T, Sugiki K, Hakozaki T, Beppu S, Anraku M, Kato N, Iwashita T, Kamijo H, Kitagawa Y, Nagashima M, Nishimaki H, Tokuda K, Nishida O, Nakamura K. Funding acquisition: Nakamura K, Hatakeyama J. Project administration: Nakamura K, Hatakeyama J. Writing – original draft: Oku S. Writing – review and editing: Nakamura K, Tojo K, Idei M. Approval of final manuscript: all authors.

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Corrigendum

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Correction: A Fully Immersive Virtual Reality Method for Upper Limb Rehabilitation in Spinal Cord Injury

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The original article has been updated accordingly.
We sincerely apologize for any confusions that we may have caused.

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Journals

1. Jeon JH, Jung YJ, Lee JY, Choi JS, Mun JH, Park WY, et al. The effect of extracorporeal shock wave therapy on myofascial pain syndrome. Ann Rehabil Med 2012;36:665-74.
2. Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatripan. Headache 2002;42 Suppl:S93-9.

Book & Chapter of book

3. Frontera W, Silver JK, Rizzo TD. Essentials of physical medicine and rehabilitation. 2nd ed. Saunders; 2008. p. 579-82.
4. Esquenazi A. Upper limb amputee rehabilitation and prosthetic restoration. In: Braddon RL, editor. Physical medicine and rehabilitation. 2nd ed. Saunders; 2000. p. 263-78.

Proceedings of academic conference

5. Harnden P, Joffe JK, Jones WG. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Thesis (Dissertation)

6. Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant, MI: Central Michigan University; 2002.

(11) Tables

Tables should be submitted separately from the text, and each table should be created in MS Word on separate pages, using double space throughout. They should be simple, self-explanatory, and not redundant with the text or the figures. Limit 5 tables per manuscript. The title of the tables should be written in phrases, and capitalized the first letter of the first word. The title should be placed above the table, and abbreviations and footnotes should be placed under the table. Number the tables in order of appearance in the text (e.g., Table 1, Table 2). All abbreviations used in the table must be spelled-out in full under the table in the following order: abbreviation, comma, full word (e.g., RM, rehabilitation medicine;). Table footnotes should be indicated in superscripts in the following order: [a], [b], [c]… but p-values should be indicated by asterisk (e.g., *$p<0.05$, **$p<0.01$. ***$p<0.001$).

(12) Figure legends

Legends should be submitted separately from the text, and each legend should be typed on separate pages. They should be written in full sentences to describe the content of the figure, and only the first letter of the legend should be capitalized. For lengthy legends continuing beyond one line, the left margin of the following lines should start at the same point as the first line. Any symbols, marks or abbreviations made in the figure must be explained in the legend. Figures containing histologic slides should be accompanied by legends explaining tissue origin, stain method, and microscopic amplification.

(13) Figures

Figures should be uploaded online as separate files and numbered in order of appearance in the text (e.g., Fig. 1). When a single numbered figure contains 2 or more figures, the figure should be numbered with an alphabet letter following the number (e.g., Fig. 1A, Fig. 1B). Indicate focus points in the figures with markers such as arrows and arrowheads, etc. Image files must be of resolutions higher than 300 dpi, and less than 3 MB, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. A single numbered figure containing more 2 or more figures such as Fig. 1A and Fig. 1B should be uploaded as a single file.

2) REVIEW ARTICLES

The abstract should contain no more than 250 words and 5 keywords. The text is structured in the order of Introduction, Main text, Conclusion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures.

3) BRIEF REPORTS

General guidelines are the same as for the original article. The manuscript is structured in the order of Abstract, Main text, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. A structured abstract is required and limited to 150 words, with no more than 3 keywords attached. Manuscripts

should be limited to 1,500 words of text including references and figure legends (not including abstract, tables, and figures), and no more than 10 references. The total number of figures and/or tables is limited to 3.

4) CASE REPORTS

General guidelines and order of manuscript preparation are the same as for the original article. Case reports are considered for publication only if they report rare conditions, atypical symptoms and signs, novel diagnostic or therapeutic approaches, or describe atypical findings for populations residing in Asia and the Pacific Rim. The editorial board will determine whether the case report fulfills the above criteria for acceptance of publication. The manuscript is structured in the order of Abstract, Introduction, Case report, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. The abstract should be nonstructured and limited to 150 words, with no more than 3 keywords attached. The introduction should briefly state the background and significance of the case. The actual case report should describe the clinical presentation and the diagnostic and therapeutic measures taken. The discussion should focus on the uniqueness of the case and should not contain extensive review of the disease or disorder. The combined number of tables and figures is limited to 5, and the number of references is limited to 10. Maximum word count is limited to 1,500 words including references and figure legends.

5) IMAGES IN THIS ISSUE

All images should be accompanied by a short description of the image and a brief and concise clinical review of the specific patient or clinical issue of no more than 500 words (excluding references) with references limited to 5. Image files must be of resolutions higher than 300 dpi for photographs, and 900 dpi for line art, waveforms, and graphs, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. Images should make up a single figure, although they may contain more than one frame. The manuscript does not have an abstract.

6) LETTERS TO THE EDITOR

Letters should not have an abstract, tables, figures, and data supplements. Letters must be limited to roughly 500 words of text and no more than 5 references, 1 of which should be to the recent *ARM* article. Letters may have no more than 3 authors.

7) REPORTING GUIDELINES FOR SPECIFIC STUDY DESIGNS

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and metaanalyses	http://www.prisma-statement.org
STROBE	Observational studies	http://www.strobe-statement.org
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8. SUBMISSION APPLICATION & COPYRIGHT TRANSFER

All submitted manuscripts must be accompanied by the official Submission Application & Copyright Transfer Form of the Korean Academy of Rehabilitation Medicine. The Submission Application & Copyright Transfer Form must contain the title of the manuscript, date of submission, names of all authors, authors' affiliations, and written signatures. Note the corresponding author and provide his/her affiliation, e-mail, telephone and fax numbers, and mailing address.

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9. MANUSCRIPTS AFTER ACCEPTANCE

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1) FINAL VERSION UPLOAD

When accepted for publication, the authors' institutional affiliations should be inserted into the text of the final revised manuscript and uploaded to the online submission system. Files containing figures should be of the highest resolution (at least 300 dpi for color figures, and 900 dpi for line art and graphs) should be also be uploaded in JPEG, GIF, or TIFF format, and must be named according to the figure number (e.g., Fig. 1.jpg).

2) GALLEY PROOF

Galley proofs will be sent to the corresponding author for final corrections. Corrections should be kept to a minimum, must be returned within 2 days, otherwise publication may be delayed. Any fault found after the publication is the responsibility of the authors. We urge our contributors to proofread their accepted manuscripts very carefully. After the publication, if there are critical errors, they should be corrected as Corrigendum or Erratum.

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The editorial board retains the right to request minor stylistic and major alterations that might influence the scientific content of the paper. The final manuscript will be published following final approval by the editor-in-chief.

Checklist for Authors

Annals of Rehabilitation Medicine

General

☐ All elements of the manuscript are printed in English and double-spaced with 1-inch margins at top, bottom, and sides. Right margins are unjustified.

☐ All pages are numbered in the following order: title page, structured or standard abstract, body of the text, conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), references, legends, and tables.

☐ The text is consecutively line numbered.

☐ The Submission Application & Copyright Transfer Form is signed by the guarantor at original submission.

Abstract (applied to original articles, review articles, brief reports, and case reports)

☐ A structured abstract with the headings of Objective, Methods, Results, and Conclusion (A nonstructured abstract for case reports) must succinctly describe the paper.

☐ At the end of the abstract, relevant keywords are listed.

References

☐ All references have been checked for accuracy and completeness.

☐ Cite only references which are quoted in the text. Limit the number of references 40 for original articles, 10 for brief reports and case reports, and 5 for images in this issue and letters to the editor.

☐ Are numbered consecutively in the order they are cited in the text; all listed references have been cited in the text.

☐ Do NOT parenthesize the superscript numerals, and hyphenate (-) when citing 3 or more references in consecutive order.

☐ The format prescribed by the "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" has been followed. Examples provided under Instructions for Authors have been uploaded.

☐ List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."

☐ Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).

Figure Legends

☐ Figure legends are provided for each figure.

☐ Figure legends are numbered and presented together in numeric order following reference page(s).

Tables

☐ Each table is headed by a title and numbered in Arabic numerals on a separate page.

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☐ There are less than 5 tables in the text of original articles.

☐ Tables are cited in numeric sequence in the text.

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