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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, nearly 8,000 physiatrists receive this journal every two months as a member benefit. 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 and conduct peer-review of submitted manuscripts.

The journal encompasses all aspects of physical medicine and rehabilitation, including clinical practice, experimental and applied research, and education. Research areas covered by this journal include rehabilitation of brain disorders and spinal cord injury; electrodiagnosis; musculoskeletal disorders and pain; pediatric, geriatric, cardiopulmonary, sports, cancer, cognitive, and robotic rehabilitation; neuromodulation; neuroimaging; orthotics and prosthetics; physical modalities; clinical trials; quality of life issues; and basic research, as well as other emerging fields in rehabilitation medicine.

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Early Is Better, Then, How Early and How to Apply: Practical Approach of Botulinum Toxin Injection

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Early rehabilitation after stroke has been one of key principles for successful rehabilitation [1]. It helps prevent secondary complications such as contractures or deep vein thrombosis and facilitates neuroplasticity. However, the AVERT (A Very Early Rehabilitation Trial) trial presented some cautionary findings. However, results of AVERT study reminded us that there are things to be careful about early rehabilitation and there is no one-size-fits-all approach to stroke patients. Moreover, it emphasizes the need for a personalized approach in stroke rehabilitation [2,3].

Similarly to early rehabilitation, early management of post-stroke spasticity (PSS) has been recommended, as it improves function and quality of life [4]. As for botulinum toxin injection (BoNT) which is a first-line treatment for PSS, early injection of BoNT is also advocated [5,6]. Still, there is no consensus regarding the “early” in early BoNT injection, such that variety of criteria have been used from 3 weeks after stroke to 6 months after stroke [7,8]. This heterogeneity is one of obstacles to widespread of early BoNT injection in clinics. Review on the post-stroke spastic movement disorder and botulinum toxin A therapy: early detection and early injection published in the previous issue of the *Annals of Rehabilitation Medicine* recommended injection within 3 months following stroke (until early subacute phase of stroke) based on several reasons including prevalence, pathophysiology, and neural plasticity of PSS [9]. Therefore, 3 months after stroke, that is until early subacute phase of stroke seems correct to define “early” in early BoNT injection.

Despite of this general recommendation on early BoNT injection, concern about optimal timing and dose remains. It is difficult to estimate optimal dose at the time of injection because it is difficult to predict spasticity in the future based on the present status, especially at the early injection time. If the current spasticity is on the plateau at the peak and there is no significant change in the future, there will be no difficulty in determining the injection dose. Problems can occur when spasticity changes at the time of early injection. When it is expected that the spasticity will become more severe than at the current time, the BoNT dose will be adjusted higher than the currently needed dose. However, if the spasticity does not get more severe than expected in the future after the injection, over-weakness secondary to BoNT will occur. On the contrary, if the spasticity becomes more severe than expected, the effect of the BoNT injection will be insufficient secondary to insufficient amount of BoNT. This lack of BoNT dose is also problematic because even if additional injections are needed, the patient must wait three months to

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prevent BoNT antibody production. At this point, it would be right to evaluate the state of spasticity through continuous follow-up and determine the optimal BoNT-A injection time and dose accordingly, rather than determining the BoNT-A dose through a single evaluation of spasticity.

Of note, over-weakness might not be a major consideration in early BoNT injection. Well-known concept “deforming spastic paresis,” which emphasized muscle extensibility as well as neural disorder of motor command, recommended prevention or minimization of emergence of spastic myopathy [10]. Furthermore, the concept of “therapeutic weakness” emphasized the BoNT-induced weakness of spastic antagonist, which is followed by less resistance to voluntary activation of agonist leading to improved voluntary control of both agonist and antagonists [11]. These conceptual approaches were confirmed to be effective among patients with chronic stroke and the beneficial effects is expected to be profound with early BoNT injection considering the chance to regain muscle strength, less developed deforming spastic paresis, and neuroplasticity [12].

Early BoNT injection, specifically within early subacute phase of stroke is strongly recommended as a standard care in stroke rehabilitation. Furthermore, decisions of optimal time and dose should be made on a case-by-case basis taking into account the individual's goal, strength as well as spasticity, keeping in mind that early BoNT-injection is not a one-size-fits-all solution.

CONFLICTS OF INTEREST

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Patient-Reported Outcome Measure of Knee Function: Knee Injury and Osteoarthritis Outcome Score (KOOS)

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A plethora of instruments have been developed to assess function in patients with knee problems. These measurements have focused on patient-reported measures from the patient's perspective rather than clinician-based measures because of superior validity [1]. Grounded in the psychometric properties such as reliability, validity, and responsiveness, recommended patient-reported measures include the International Knee Documentation Committee (IKDC) Subjective Knee Form, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Lysholm Knee Scoring Scale, Cincinnati Knee Rating System, Activity Rating Scale, Knee Outcome Survey Activities of Daily Living Scale, and Oxford Knee Score [1,2]. The IKDC Subjective Knee Form, in particular, was instituted to standardize international documentation of the evaluation after knee surgery or treatment and has strengths in being responsive to change in surgical interventions [2,3]. The WOMAC, initially developed in 1982, was designed to evaluate the progression of disease or efficacy of treatments in patients with knee or hip osteoarthritis (OA). It comprises three domains: pain severity during various positions or movements, severity of joint stiffness, and difficulty performing daily functional activities, with 5, 2, and 17 items, respectively. The Likert version is rated on 5 levels, with scores ranging from 0 ("none") to 4 ("extreme"). Cumulative scores for each domain range from 0–20 for pain, 0–8 for stiffness, and 0–68 for physical function, with higher scores indicating a more severe condition. Self-administered or interview-administered questionnaire takes 5–10 minutes [4,5]. Its psychometric evidence is sufficiently reliable and valid for use in clinical and research setting [1,2,4]. A Korean version of the WOMAC has been authenticated for reliability, validity, and responsiveness [6]. Notably, items from the three WOMAC sub-types are incorporated into the KOOS.

The KOOS, developed based on the WOMAC, offers patient-reported outcome measures to evaluate both short and long-term outcomes. Suitable for assessing knee injuries and/or OA across various age groups, it also gauges the course of the disease and the effect of treatments, interventions, and surgeries [7]. The self-administered KOOS evaluates 5 domains: Pain (9 items); other Symptoms (7 items); Activities of Daily Living (ADL) (17 items); Sport and Recreation function (5 items); and knee-related Quality of Life (4 items) [8]. The KOOS, added to Domains from WOMAC, has been shown in previous studies to be more responsive and sen-

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Table 1. Domains in the WOMAC and KOOS and their respective scoring

	WOMAC	KOOS
Domains (items)	Pain (5) Joint stiffness (2) Daily functional activities (17)	Pain (9) Other Symptoms (7) Activities of Daily Living (17) Sport and Recreation (5) Knee-related Quality of Life (4)
Score range	5-Point Likert scale (0–4) Cumulative scores Pain (0–20) Stiffness (0–8) Physical function (0–68) The higher the score, the worse	Cumulative scores, then converted to 0%–100% The lower the score, the worse
Time (min)	5–10	8–10

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score.

sitive than WOMAC in younger or more active elderly [9,10]. Subsequently, through Rasch analysis, the KOOS Physical Function Short Form (KOOS-PS) was derived from Sport and Recreation function and knee-related Quality of Life subscales of the KOOS, and could quickly evaluates the difficulty level of seven physical functions (rising from bed, putting on socks/stockings, rising from sitting, bending to the floor, twisting/pivoting on injured knee, kneeling, and squatting) over recent weeks due to knee pain. All items of KOOS and KOOS-PS are rated on 5-point Likert scale scored from 0–4. The raw score is the sum of 7 items, and is converted to a score of 0 to 100 using a conversion chart or program. The lower the score, the worse. The KOOS takes 8–10 minutes to complete, while the KOOS-PS takes about 2 minutes [2,8,11]. Although the Sport and Recreation function is more valid for younger patients and ADL subscale for elderly, KOOS has adequate internal consistency, test-retest reliability and construct validity for young and old patients with knee injuries and OA [2,8]. The Korean version of KOOS, as a patient-centric clinical measure for knee injury treatments, has also been verified for validity, reliability and responsiveness [12]. National record-based reference values for KOOS subscale were pain 85.3 (95% confidence interval [95% CI], 84.6–85.9), symptoms 85.1 (95% CI, 84.5–85.8), ADL 86.7 (95% CI, 86.0–87.3), Sport and Recreation function 70.9 (95% CI, 69.8–72.0), and QOL 74.9 (95% CI, 73.9–75.8) [13]. In previous study that confirmed changes in KOOS and WOMAC scores according to patients' age, sex, and BMI in 714 healthy populations, older subjects had a worse score on the ADL and Sport and Recreation function, especially "Sport and Recreation function subscale" [14]. The minimal detectable change for KOOS subscales ranges from 6–12 for knee injuries and from

13.4–21.1 for knee OA, 14.3–19.6 for younger individuals, and >20 for older individuals [2,8]. The minimal important changes in KOOS after rehabilitation after total knee arthroplasty in 148 patients were 16.7 for Pain (sensitivity, 83%; specificity, 82%), 10.7 for Symptoms (sensitivity, 80%; specificity, 80%), and 18.4 for ADL (sensitivity, 82%; specificity, 82%), 12.5 for Sport and Recreation function (sensitivity, 96%; specificity, 78%), and 15.6 for Quality of Life (sensitivity, 88%; specificity, 67%) [15].

In summary, the KOOS was developed based on WOMAC to measure not only knee OA but also various age groups and knee injury. Both KOOS and WOMAC possess robust psychometric evidence, making them suitable for clinical and research outcomes. While the KOOS is more time-consuming than the WOMAC, the burden on respondents is minimal. The KOOS, which integrates the three WOMAC sub-scales, offers comparability with prior WOMAC-based research and may be more advantageous for younger demographics, those with high physical activity levels, or interventions primarily focused on physical function (Table 1). However, missing data might arise in the high level of ADL and Sport and Recreation function subscales for older or less physically active individuals. When selecting an appropriate patient-reported outcome measure of knee function in clinical and research settings, factors like the patient's age, physical activity level, disease characteristics, and intervention types should be considered.

CONFLICTS OF INTEREST

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AI in Rehabilitation Medicine: Opportunities and Challenges

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Artificial intelligence (AI) tools are increasingly able to learn from larger and more complex data, thus allowing clinicians and scientists to gain new insights from the information they collect about their patients every day. In rehabilitation medicine, AI can be used to find patterns in huge amounts of healthcare data. These patterns can then be leveraged at the individual level, to design personalized care strategies and interventions to optimize each patient's outcomes. However, building effective AI tools requires many careful considerations about how we collect and handle data, how we train the models, and how we interpret results. In this perspective, we discuss some of the current opportunities and challenges for AI in rehabilitation. We first review recent trends in AI for the screening, diagnosis, treatment, and continuous monitoring of disease or injury, with a special focus on the different types of healthcare data used for these applications. We then examine potential barriers to designing and integrating AI into the clinical workflow, and we propose an end-to-end framework to address these barriers and guide the development of effective AI for rehabilitation. Finally, we present ideas for future work to pave the way for AI implementation in real-world rehabilitation practices.

Keywords: Machine learning, Rehabilitation outcome, Wearable devices, Computer vision systems, Precision medicine

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INTRODUCTION

Artificial intelligence (AI) is poised to revolutionize the healthcare industry. By combining intelligent algorithms with massive volumes of training data, AI systems can solve problems and make logical inferences more quickly and reliably than humans, and they can also learn from larger and more complex datasets [1]. While early healthcare AI applications have focused on automating technical tasks (e.g., detecting arrhythmia from electrocardiograms [ECG], or segmenting and interpreting medical images), new advances are shifting AI into broader areas of

screening, diagnosis, treatment, and prevention of disease and injury, as well as clinical decision support [2,3]. Within these emerging domains, AI offers many unique and exciting opportunities in rehabilitation.

The portfolio of rehabilitation therapies and interventions has expanded significantly over the last few decades, including new strategies for high-intensity training, assistive robotics, pharmacologics, and neurostimulation. However, many clinicians struggle to identify the most effective strategies for individual patients that will maximize their functional recovery and minimize their impairments [4]. Often, rehabilitation systems favor a

one-size-fits-all approach, wherein patients receive similar therapy structures and dosages based on the best-known evidence and nationwide insurance reimbursement models. Another challenge is that patient information is often *siloes* in each care setting. That is, although a wealth of patient information is scattered throughout the healthcare system (e.g., regular check-ups with a primary care physician, or emergency room visits from previous trauma), there is limited accessibility and interoperability of information between different settings (Fig. 1A) [5,6]. As a result, clinicians may not have all the information they need to design the best treatments for a patient, which reduces the efficacy and efficiency of care.

With progressive shifts toward digitalized medicine and portable technology, there is more data available than ever before for us to understand the time course of disease and recovery for different patient cases. AI models—specifically, machine learning algorithms—can be trained to mine the existing data silos and combine complex data to identify patient- or population-specific biomarkers of disability, disease, and injury (Fig.

1). This approach has the potential to revolutionize how we assess patients, both in the clinic and out in the community, and empower us with actionable knowledge. For instance, AI tools could support the design of tailored rehabilitation programs precisely matched to specific impairments [5], timely referral decisions [7], and comprehensive care plans for clinicians and families. The result would directly address the surging demand for personalized and precision medicine in healthcare [2], enhancing patient engagement, cost-effectiveness, and the overall quality of care [8].

In this perspective, we examine the opportunities and challenges for AI in rehabilitation medicine. First, we explore the current research trends in this field, highlighting unique insights from different types of data. Second, we identify key barriers that are impeding the translation of AI into everyday clinical practice. Third, we propose an end-to-end framework for creating clinically meaningful AI models for rehabilitation applications. Lastly, we discuss potential directions for future work.

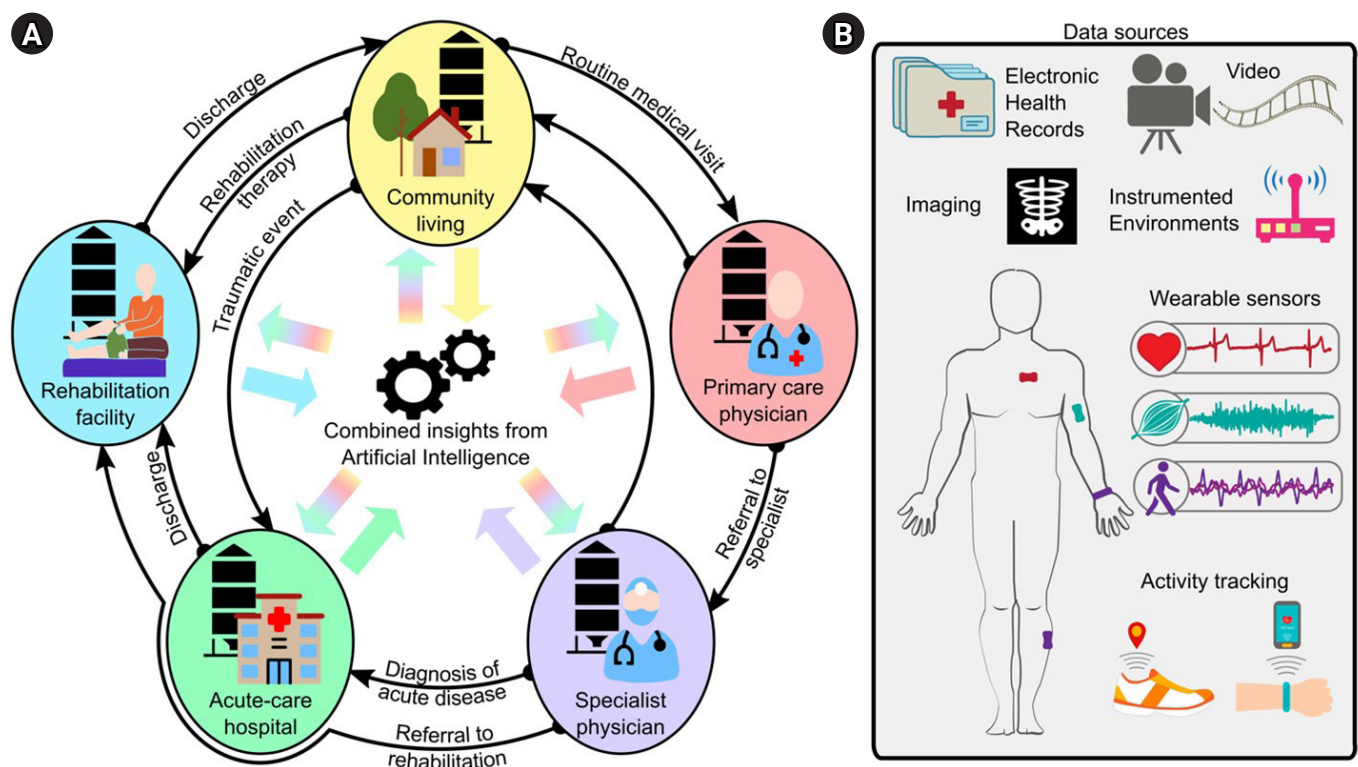


Fig. 1. Data for rehabilitation medicine. (A) Traditionally, data is siloed in the different stages of medical care (e.g., community living, primary care physician, specialist physician, acute-care hospitals, rehabilitation facilities, etc.), with limited data mobility as patients transition between care settings. Artificial intelligence (AI) can integrate this information for a tailored and comprehensive evaluation of the health status of an individual. (B) Example data sources for AI applications in rehabilitation medicine.

THE DATA LANDSCAPE: WHICH DATA ARE USED FOR AI IN REHABILITATION?

A person's health can be described by an extensive amount of data (Fig. 1). In a medical care setting, health data may include diagnostic exams, functional test scores, medications, and laboratory analyses, complemented by demographic information, medical history, comorbidities, and additional clinical notes [9,10]. These data are usually recorded in an electronic health record (EHR) for each patient, which is continuously updated and reviewed by the clinical team. Additionally, advances in wearable sensor technology have enabled continuous, high-resolution monitoring of vitals and activity during the hospital stay and, notably, in people's homes and community [11]. Instrumented environments and video recordings can also collect these data in a contactless, non-intrusive way. Each of these data sources and example applications for rehabilitation are discussed below.

Electronic health records

EHRs are a wellspring of information for AI, often serving as the *de facto* data source for models that are targeting automatic patient screening, early detection, and prognosis.

Screening and early detection are among the most popular and widespread applications of EHR-based AI in healthcare research. In contrast to traditional screening tools that require expensive, time-consuming procedures, AI models can learn subtle patterns and precursors of disease, and then automatically identify at-risk patients using longitudinal information stored in EHRs [12,13]. For instance, models trained on routine EHR data have detected autism spectrum disorder in infants as early as 30 days after birth (nearly one year earlier than standard autism screening tools) [14], and they have detected latent diseases in adults such as peripheral artery disease [15]. They have also identified individuals at high risk of falling [16], and predicted the development of pressure ulcers within the first 24 hours of admission to an intensive care unit [17]. In these examples, earlier detection and more accurate screening can help clinicians intervene with appropriate care or prevention strategies, thereby improving patient care quality in rehabilitation.

Additionally, EHR-driven AI can be used for early, data-driven prognosis, which would assist with short- and long-term care planning, patient goal setting, and identifying appropriate candidates for different treatments [18,19]. In acute stroke rehabilitation, prognostic models have recently shown promise in pre-

dicting future walking ability [20–22], functional independence [21,23], and balance [21] at an inpatient rehabilitation facility (IRF). These models have incorporated EHR data (e.g., demographic and clinical information) collected at IRF admission to predict a patient's ability at IRF discharge. Beyond the inpatient setting, longitudinal predictions of postdischarge recovery can assist with outpatient therapy planning [24]. For instance, the TWIST algorithm was designed to predict the probability of independent walking recovery up to 26 weeks poststroke using early EHR data [25], while the PREP2 combines EHR and imaging data to predict upper limb function three months poststroke [26].

Imaging

AI can be trained to segment and interpret medical images, such as from X-ray radiography or magnetic resonance imaging, to detect disease-related anomalies such as tumor masses [27,28], cardiovascular abnormalities [29], retinal glaucoma [30], and reduced grey matter [31]. Markers extracted from medical imaging have supplemented EHR data in AI models to increase diagnostic accuracy, determine disease severity, or evaluate recovery potential [32].

Wearable sensors

Today's wearable sensors can record a plethora of health-related information, spanning physiological, biomechanical, behavioral, and activity measures. Unlike EHR data, which are collected during brief patient-clinician interactions, wearable sensors can collect biometric data continuously and at much higher resolutions [33]. In the past, obtaining precise measurements of body kinematics, muscle activity, or vital signs required specialized environments, trained experts, and costly equipment. But ongoing technological advancements are bringing these and other measurements to wireless, portable, and cost-effective body-worn devices that can be deployed easily in any setting, including the community [11].

Wearable sensor data paired with AI are fostering new ways of measuring disease-specific indicators of function and impairment, complementing traditional clinical assessments [34]. For instance, inertial measurement units (IMUs), electromyography (EMG), or ECG sensors capture valuable data related to patient movement and neurological function. In acute stroke rehabilitation, we observed that sensor data improved the performance of a model predicting future walking ability, surpassing models using only EHR and other standard clinical information [35].

Similarly, sensor data during walking have been combined with clinical information to estimate dynamic balance ability in individuals with stroke, multiple sclerosis, and Parkinson's disease [36]. In the upper limb, IMUs have shown promise in assessing motor deficits in stroke and traumatic brain injury during the Wolf Motor Function Test [37], or evaluating tremor and bradykinesia for individuals with Parkinson's disease [38,39]. Novel sensors recording high-frequency vibrations can also quantify and monitor swallowing impairment for individuals with dysphagia [40]. These and other sensor-based AI tools can be used to monitor disease progression and therapy impact [41].

Consumer smartphones and smartwatches also incorporate various sensors, including IMUs to capture movement, GPS (Global Positioning System) modules to track geographic location, and optical sensors to estimate vitals such as heart rate and blood oxygenation. AI analysis of these signals can generate diverse measures of physical activity and step count [42], movement impairment [33], community mobility [43], heart rate and cardiovascular health [44], sleep [45], fall risk [46], and more. We recently applied AI to consumer wearables data to assess postoperative recovery in patients who underwent pediatric appendectomy, analyzing patterns in patient activity, heart rate, and sleep measures to detect early signs of complications [47]. Activity recognition algorithms from wearable devices can also indicate exercise adherence or changes in daily activities post-IRF discharge [48].

Instrumented environments

Instrumented environments are an emerging technique for patient monitoring. By strategically installing sensors in the patient's surroundings, this approach is a markerless and contactless method of collecting clinically-meaningful data in the hospital or at home. For example, devices emitting low-power radio signals can estimate respiration and heart rate by analyzing the signals reflected off the body [49]. Combining these data with AI could enable continuous vitals monitoring or symptom evaluation for COVID-19 [50], Parkinson's disease [51], and other conditions. Like wearable sensors, instrumented environments may offer significant economic advantages by reducing the need for regular clinic visits [52].

Videos

Another markerless data acquisition technique is human pose estimation, which uses AI to automatically detect body landmarks from videos and quantify movement, function, and im-

pairment [53]. Pose estimation is becoming more commonplace in applications like gait analysis, since it reduces dependency on costly optoelectronic motion capture equipment. Video-based gait metrics have been computed in healthy populations [54], people with Parkinson's disease [55] and stroke [56], as well as for general functional assessment [57].

More recently, AI has been applied to automatically score clinical assessments from video, such as the Movement Disorder Society Unified Parkinson's Disease Rating Scale in individuals with Parkinson's disease [58], or the General Movements Assessment in young infants [59]. In these examples, video-based AI offers a scalable solution to enhance the reliability and accessibility of valuable clinical assessments, which require specialized training and considerable practice for scoring.

BARRIERS TO AI IN CURRENT REHABILITATION PRACTICES

Despite the extensive research in AI and the burgeoning availability of healthcare-related data, integrating these models into real-world clinical practice remains a significant open challenge. We believe there are three key barriers that can fundamentally limit the translation of AI models in rehabilitation:

1. Lack of interoperability: As described above, AI can combine clinical and community data to make intelligent inferences about a patient's current, past, or future health. However, the heterogeneous nature of data reporting across different sources can lead to biased, inaccurate, or inexecutable models [7]. To mitigate this, data reporting should be standardized to ensure the *interoperability* of data that can be curated for the models [60].
2. Lack of transparency: The black-box nature of AI can also limit its widespread adoption in rehabilitation [61]. Uncertainty about the computational processes or validity of AI, paired with inevitable model errors and performance fluctuation during initial deployment and ongoing tuning, can easily generate feelings of distrust for AI decision-support tools. To make models *transparent*, developers should provide clinicians with accountable and user-friendly guidelines to interpret the goodness of AI predictions and potential sources of error.
3. Lack of actionability: Insights from AI should also be *actionable*, enabling clinicians to identify or modify care strategies to improve patient outcomes [62]. Different techniques have emerged in recent years to explain the complex

interactions across features used by the models [61,63]. Information from the most predictive or model-driving features could help clinicians design new treatment strategies for their patients. However, all models and their underlying features should be interpreted with caution since they do not always reveal causal effects.

Additional operational or performance barriers—including requirements for data storage and security, cost constraints, resource limitations, education and training challenges, regulatory and ethical complexities, and issues related to scalability and generalization—can also impede AI implementation. Overcoming these additional barriers at the site will require close collaboration between AI developers, healthcare providers, institutional regulators, and policymakers.

FRAMEWORK FOR AI DEVELOPMENT IN REHABILITATION

We offer an end-to-end framework to address the three key barriers above and guide AI development for rehabilitation. The framework identifies the high-level processes needed to bridge the gap between multidimensional data input and meaningful model output in the clinical or research setting. The framework also details the specific steps at which to incorporate the attributes of interoperability, transparency, and actionability to maximize the translational impact of AI in rehabilitation.

Defining the target output

When developing AI for any application, defining the model's output and use case is essential. In rehabilitation, the model output may be automated scores from standard clinical processes (e.g., gait speed, balance score, heart arrhythmia count), novel measures of body function and impairment not typically available in a clinic (e.g., joint kinematics, gait symmetry, muscle activation), or a prediction of a patient's outcomes (e.g., disease detection, prognosis, discharge location). The model may be intended for use in specific circumstances in the clinic or community, across or within patient groups, and/or during continuous, real-time monitoring or a snapshot in time. Clinicians and researchers familiar with the target output can provide insights on appropriate data to capture the target output based on potential confounds of disease, medication, comorbidities, and so forth. These expert collaborations are critical for robust AI development in the highly specialized rehabilitation setting, increasing the chances of successful translation.

Translating healthcare data into the target output

After defining the target output, AI developers can follow a 7-step framework to obtain the output from available healthcare data (Fig. 2). Although the attributes of interoperability, transparency, and actionability should be considered throughout the framework, we will identify the particularly relevant attributes for each step.

Step 1. Data configuration

The first step is selecting and configuring the data source(s) for the AI model (e.g., see Fig. 1B). For example, developers may need to decide the specific variables to be collected from each source, the recording parameters and placement of sensors/cameras/instrumentation, and the recording duration and frequency. These and other configuration decisions will directly impact the nature and quality of recorded data, as well as the downstream *interoperability* and *actionability* of the AI model.

When using EHR data in an AI model, developers should include EHR variables with established or hypothesized relationships to the target AI output. For instance, age, comorbidities, and medication use have all been linked to gait speed prediction [64]. Including known predictors of the target output will likely account for more inter- and intrasubject variance, thereby maximizing model performance.

When using wearable sensor data, developers should carefully consider options for different sensing modalities, body location, adhesion methods, and sampling characteristics to capture the signal of interest while minimizing problematic noise. For example, detecting gait events from IMUs is typically improved by placing a body-worn sensor closer to the point of impact with the floor [65]. Using multiple sensors on different body locations can increase the accuracy of activity detection [66] or sleep stage monitoring [45], although it may also increase power consumption and reduce patient compliance. Preliminary studies considering multi-sensor systems should begin with more complex configurations to capture enough predictors and data resolution for the target output, then streamline as necessary (see Step 6. *Streamlining*).

When using video recordings, the choice of cameras can affect the AI model performance [52]. Conventional 2D RGB cameras are generally suitable for automatic annotation and pose estimation. Depth cameras may offer improved accuracy for certain applications, such as activity recognition, particularly when combined with other sources like wearable sensors [67] or thermal cameras [68]. Video recording configurations, such as

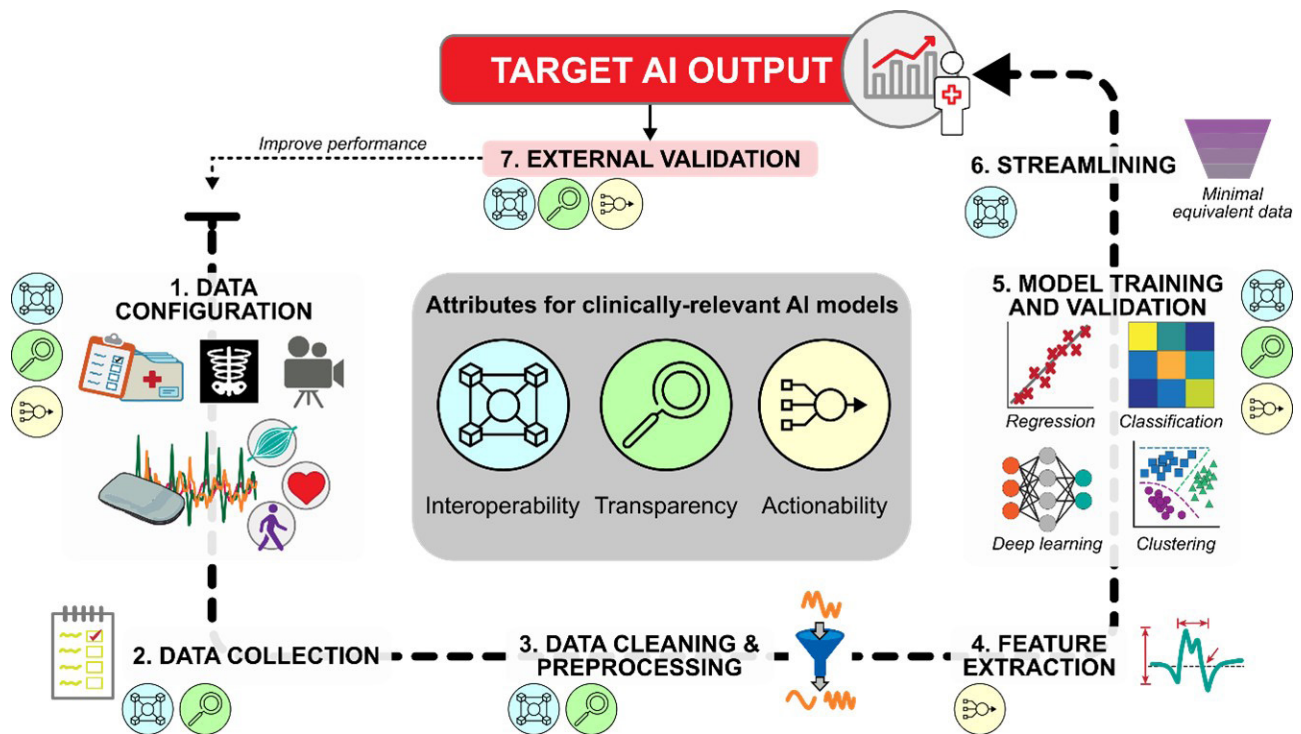


Fig. 2. Framework for developing artificial intelligence (AI) models with clinically relevant attributes. Input data, such as EHR (electronic health record), imaging, sensor data, or video recordings (see Fig. 1B), are first selected and validated for their ability to capture the desired target output. Single/multimodal data streams are collected, processed, and passed to AI algorithms for inferential and/or predictive analytics. After establishing baseline model performance, streamlined datasets can be tested to determine the minimal data needed to achieve this performance, thereby supporting practical clinical implementation. The final model should be externally validated to determine its generalizability to an independent dataset. If performance is not satisfactory, the framework can be revisited in whole or in part.

frame rate or resolution, and environmental conditions, such as lighting or occlusions, should be carefully considered, as these decisions can impact data quality, storage, and processing time.

Before using technology-acquired data as inputs to an AI model, such as measurements from sensors or video, there should be established evidence that these measurements accurately represent the true values (e.g., of motion, vitals, activity, etc.). These measurements should be validated against the “gold standard” measurement technique to assess their accuracy, reliability, and agreement level [69-71]. Measurement validation should, as best as possible, include the expected environmental conditions and patients that are representative of the model’s expected use case [48,72,73]. Protocols for measurement validation should be reported in detail to increase the later AI model’s *transparency* to potential sources of error. This will help users understand whether the input data and model can be used, or whether they should be interpreted differently, outside of the

validation conditions.

Step 2. Data collection

Data collection for AI training and testing should obtain high-quality data that are representative of the expected use case, such as during real-world clinical scenarios and from a diverse patient cohort.

Determining the appropriate sample sizes for training and testing data for robust AI is an ongoing challenge in this field. Generally, large amounts of data from diverse samples will create a more generalizable model, and multiple repetitions of the data collection protocol for each patient will account for intra-subject and intersubject variability.

Data annotations are critical to contextualize and select appropriate data during model training. Example annotations might include the activity type (e.g., walking, plantarflexion, sleep stage, etc.), clinical test scores, EHR items, use of assistive

devices or orthotics, or required assistance levels for activity completion. Failure to collect a well-distribution set of annotated data leads to imbalanced datasets and/or algorithms with inherent biases, such as to race, gender, and age [74,75]. Understanding the interactions between algorithm performance and the contextualized data, as well as their ethical implications, should guide data collection practices to mitigate potential sources of bias. This will also allow other developers to reproduce the models and integrate new data, leading to larger, more diverse datasets and enhanced AI reliability and validity.

Step 3. Data cleaning & preprocessing

Data collected in controlled laboratory or research environments is often cleaner and easier to annotate than data collected in real-world settings like clinics, homes, and communities. Data sources like EHR, wearable sensors, and videos often contain data artifacts, such as transcription errors, discrepancies in patient documentation, missing values, poor recording conditions, and technology failures. To mitigate these issues, the dataset undergoes cleaning and initial processing, such as harmonization, handling missing data, resampling, filtering, and other transformations.

Data harmonization involves expressing data into a common architecture, thereby facilitating *interoperability* between data sources and rehabilitation sites. For EHR data, harmonization might include standardizing categorical information, such as patient demographics or medical conditions, in formats or categories used in different EHR datasets [76]. For other data sources, harmonization can include using uniform measurement scales or synchronizing temporal data, such as when recording multiple time-varying signals (e.g., from sensors, video, imaging, etc.) during a single clinical task.

Missing data poses a critical challenge for AI. Missing data might arise for numerous reasons, such as incomplete data entry, data loss from devices not being worn (or worn with a depleted battery), software glitches, or patient noncompliance. The most straightforward solution is to exclude samples with missing data from the dataset, but this drastically reduces the available data for model training. Alternatively, imputation approaches, such as statistical deduction, regression, or deep learning, can fill in missing data based on existing values in the dataset.

Data resampling is often required to align data from different sources and extrapolate missing samples. Depending on the scope of the analysis, the temporal granularity of the data can be either decreased (i.e., down-sampling, to simplify the data while

keeping essential information) or increased (i.e., up-sampling, to capture finer details).

Filtering may also be required to isolate the bandwidth of interest of the signal from low-frequency noise (such as offsets and drifts), high-frequency noise (such as magnetic coupling), and interferences from other signals.

Depending on the data source, additional transformations may be necessary to improve data quality. For instance, sensors deployed to a patient in the community may not be worn in the exact orientation or placement as they were intended in the laboratory. Therefore, sensor calibration or baseline recordings can be used to “correct” the sensor signals with respect to a reference condition. Reporting transformations and other processing steps is important for *transparency*, allowing developers to generate replicable models based on the handling of the training data.

Data warping is an important concern during the cleaning and processing step. Although a primary goal is removing noise and enhancing the true target signal, an overly aggressive approach can obscure the authentic signal. This may reduce measurement resolution (e.g., aliasing), or prove impracticable with real-world datasets, ultimately compromising the performance and generalizability of an AI model.

Step 4. Feature extraction

Features are a set of values derived from processed data containing information related to the target output. This is a pivotal step to drive the *actionability* of the model, since these features can later be interpreted and acted upon.

Feature extraction varies in complexity, from extracting EHR fields to computing statistical moments from time-series signals (such as mean, standard, deviation, skewness, kurtosis from sensor or video data). Signal characteristics, including spatial, temporal, and frequency aspects, can also be engineered for clinical relevance. For example, wavelet transformations can estimate step length and stance time from IMU data [77,78] or fast Fourier transforms identify frequency bandwidths during muscle contraction in EMG signals [79]. EHR and annotation data offer additional contextual features [80], such as medications or assistive device use. For categorical or ordinal features, operations like one-hot encoding or ordinal encoding should be applied to prevent model bias [81].

Often, many extractable features are redundant (i.e., highly correlated) or irrelevant to the model. A feature set with high dimensionality increases the risk of overfitting the training

data [82]. Feature selection techniques, such as dimensionality reduction or regularization, should be considered to reduce the feature set to those more strongly associated with the target AI output. This is often done in conjunction with *Step 5. Model training and validation*. Ultimately, the complexity of feature extraction and engineering is strictly linked to the modeling technique, since not all models require predefined features before training (e.g., deep learning).

Step 5. Model training and validation

Processed data and/or their features find utility in descriptive, predictive, or prescriptive models. Descriptive models elucidate underlying data measures not readily available in clinic settings. In contrast, predictive and prescriptive models infer current or future patient outcomes and offer clinical decision support, respectively, within the clinical context.

Algorithm selection depends on the intended use case of the AI tool, and each algorithm's architecture and assumptions will affect data utilization (i.e., inductive bias [83]) and performance. For example, clustering algorithms group similar patients by measuring distance from decision boundaries [84]. Regression algorithms are used to estimate a function between input features and continuous outputs like time to hospital discharge or clinical score [85]. Classification algorithms identify discrete quantities, such as activities [48,72], or impairment and disease categories [38,40,86,87]. Deep learning models, including neural networks, directly learn patterns from data via reinforcement techniques [88]. Leading AI models can handle complex tasks, such as labeling unannotated data [89], generating new data [90], or interpreting unstructured text [91]. While the training process varies among different approaches, some common elements impact AI *interoperability*, *transparency*, and *actionability*.

Selecting appropriate validation techniques is crucial for reliable and robust AI development. Cross-validation (CV) is a process to optimize hyperparameters, scale data, select features, and evaluate model performance. In CV, a model is trained on one set of input data and evaluated on separate ("held out") testing or validation datasets. Various methods are available to separate the training, testing, and validation datasets during AI development, including a ratio-based train-test-validation split, leave-one-out, k-fold, or Monte Carlo sampling [60]. For models intended to generalize to new patients, CV should be subject-wise, meaning that the training, testing, and validation datasets contain data from different patients, with no leakage

between them [92]. For personalized models predicting outcomes for a single patient, these datasets might contain information from the same patient but recorded at different times. Improper CV can produce overly optimistic or even completely invalid models [92].

Postdevelopment, model evaluation should extend beyond traditional performance metrics like accuracy, F-scores, absolute error, or regression coefficients. Systematic analyses should examine performance variations when training or testing across different data or patient subgroups [60], as well as the consistency and importance of the features selected across iterations. These sensitivity analyses aid in understanding model stability, considering clinical use cases, and evaluating potential biases and overfitting.

Step 6. Streamlining

Comprehensive data and complex transformations may be needed to achieve the highest AI performance; however, practical considerations such as computational cost, processing time, data recording duration, data storage limits, and user burden can limit the real-world usability of AI models. In these cases, streamlining is an important step to determine the minimal equivalent data that are necessary to attain sufficient performance (Fig. 3). Example methods of streamlining are to reduce the number of data sources, reduce the data sampling frequency, or reduce the complexity of features used for the model. The goal of streamlining is to simplify the model to enhance its *interoperability* for scalable, real-world deployment.

Step 7. External validation of the target output

A sufficiently regularized model should generalize well to unseen data. External validation determines the reproducibility of the AI's performance when applied to an entirely new dataset, such as a different cohort, location, or later time point [93]. Successful external validation increases confidence in the model's performance and enhances its credibility for practical use in the desired context. At this stage, user feedback can also help developers understand the model's deployment feasibility in new clinical settings, as well as identify the frequency and consequences of potential errors.

CHALLENGES FOR FUTURE WORK

By combining large quantities of multimodal data, AI tools offer an exciting possibility to transform rehabilitation medicine

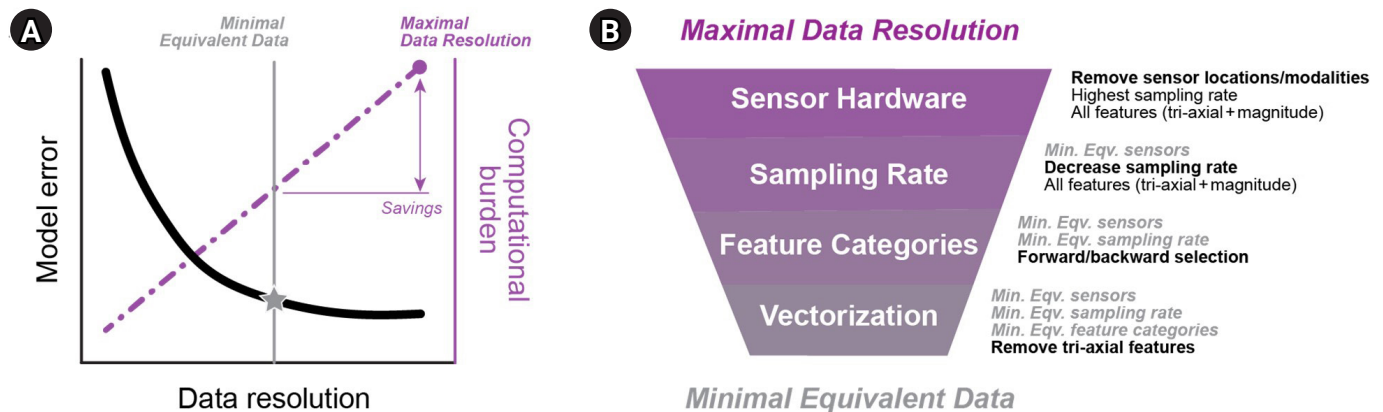


Fig. 3. Model streamlining. (A) Hypothetical illustration of the minimal equivalent data needed for a model. When paired with appropriate AI (artificial intelligence) practices, increasing the data resolution (e.g., adding data sources, increasing measurement frequency, increasing data complexity) can decrease model error (black curve) at the expense of greater computational burden (purple line). The minimal equivalent dataset (grey star) reduces the data resolution without substantial increases in error, thereby streamlining the model for more practical real-world deployment. (B) Example of a streamlining process for wearable sensor data. Descriptions on the right include data input during model training and testing, and the stepwise methods of streamlining in bold. Min. Eqv., minimal equivalent.

from a one-fits-all paradigm to personalized, precision treatments for individual patients. However, small and potentially biased datasets, as well as difficult-to-interpret models, may impede AI adoption at scale. Here, we offer some considerations for future work to address these ongoing challenges.

Large datasets are not always feasible

The quantity and quality of model training data are fundamental considerations when creating scalable, accurate AI tools for rehabilitation. Ideally, these training data would be recorded from a massive, fully representative patient cohort to capture the complete range of disease and recovery conditions that can arise for the model's target population. However, the practical challenges with collecting such datasets and the lack of data standardization mean that large, interoperable datasets are scarce in rehabilitation. Although data from large, multisite clinical trials and open-source repositories are beginning to address this gap, AI itself offers possible solutions to lengthy and costly data collection protocols.

Transfer learning is one such technique to harness knowledge from a previous AI model for a new application. Transfer learning involves adapting a model initially trained on one task or dataset to a different but related task or dataset. Importantly, this technique can drastically reduce the amount of data and computational resources needed for model training or retraining. For instance, transfer learning has been applied to classify

lower-limb movements from EMG data using a previous model that predicted joint angle [94].

Annotating datasets with precise labels is time-intensive. Self-supervised learning (SSL) addresses this issue by automatically generating annotations from unlabeled data. SSL is valuable for unstructured, large datasets where defining annotations is challenging or impractical. SSL uses contrastive learning to compare similar and dissimilar samples, identifying features for sample description and classification [89]. Recent studies show SSL models perform on par with manually annotated data, especially with multimodal data [89], and they can be generalized across external factors [95]. However, SSL-generated labels may not always be accurate, requiring continuous external supervision and comparison to exemplary annotations.

AI can also generate synthetic data to build larger, more diverse, and more representative datasets for algorithm training. Synthetic data mitigates the challenges of collecting sensitive patient information or handling imbalanced and potentially biased datasets [96]. Synthetic data can also be utilized as external datasets to further test and validate AI tools before clinical deployment [97]. However, evaluating synthetic data quality is difficult. Some state-of-the-art algorithms such as generative adversarial networks employ a generator module to produce synthetic data and a discriminator to compare it against real-world data [90], facilitating authenticity controls by developers.

AI insights are not always interpretable

To create interpretable AI tools, data in the AI workflow should be both intuitive and relevant to the intended audience (Fig. 4). Intuitive data are easily interpreted within a clinical context and offer actionable insights, while relevant data transparently align with the question of interest. These characteristics are not mutually exclusive and can be considered on separate scales—ranging from intuitive to unintuitive, and from relevant to irrelevant [98]. Intuitive and relevant data development often accompanies *Step 4. Feature extraction* in the proposed framework.

Highly relevant but unintuitive data may be less actionable for clinicians during treatment (quadrant IV, yellow). For example, if a model indicates that the “second moment of the sample

entropy” from an accelerometer during walking predicts the risk of knee injury, this may not give a clear, actionable insight for clinicians on reducing injury risks. Conversely, highly intuitive but irrelevant data may not provide the necessary information for the target AI output, rendering it even less meaningful (quadrant II, red). For example, precise measurements of skin hydration would not be useful to predict risk factors of cardiovascular disease, if there is no link between these two factors.

Complex data interpretation and novel treatment design can be supported by generative AI with large language models (LLMs) [99], similar to ChatGPT. LLMs trained on extensive EHR data show promise to reduce the administrative workload on clinicians, allowing them to generate automated reports or query specific patient information [91]. However, the safe and effective use of LLMs depends heavily on the quality of training data. Currently, these systems can still mislead users with outputs that are factually inaccurate and inconsistent with the input text [100]. Insights from experienced clinicians are vital to review and interpret AI output [101]. Developers and users should continuously assess AI models for factuality, comprehension, reasoning (i.e., by asking the model to show its reasoning process), possible harm, and bias [102].

Continued AI development after deployment

Evolving AI technologies, enhanced data infrastructure, and pervasive monitoring systems will gradually transform rehabilitation medicine, and more generally, healthcare. What are the challenges for researchers working in the field once AI tools are deployed?

Patients have multiple morbidities and a broad range of impairments that can complicate model predictions, especially for models trained under the assumption of a single and well-defined disease. As discussed, training models for every patient scenario is impractical, leading to inevitable errors. Until rigorous validation and trivial error rates are achieved, AI tools are best considered clinical support tools rather than autonomous agents, with clinicians playing the ultimate role in decision-making [103]. Consequently, we envision that there will be an increasing demand for AI implementation and usability studies in the near future. These studies may examine different user dashboards to convey AI output to clinicians, or the impact of AI tools on actual clinical practice and patient outcomes. There will also need to be additional regulations, such as the European AI Act, to define standards for a transparent, safe, secure, non-discriminatory AI-tools use before widespread

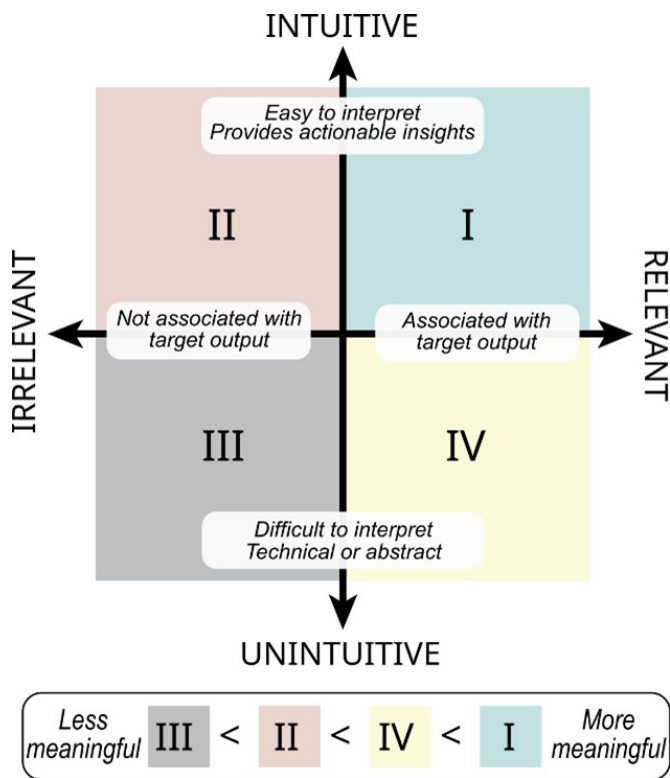


Fig. 4. Data characterization for interpretable artificial intelligence (AI). The most meaningful data for interpretable AI models are both intuitive and relevant in clinical care (quadrant I, green). Data can be highly relevant to model performance but less intuitive, thus rendering it less actionable to a clinician during treatment (quadrant IV, yellow). Other data are highly intuitive and understandable to a treating clinician but less relevant, providing little-to-no value to the model (quadrant II, red). Data that are unintuitive and irrelevant should not be included in a model (quadrant III, grey).

adoption.

AI models should regularly integrate new training data to improve their representation and performance. Integrating new data can also reduce the likelihood of data drift, which occurs when new data introduced to an AI model differs from the data used for initial training. Data drift can arise from gradual or sudden changes in data acquisition methods, clinical treatments, disease patterns, or patient characteristics [104]. Therefore, it is crucial to monitor model performance and make adjustments even after AI deployment.

CONCLUSION

Rehabilitation medicine can benefit from recent advances in new data sources and modeling techniques to transition towards customized, precise, and predictive approaches. AI can help extract meaningful clinical insights from a wealth of healthcare data, but many challenges related to the development and interpretation of these tools can limit their success in real-world settings.

We proposed a general framework to build interoperable, transparent, and actionable AI tools for rehabilitation. In this framework, training data are configured and acquired in a manner that captures the use case of the intended AI tool, with a systematic approach to validation and interpretation for the patient group(s) of interest. Decisions should be made in consultation with expert clinicians who understand the pathophysiology of the impairment or condition being studied, and who can advise on potential confounds during real-world clinical or community scenarios. AI tools that consider these factors have great potential for automatically computing measures of activity and performance, illuminating novel biomarkers of injury and disease, and predicting patient outcomes using multidimensional factors related to health.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

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The Relationship Between Low Back Pain and Sagittal Spinal Alignment and Back Muscle Mass in Korean Fishery Workers

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Objective: To investigate the relationship between low back pain (LBP) and sagittal spino-pelvic parameters along with the relationship between LBP and back muscle mass in Korean male and female fishery workers.

Methods: This retrospective study included a total of 146 subjects who underwent Fishermen's health survey conducted between June 2018 and August 2020. LBP was evaluated through visual analogue scale (VAS) and Oswestry Disability Index (ODI). Sagittal spino-pelvic parameters were measured from whole spine standing X-rays. Back muscle cross-sectional areas were identified through lumbar spine magnetic resonance imaging and body composition was analyzed through bioelectrical impedance analysis.

Results: The study included 75 males and 71 females, with an average age of 58.33 years for males and 56.45 years for females. Female subjects exhibited higher VAS and ODI scores, larger pelvic tilt (PT) and trunk fat mass and smaller trunk muscle mass compared to males. In female, ODI positively correlated with sagittal vertical axis (SVA) and PT. No significant correlations were found between ODI scores and body composition in either sex. The high ODI group showed greater SVA, PT, and pelvic incidence-lumbar lordosis and higher trunk fat/muscle ratio. Psoas muscle mass, total and skeletal muscle mass and trunk muscle mass of that group were smaller than those of low ODI group.

Conclusion: Spino-pelvic parameters and back muscle mass were associated with ODI and there were differences between Korean male and female fishery workers.

Keywords: Low back pain, Spine, Body composition, Back muscles, Fisheries

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INTRODUCTION

Low back pain (LBP) is a very common musculoskeletal problem around the world and is known as a major health problem as it causes disability. In particular, Korea is a world's leading

aging country and the prevalence of LBP is on the rise with increasing personal and social costs, raising its importance [1].

Occupation is known as a factor that affects the prevalence of LBP [2]. Occupational groups with increased prevalence of LBP included construction and extraction workers, community

and social service workers, health care practitioners, technician, farmer, fisher, and forestry [2]. Among all male workers' occupations, health care practitioners had the highest risk for LBP, whereas among female and middle-aged (41–64 years) workers, farming, fishing, and forestry occupations had the highest risk [2]. It is reported motions causing LBP include lifting, pushing, pulling, standing, or walking for a long time [3,4].

Various clinical factors including sagittal spino-pelvic alignment and back muscle mass are known to be associated with LBP. A number of studies have been conducted on the association between LBP, sagittal spino-pelvic parameters. Previous studies found that parameters like sagittal vertical axis (SVA), lumbar lordosis (LL), sacral slope (SS), pelvic incidence (PI) and pelvic tilt (PT) were associated with prevalence of LBP [5,6].

There are studies that have investigated the relationship between the incidence of LBP and sagittal spino-pelvic parameters in certain occupational group. A study found that larger SVA and smaller LL were observed in Korean farmers compared to the general population, and there was a positive correlation between their working time and SVA [7]. Additionally, a study reported that sagittal spino-pelvic alignment was identified as a strong determinant of LBP and blue-collar occupation is associated with increased SVA and PT/PI ratio [8]. However, research on fishery workers is insufficient, although they are known to be vulnerable to LBP.

In addition to spino-pelvic alignment, recent studies have documented the relationship between LBP and back muscle strength, size and structures [9]. To evaluate back muscle mass, various tools were used such as dual-energy X-ray absorptiometry (DEXA), muscle cross-sectional area (CSA) and bioelectrical impedance analysis (BIA). Some studies found that erector spinae or multifidus CSA were smaller in LBP group, compared to normal group [10,11]. In contrast, there is a study which found no difference in average trunk muscle area according to LBP severity [12]. A study also reported the correlation between trunk muscle mass measured with BIA, Oswestry Disability Index (ODI) and EuroQol 5 Dimension (EQ5D) score [13].

The aim of this study is to investigate the relationship between LBP and sagittal spino-pelvic parameters along with the relationship between LBP and back muscle mass in Korean male and female fishery workers. Furthermore, we aimed to find out how this correlation differs from general population or other occupational group.

METHODS

Subjects

This retrospective study enrolled 387 subjects who went through fisher's low back musculoskeletal disorder health survey conducted from June 2018 to August 2020 in Inje University Busan Paik Hospital Center for Fishermen's Safety and Health funded by Ministry of Oceans and Fisheries Affairs of the Republic of Korea. Institutional Review Board (IRB) of Inje University Busan Paik Hospital had reviewed and approved this study and informed consent requirement was waived based on the retrospective nature of this study (IRB No. 2022-11-048). Inclusion criteria for the study were as follows: (1) age between 40 to 64, (2) active fisherman, and (3) engagement in fishery for a minimum of 3 consecutive years at the point of examination. The exclusion criteria were as follows: (1) previous history of spinal accident or spine surgery, (2) presence of spinal tumor or fracture, and (3) insufficient data of exam such as questionnaire, whole spine standing X-ray, lumbar spine magnetic resonance imaging (MRI) and BIA (Fig. 1). Finally, a total of 146 subjects were included for statistical analysis.

Demographic characteristics

Data were collected from questionnaires and medical records. Variables included sex, age, work period in fishery, job classification, history of spinal surgery or accident. Job classification were as follows: fishing fishery (trap gill net, long line), aquaculture (shellfish, fish, and seaweeds), diving fishery such as Haenyeo (Korean female sea divers) and others like oyster

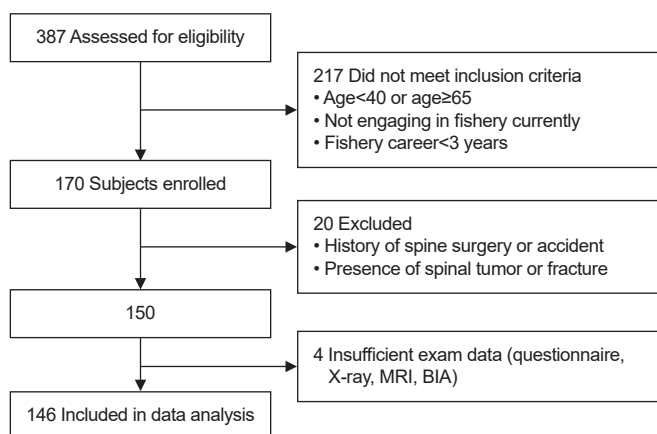


Fig. 1. Flow chart of study population selection. MRI, magnetic resonance imaging; BIA, bioelectrical impedance analysis.

shucker. Regarding spinal disorders, we retrospectively collected the data from prior MRI readings by a musculoskeletal specialized radiologist.

LBP

LBP severity were investigated through data collected from a face-to-face questionnaire. LBP severity was assessed using visual analogue scale (VAS) and ODI.

The ODI is considered as the gold standard of LBP functional outcome measure [14]. The ODI questionnaire consists of 10 items (pain intensity, difficulty in managing personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling). Each item scores from 0 (no pain or disability) to 5 (worst pain or complete disability). The item associated with sex life is recommended to be conducted only if applicable. In this study, except for that one item, the scores for the nine items were added together. Final score was reported as percent using the following formula: $ODI = \frac{\text{sum of item scores (0-45)}}{\text{maximum score (45)}} \times 100$. The subjects were divided into two groups based on the ODI score, with a cutoff of 20%. Less than 20 was categorized as the low ODI group, while 21 or higher was classified as the high ODI group.

Sagittal spino-pelvic parameters

Whole spine standing lateral X-ray images were reviewed. The following parameters were measured by 2 examiners on the whole spine standing X-ray. The SVA is defined as the distance between C7 plumb line and superior-posterior corner of sacrum. LL is defined as the angle between upper margin of the first lumbar vertebra and upper margin of sacrum. SS is defined as the angle between upper margin of sacrum and the horizontal line. PI is defined as the angle between perpendicular bisector line of upper margin of sacrum and the line connecting the center of femoral head and the midpoint of upper margin of sacrum. PT is defined as the angle between the vertical line and the line connecting the center of femoral head and the midpoint of upper margin of sacrum (Fig. 2). Then the average value of two examiners' measurements was used to reduce the measurement error.

Muscle mass measurement

Muscle mass was assessed using data from two methods: BIA and CSA measured on lumbar MRI. BIA had been conducted using InBody 370S (InBody). Whole body measurements had been taken with the subject in a standing barefoot on the

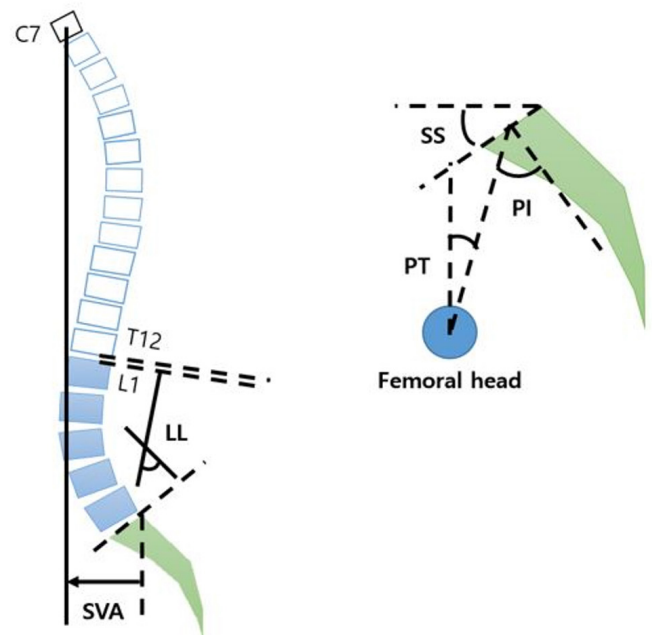


Fig. 2. Measurement of spino-pelvic parameters. LL, lumbar lordosis; SVA, sagittal vertical axis; SS, sacral slope; PI, pelvic incidence; PT, pelvic tilt.

rear sole electrodes of device with the arms abducted from the trunk. Subjects had been asked to hold the hand electrode so that the 4 fingers wrap the surface of the bottom hand electrode, and place the thumb on the oval electrode. All subjects had been required to be examined in the morning on an empty stomach. All tests had been performed by one examiner. Total fat mass, total muscle mass and skeletal muscle mass had been obtained. In addition, trunk fat/muscle ratio had been calculated by dividing trunk fat mass by trunk muscle mass.

Lumbar spinal MRI images taken in supine neutral position were reviewed by 2 examiners for CSA parameters. Gross CSA of psoas muscle and paraspinal muscle (PSM) were measured at the lower edge of L4 vertebral level. PSM consist of erector spinae and multifidus muscle (Fig. 3). Each muscle's CSA was obtained by adding both side measurements for each subject. Then, the final value was obtained calculating the average of two examiners' measurements.

Statistical analysis

To compare the difference of variables between male and female, independent t-test was performed. Independent student t-test was used for the comparison of sagittal spinal alignment, back muscle CSA, body composition between low ODI group,

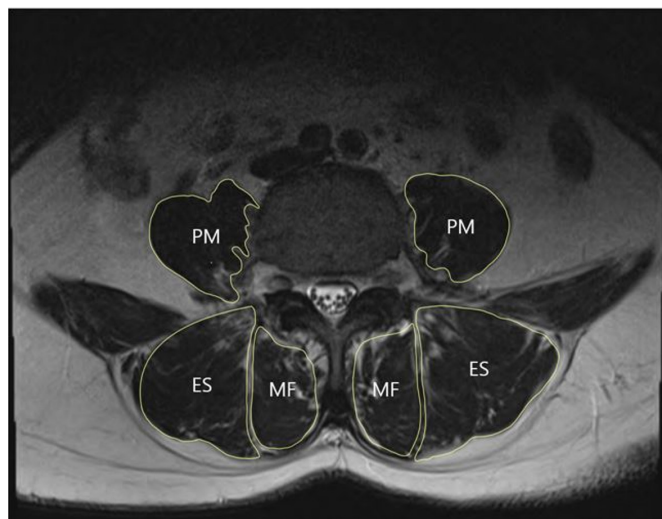


Fig. 3. Axial view of lumbar spine magnetic resonance imaging. The cross-sectional area of psoas major (PM), erector spinae (ES), and multifidus (MF) muscles were obtained on axial T2 weighted image at the lower edge of L4 spinal level.

and high ODI group.

Correlation between ODI, spinal parameters and body composition mass were analyzed using Pearson's correlation test. A p-value less than 0.05 was considered statistically significant. All statistics were analyzed using IBM SPSS version 23.0 (IBM Corp.).

RESULTS

Table 1 shows subject demographic characteristics and variables. Among all subjects, 75 (51.4%) were male and 71 (48.6%) were female. The average age was 58.33 ± 4.98 years in male and 56.45 ± 5.17 in female. Statistically significantly higher VAS, ODI score and greater PT, total fat mass, trunk fat mass, and trunk fat/muscle ratio were found in female compared to male. Male showed significantly higher age and larger PSM and psoas muscle mass, total muscle mass, skeletal muscle mass, and trunk muscle mass than female. There was a difference in the proportion of fishery type that female and male engaged in.

Table 1. Demographic characteristics and variables of subjects

Characteristics	Male (n=75)	Female (n=71)	p-value
Age (yr)	58.33 ± 4.98	56.45 ± 5.17	0.03*
Visual analogue scale	2.45 ± 2.89	3.49 ± 2.86	0.03*
Oswestry Disability Index (%)	6.13 ± 9.61	13.86 ± 14.58	<0.001**
Body mass index (kg/m ²)	25.21 ± 3.14	25.67 ± 3.44	0.40
Spino-pelvic parameter			
LL angle (°)	43.46 ± 9.19	44.24 ± 8.25	0.59
SVA (mm)	5.51 ± 23.55	4.29 ± 25.35	0.76
PI angle (°)	49.10 ± 8.97	51.05 ± 8.77	0.19
SS angle (°)	35.08 ± 6.66	35.11 ± 8.02	0.98
PT angle (°)	14.02 ± 6.65	17.17 ± 9.10	0.02*
PI-LL (°)	5.56 ± 10.78	7.01 ± 10.38	0.44
Cross-sectional area			
Paraspinal muscle mass (cm ²)	24.69 ± 6.14	20.59 ± 5.30	<0.001**
Psoas muscle mass (cm ²)	12.69 ± 3.39	7.83 ± 2.04	<0.001**
BIA			
Total fat mass-BIA (kg)	17.57 ± 5.41	22.54 ± 5.87	<0.001**
Total muscle mass-BIA (kg)	51.66 ± 5.88	39.37 ± 5.60	<0.001**
Skeletal muscle mass-BIA (kg)	30.54 ± 3.73	22.67 ± 3.52	<0.001**
Trunk fat mass-BIA (kg)	9.39 ± 3.17	11.72 ± 3.26	<0.001**
Trunk muscle mass-BIA (kg)	25.60 ± 2.84	19.70 ± 2.72	<0.001**
Trunk fat/muscle ratio-BIA	0.37 ± 0.10	0.60 ± 0.14	<0.001**
Fishery types			
Fishing fishery	68 (90.7)	46 (64.8)	
Aquaculture	6 (8.0)	9 (12.7)	
Diving fishery	0 (0)	15 (21.1)	
Other	1 (1.3)	1 (1.4)	

Values are presented as mean \pm standard deviation or number (%).

LL, lumbar lordosis; SVA, sagittal vertical axis; PI, pelvic incidence; SS, sacral slope; PT, pelvic tilt; BIA, bioelectrical impedance analysis.

p-values from mean comparisons are also reported *p<0.05 and **p<0.01.

The prevalences of other spinal disorders are presented in [Supplementary Table S1](#). The prevalence of at least one level of herniated intervertebral disc (HIVD) was found to be 19.18%, and the prevalence of advanced disc degeneration was 63.01%. In the case of facet joint degeneration (FJD), moderate degenerative disease was observed in 27.40% and severe degenerative disease was observed in 15.75% of subjects. When evaluating spondylolisthesis, 19.9% had mild spondylolisthesis.

[Table 2](#) presents correlation between ODI, spino-pelvic parameters and body composition in male and female group. In female, positive correlation with ODI was found SVA ($r=0.422$, $p<0.001$) and PT ($r=0.335$, $p=0.004$). No statistically significant correlation was found in male. In both groups, no parameter measured by BIA showed statistically significant correlation with ODI. The ODI score did not correlate with any of muscle mass calculated by CSA on spine MRI.

The high ODI group revealed greater SVA, PT and PI-LL ([Table 3](#)). They showed greater trunk fat/muscle ratio and smaller psoas muscle mass, psoas muscle mass divided by weight, total muscle mass, skeletal muscle mass, and trunk muscle mass ([Table 4](#)).

Table 2. Pearson's correlation coefficients (r) for sagittal spino-pelvic alignment and body composition with the Oswestry Disability Index score

	Male (n=75)		Female (n=71)	
	r	p-value	r	p-value
Spino-pelvic alignment				
LL angle (°)	-0.057	0.629	-0.127	0.293
SVA (mm)	0.202	0.082	0.422**	<0.001**
PI angle (°)	0.076	0.515	0.090	0.456
SS angle (°)	0.004	0.971	0.020	0.866
PT angle (°)	0.099	0.399	0.335**	0.004**
PI-LL (°)	0.112	0.339	0.214	0.073
Body mass index (kg/m ²)	-0.115	0.325	-0.099	0.412
Bioelectrical impedance analysis				
Total fat mass (kg)	-0.141	0.226	-0.052	0.664
Skeletal muscle mass (kg)	-0.008	0.946	-0.058	0.631
Trunk fat mass (kg)	-0.139	0.233	-0.050	0.679
Trunk muscle mass (kg)	0.010	0.930	-0.051	0.671
Trunk fat/muscle ratio	-0.117	0.317	-0.030	0.805
Cross-sectional area				
PSM mass (cm ²)	0.133	0.257	0.141	0.240
Psoas muscle mass (cm ²)	-0.20	0.085	-0.160	0.184
PSM mass/weight (cm ² /kg)	0.133	0.257	0.141	0.240
Psoas muscle mass/weight (cm ² /kg)	-0.200	0.085	-0.160	0.184

LL, lumbar lordosis; SVA, sagittal vertical axis; PI, pelvic incidence; SS, sacral slope; PT, pelvic tilt; PSM, paraspinal muscle.

* $p<0.05$ and ** $p<0.01$.

DISCUSSION

Studies have been conducted on the relationship between spinal alignment, back muscle and LBP. In addition, sex differences have been noticed widely in the field of research about LBP and spine pathology. However, research on the relationship between LBP and spinal alignment has not been done for fishermen, although they are known to be highly exposed to working environment inducing LBP. This study is the first presented research that focused on a specific occupational group of Korean fishery workers. In this study, spino-pelvic parameters that showed differences among the ODI groups were SVA, PT, and PI-LL. Significant differences were observed in body composition pa-

Table 3. Comparison of sagittal spino-pelvic alignment between low ODI group and high ODI group

	Low ODI (n=118)	High ODI (n=28)	p-value
LL angle (°)	44.13±8.99	42.61±7.51	0.408
SVA (mm)	1.97±23.05	17.31±26.24	0.002**
PI angle (°)	49.56±8.62	52.10±9.88	0.175
SS angle (°)	35.00±6.39	35.50±10.55	0.748
PT angle (°)	14.56±6.68	19.73±11.56	0.002**
PI-LL (°)	5.43±10.36	10.00±10.84	0.04*

Values are presented as mean±standard deviation.

ODI, Oswestry Disability Index; LL, lumbar lordosis; SVA, sagittal vertical axis; PI, pelvic incidence; SS, sacral slope; PT, pelvic tilt.

* $p<0.05$ and ** $p<0.01$.

Table 4. Comparison of back muscle CSA and body composition between low ODI group and high ODI group

	Low ODI (n=118)	High ODI (n=28)	p-value
Body mass index (kg/m ²)	25.47±3.23	25.30±3.59	0.816
CSA			
PSM mass (cm ²)	22.85±6.37	21.97±4.77	0.494
Psoas muscle mass (cm ²)	10.90±3.78	7.91±2.18	<0.001**
PSM mass/weight (cm ² /kg)	0.33±0.08	0.34±0.07	0.46
Psoas muscle mass/weight (cm ² /kg)	0.16±0.05	0.12±0.03	<0.001**
BIA			
Total fat mass (kg)	19.63±6.07	21.48±6.34	0.154
Total muscle mass (kg)	46.85±8.38	40.74±6.62	<0.001**
Skeletal muscle mass (kg)	27.46±5.33	23.59±4.28	<0.001**
Trunk fat mass (kg)	10.38±3.42	11.12±3.36	0.303
Trunk muscle mass (kg)	23.29±4.02	20.39±3.39	0.001**
Trunk fat/muscle ratio	0.46±0.16	0.56±0.16	0.004**

Values are presented as mean±standard deviation.

CSA, cross-sectional area; ODI, Oswestry Disability Index; PSM, paraspinal muscle; BIA, bioelectrical impedance analysis.

* $p<0.05$ and ** $p<0.01$.

rameters, including trunk fat/muscle ratio, psoas muscle mass, psoas muscle mass divided by weight, total muscle mass, skeletal muscle mass, and trunk muscle mass. We also found that ODI positively correlated with SVA and PT only in female.

According to previous studies, it is known that greater SVA, PI-LL, smaller LL, SS are associated with LBP [5,6]. The SVA is the most widely used measure of global sagittal balance and higher SVA value correlates with increased disability [6]. Regarding the relationship between LBP and PT, controversial results have been reported in previous studies [5,15]. Several studies were conducted on spinopelvic alignment of specific occupation like farmer [8,16]. Especially, a study recruiting Korean farmers revealed that LL was significantly smaller in subjects with LBP than in those without [17].

In our study subjected to Korean fishery workers, several parameters reflecting spino-pelvic alignment were observed to be related with ODI. Especially in female, there was a positive correlation between ODI score and SVA and PT, while no correlation was found in male. Based on an ODI score of 20, subjects were divided into low ODI group and high ODI group. The latter group showed greater SVA, PT, and PI-LL. It has been reported that $SVA \geq 14.8$ mm, $PT \geq 17.9^\circ$, $PI-LL \geq 2.7^\circ$ are radiographic thresholds that predict moderate disability ($ODI > 20\%$) [15]. Consistent with previous research findings, larger SVA and PI were associated with more severe disability, and the previously controversial PT value also demonstrated such associations. Unlike the study of Korean farmers, there was no statistically significant LL difference between the low ODI group and the high ODI group in this study [17].

Recently, sarcopenia has attracted attention as one of the major causes of LBP. A number of papers have been published on the relationship between LBP and back muscle mass. Measuring CSA on MRI or computed tomography (CT) is widely used as accurate method of measuring the lumbar muscle mass. Studies found CSAs of back muscles such as multifidus, psoas and erector spinae were smaller in LBP patients [10,18]. A study also revealed that CSA of erector spinae was significantly smaller in chronic LBP group than that of the improved LBP group, suggesting the possibility of CSA of erector spinae as a prognostic factor [19]. However, it is still controversial which muscle is responsible among them.

DEXA, MRI, and CT require a lot of time, dedicated space for exam, are expensive, and there is also a limitation that DEXA and CT have the risk of radiation exposure. Therefore, interest in usefulness of BIA, which is easy, safe and cost-effective, is

increasing. Several studies showed the amount of trunk muscle measured through BIA is proportional to the CSA of the actual back muscle and is also associated with the back muscle strength [20,21]. Additionally, a study demonstrated significant correlation between trunk muscle mass measured with BIA, ODI and EQ5D, and suggested the potential of BIA as an evaluation tool in patients with LBP [13].

In a paper on Korean farmers, ODI was found to have positive correlation with trunk fat/muscle ratio, total fat and visceral fat muscle mass in female farmers [22]. Back muscle mass and psoas muscle mass had no statistically significant correlation with the ODI score [22]. In this study of Korean fishery workers, no parameters measured by BIA or muscle mass calculated by CSA on spine MRI showed statistically significant correlation with ODI score in both male and female. Divided by ODI score, high ODI group had a larger trunk fat/muscle ratio and smaller total muscle mass, skeletal muscle mass, and trunk muscle mass. Similarly, it was found that psoas muscle CSA and psoas muscle CSA divided by weight are significantly smaller in high ODI group. As we did not reflect the muscle density, it can be thought that the psoas muscle, which is known to be less affected by fat infiltration than multifidus and erector spinae, showed significant difference [23].

The prevalence of LBP had been reported to be higher in female than in male, showing 1.28-fold higher among female in the 50-years or older age group [24]. In this study, VAS and ODI score of female were higher with statistical significance than those of male. Among spino-pelvic parameters, only PT angle presented statistically significant difference between sexes, in contrast to a previous study on healthy population which reported that PI and PT were larger in female [25]. These sex differences can be affected by the subtypes of fishery work that they mainly engage in. 21.1% of female engaged in diving fishery while none of male did.

Workload and working posture also can contribute to the sex difference of LBP prevalence. A study found high workload is significantly associated with increased incidence of LBP in Danish fishermen [26]. A research showed that female were more likely to report back pain if they were “skilled agricultural, forestry, and fishery workers,” while LBP was found to be common in male engaging in “elementary occupation” [27] and contributed to our finding that specific pattern and posture of work, female generally assigned in, can provoke LBP. Regardless of the type of fishery, such as fishing fishery or aquaculture, male and female tend to have different division of roles. Females tend to

work in squatting position doing manual jobs such as shucking oysters and trimming seafood or equipment. Working in sitting position with trunk flexion was suggested to be responsible for LBP in a research, which reported that the prevalence of lower back musculoskeletal disorders were 1.24 times higher in female shellfish gatherers [28]. Workload analysis for each fishery type is complicated because the environment and individual ways of work are not standardized and needed for further exploration of pathology of LBP.

For the sex differences in the correlation between LBP and spino-pelvic parameters, two other potential explanations are relevant based on our data. First, when comparing male and female in this study, female had higher ODI scores, which implies that a clear correlation with spino-pelvic alignment may only be observed when there's a certain degree of disability. Second, based on the results of body composition analysis, female had smaller trunk muscle mass and greater trunk fat mass and fat/muscle ratio than those of male. The clinical importance of trunk muscle mass in association with disabilities arising from LBP was clarified in previous studies [29,30]. A study also found that the deterioration quality of life started with trunk muscle mass approximately <23 kg [31]. In this study, the average of trunk muscle mass was smaller in female as 19.70 kg, contributing to higher ODI score in female. Trunk muscle mass of male fishery workers was maintained larger (25.60 kg) and other parameters reflecting body composition such as total fat mass and skeletal muscle mass remained to be in better condition than those of female. For this reason, it can be assumed that the lack of trunk muscle mass in female did not exert an appropriate compensation mechanism for back pain caused by abnormal spinal alignment.

As this study aimed to explore the relationship between sagittal spine alignment, body composition, and LBP, we recognized the potential influence of structural anomalies of spine, such as HIVD, degenerative disc disease (DDD), FJD and spondylolisthesis. Consequently, we undertook a comprehensive review of the spinal disorders based on MRI findings (Supplementary Table S1). In this study, HIVD was observed in 19.18% and advanced disc degeneration was observed in 63.04% of the total participants. This rates appeared similar to the results of a previous study on asymptomatic individuals, where HIVD was identified in approximately 22% of individuals aged 40 to 59, and DDD was observed in 59% [32]. The prevalence of FJD also appeared to be consistent with prior research involving community-based populations [33]. Regarding the prevalence of

spondylolisthesis, 80.14% were classified as normal and 19.86% exhibited grade 1 corresponding to less than 25% slippage. Similar finding had been identified with an earlier study targeting middle-aged individuals from the Beijing community which reported a prevalence of lumbar spondylolisthesis at 17.26% [34]. Based on these similar rates, it is assumed that these abnormal findings observed in the MRI of our study subjects can be considered not to exert a major impact on the outcomes of our research.

Several limitations should be considered in this study. First, it has targeted subjects who visited for medical check-up. Most of the subjects were able to walk independently and had almost no disability. Therefore, relatively good condition of participants made it hard to correlate variables with substantial degree of LBP that actually causes disability, as in patients visiting the spinal clinic. Second, this study was designed as a cross-sectional study. The results showed the relationships between LBP, spinal alignment and trunk muscle mass, but it could not be clearly determined which one is the cause or result of another. A longitudinal follow up and expanding to a cohort study is desirable. Third, we used gross CSA measurements within the borders of lumbar muscles not considering bias of muscle density. As we could not use Hounsfield units to reflect fat infiltration in muscle, we tried to increase the reliability of measurement by using the average value of the two examiners' measurements. Finally, the differences in fishery working experience, daily working time, specific posture and working environment were not fully understood and reflected to our analysis.

In conclusion, this study suggests the relationship between LBP, sagittal spinal alignment and body composition in Korean male and female fishery workers. Multi-dimensional approach using spinal alignment and muscle mass can be considered for LBP evaluation especially when routine radiologic interpretation can not fully explain patient's disability.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Han N, Kim H. Methodology: Han N, Kim H, Nam H. Formal analysis: Kook M, Kim I, Seo J. Funding acquisition: Kim H, Han N. Project administration: Han N, Kook M. Visualization: Kook M, Kim I, Seo J. Writing – original draft: Kook M, Kim I. Writing – review and editing: Han N, Kook M, Nam H. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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Comprehensive Physical Work Capacity Evaluations for Korean Farmers Assessed in Healthy Volunteers

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Objective: To establish the lower limits of normative values of the physical work capacity for Korean farmers in healthy working individual.

Methods: We developed a comprehensive set of physical work capacity evaluation items that encompass common farming tasks. These items include measurements of trunk flexion/extension angles, strength (hand grip, trunk flexion/extension, leg/ back lifting, and pushing/pulling), and positional tolerances. We calculated the normative values for the items and defined the normal range in 124 healthy volunteers aged 20–79 years. We calculated the intra-class correlation coefficient (ICC) to validate the test-retest reliability of the measurements protocol.

Results: The normal values for each measurement item were as follows: trunk flexion and extension angle ($65.3^{\circ} \pm 11.6^{\circ}$ and $29.6^{\circ} \pm 6.6^{\circ}$), dominant hand grip strength (32.2 ± 10.5 kgf), trunk flexion and extension strength (288.4 ± 119.0 N and 297.3 ± 129.9 N), leg and back lifting strength (452.9 ± 233.5 N and 349.2 ± 166.7 N), pushing and pulling strength (214.7 ± 75.1 N and 221.7 ± 63.3 N), and positional tolerance time (squat: 76.8 ± 9.0 seconds, front: 73.8 ± 7.7 seconds, twist: 82.2 ± 8.8 seconds, upward: 71.9 ± 11.3 seconds). Regarding test-retest reliability, all strength measurements demonstrated excellent absolute agreement (ICC, 0.91–0.96). However, positional tolerance showed poor-to-moderate absolute agreement (ICC, 0.37–0.58).

Conclusion: We conducted measurements of muscle strength and positional tolerance in healthy participants of various ages, focusing on tasks commonly performed by Korean farmers. The outcomes hold significant value as they offer a pertinent instrument for assessing the appropriateness of workers, thereby carrying implications for rehabilitation objectives, legal evaluations, and work capacity assessments within the agricultural domain.

Keywords: Work capacity evaluation, Physical fitness, Occupational health services, Agriculture, Low back pain

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INTRODUCTION

Assessment of an employee's ability to engage in their work is a complex task, traditionally based on laws and the expertise of doctors [1,2]. Functional capacity evaluation is a standardized test that systematically assesses an individual's physical ability to perform tasks and provides recommendations for occupational participation. It includes various activities such as graded material-handling activities (e.g., lifting, carrying, pushing, and pulling objects) and positional tolerance activities (e.g., sitting, standing, walking, balancing, reaching, stooping, kneeling, crouching, crawling, object handling/manipulation, fingering, hand grasping, and hand manipulation) [3]. Performance-based measures, particularly lifting tests, have shown strong predictive value in assessing occupational participation in individuals [4]. This type of evaluation can also serve as a prognostic tool for sick leave in physically demanding jobs [5].

In agriculture, evaluating workers' physical work ability is crucial, given the high risk of musculoskeletal and related disorders [6,7]. Previous studies on farm workers have primarily focused on subjective assessments of work ability, relying on questionnaire such as the Work Ability Index questionnaire [8,9] and the Short Form-36 generic questionnaire [10]. It is a well-established health status measure utilized in general and occupational health surveys. However, it is important to note that participants may over-report their workload, leading to potential validity issues with these questionnaires. To address this limitation and obtain more accurate workload data there is a need for more objective approaches, including direct measurement of physical work capacity [11,12].

Evaluation of the physical work capacity of employee is necessary to identify any functional limitations, suggest goals for functional reinforcement training, and determine appropriate directions for specialized rehabilitation training. Additionally, determining the need for functional reinforcement training (rehabilitation) is crucial. However, it is important to selectively evaluate functional capacity evaluations related to agriculture. Understanding the specific burden in Korean agriculture such as squatting, repetitive wrist movements, shoulder flexion, trunk flexion or twisting, lifting, pushing, and pulling [13], can help determine an individual's suitability for agricultural works.

Establishing the lower limit of normative values for functional capacity evaluation items may significantly contribute to research and practice [12]. This valuable information helps address the discrepancy that may arise between work demands

and an individual's ability to perform the required tasks. Comparing an individual's physical capacity evaluation results with the lower limit of normative values for their physical demand category allows for more accurate suggestions for resuming work and establish rehabilitation goals [12].

In previous studies, the determination of normal values for functional capacity evaluation items has predominantly relied on the physical demand levels outlined in the Dictionary of Occupational Titles (DOT), which encompasses descriptions of the physical demands associated with a wide range of jobs [12]. Some studies have further classified occupations into five groups based on the physical demands indicated by the DOT: sedentary, light, medium, heavy, and very heavy. By obtaining normal values for functional capacity evaluation and predicting return to work based on these values, these studies have provided valuable insights [14,15]. However, to the best of our knowledge, there is a gap in research regarding the specific normal values of functional capacity evaluation items for occupational groups, particularly in the agricultural sector.

Thus, our objective is to bridge this gap by providing the lower limit of normative values for evaluating the physical work capacity required for common farming works. We aim to present essential data on the functional range of healthy working individuals and shed light on the systematic management of occupational musculoskeletal diseases prevalent among farmers. Additionally, we plan to investigate the relationship between physical work capacity, specifically as it pertains to common farm tasks, and trunk body composition. By focusing on these aspects, our study seeks to contribute to a more comprehensive understanding of the physical work capacity required for the agricultural field.

METHODS

Participants

The study included healthy 124 volunteers, aged between 20 and 79 years, who had no prior or current involvement in agricultural labor. Prior to participation, all individuals provided written informed consent. Certain exclusion criteria were established to ensure the integrity of the study results. Participants with medical conditions that required treatment and could potentially impact the measurements of physical work capacity were excluded. Likewise, individuals who had previously undergone spinal surgery or were currently experiencing back pain were excluded due to their potential influence on measurements

related to the back. Participants with systolic blood pressure exceeding 160 mmHg or diastolic blood pressure exceeding 100 mmHg were excluded as their elevated blood pressure could affect strength measurements. To explore trunk body composition, participants who had undergone an abdominal computed tomography (CT) scan within the past 6 months, which could result in radiation exposure, were excluded. Moreover, pregnant individuals or those suspected to be pregnant were excluded from the study.

Prior to physical work capacity measurements, the weights and heights of the participants were measured, and their body mass indices (BMIs) were calculated. In the standing posture, the heights of the eyes, elbows, and waist (at the level of the anterior superior iliac crest) were also measured. The research protocol received approval from the Institutional Review Board (IRB) of Kangwon National University Hospital (IRB No. 2016-03-009), ensuring compliance with ethical standards.

Items of physical work capacity measurement

In a previous study [13], a survey was administered to 1,001 Korean farmers using the Korean version of the 20-item Agricultural Work-related Ergonomic Risk Questionnaire. This questionnaire aimed to evaluate the frequencies of 20 actions associated with ergonomic risks in agricultural work. Respondents rated the frequency of each action on a scale ranging from “never” to “always.” Common farm tasks were defined as those with a frequency of “frequently” or “always” responses exceeding 30%. The study identified several common farm tasks based on the questionnaire responses. These tasks included squatting, highly repetitive wrist movements, shoulder flexion, trunk flexion or twisting, constant stress on the finger or wrist, neck flexion or extension, repetitive elbow flexion and extension, shoulder flexion, lifting heavy objects, and pulling and pushing with excessive force. These identified tasks formed the basis for the measurements presented in Table 1.

The measurements conducted in this study included assess-

ments of grip strength, trunk range of motion (trunk flexion and extension angles), static strength (trunk flexion/extension, lifting, pushing, and pulling strengths), and positional tolerance tests. The positional tolerance tests involved tasks such as squatting, reaching forward, twisting, and upward reaching, and the test time for these tasks was recorded (Table 1). In determining the lower limit of normative values for physical work capacity scores in clinical practice, we defined the normal range based on mean \pm standard deviation [16,17].

Hand grip strength

Participants were seated with their shoulders adducted and neutrally rotated (i.e., at an angle of 0°), elbows flexed at 90°, and forearms and wrists in neutral positions, according to the American Society of Hand Therapists’ recommendations for testing grip strength (Fig. 1A) [18]. Hand grip strength was measured first in the left hand and then in the right using a

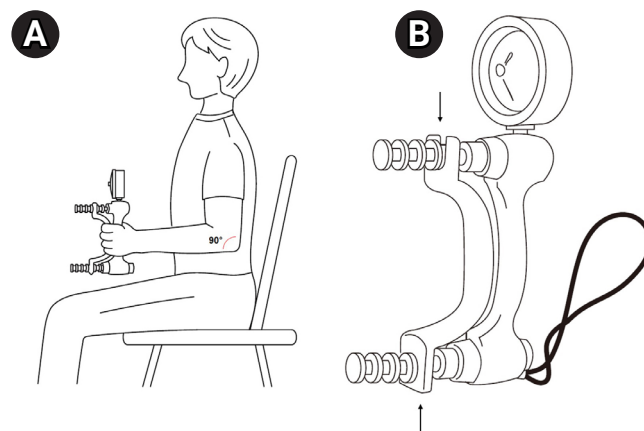


Fig. 1. Hand grip strength measured using a hydraulic hand dynamometer (SH5001[®]; Saehan Corporation). (A) The subject was seated with the shoulder adducted and neutrally rotated, the elbow flexed at 90°, and the forearm and wrist in a neutral position. (B) The handle bars are set on the second notch (arrow) for the second handle position.

Table 1. Brief description of physical work capacity evaluation components

Task	Description
Grip strength	3 Repetitions for right and left hands
Range of motion	Trunk flexion and extension angle; 3 repetitions each
Trunk flexion and extension	Static trunk flexion and extension in the sitting posture; 5 repetitions each
Lifting	Static leg and back lifting; 3 repetitions each
Push and pull	Static full-body push and full-body pull; 3 repetitions each
Positional tolerance	Squatting, front reaching, twist reaching, upward reaching; 1 repetition each

hydraulic hand dynamometer (SH5001[®], Saehan Corporation). This type of dynamometer has five different handle positions, and the recommended choice for evaluating grip strength is the second handle position, where the handle bars are set on the second notch (Fig. 1B) [18]. The maximum value for each measurement was in kilograms. The average of the three grip force values for each hand was obtained. We also analyzed the association between the dominant hand grip strength and trunk body composition.

Range of trunk flexion and extension

The range of motion during forward flexion and backward extension of the trunk was measured using a digital inclinometer (Dualer IQ Pro[™] Digital Inclinometer; JTECH Medical). The measurements were recorded in degrees. The method employed for measuring lumbar flexion and extension followed the inclinometer technique recommended by the Cocchiarella et al. [19].

To measure the trunk range of motion, a primary sensor was placed at the T12 level, while a secondary sensor was positioned over S1 in the sagittal plane to measure the angle (Fig. 2). To locate the T12 spinous process, the initial step involved identifying the highest point of the iliac crest and then moving horizontally towards the midline direction to locate the L4 spinous process. Continuing upwards from L4, the T12 spinous process was successfully located. To find the S1 spinous process, the posterior superior iliac spine was located, and then a horizontal movement towards the midline direction helped locate the S2 spinous process. By sequentially moving upwards from S2, the S1 spinous process was identified.

The trunk flexion range was determined by instructing the participants to stand and bend their trunks as much as possible without moving their legs or hip joints. The trunk extension range was obtained while the participants stood and maximally extended their trunks. Each measurement was performed three times, and the average value was calculated to obtain the final measurement.

Trunk flexion and trunk extension strengths

To measure static isometric trunk flexion and extension strengths, a physical performance evaluation instrument called PrimusRS (BTE Technologies Inc.) was utilized. The PrimusRS is an isokinetic dynamometer that can assess muscle forces in isometric, isotonic, and isokinetic modes. It has a maximum recording capacity of up to 1,800 lbs. (816 kg) of isometric force.

For the measurement, the height of the anchoring cable was adjusted to the T7 spinous process level, and participants were seated in a chair (Fig. 3) [20]. Measuring strength in a sitting position was intended to evaluate pure trunk strength and minimize power transmission from the legs by ensuring that the legs did not touch the ground as much as possible [20].

To accurately identify the T7 spinous process, initial reference points such as the C7 spinous process (vertebra prominens of the neck) were located during the gross anatomy examination. Using this reference, the T1 spinous process was identified, and subsequently, the T7 spinous process was located. To ensure the accuracy of identification, cross-verification was performed using an alternative method. According to gross anatomy, the T7 spinous process aligns with the inferior angle of the scapula.

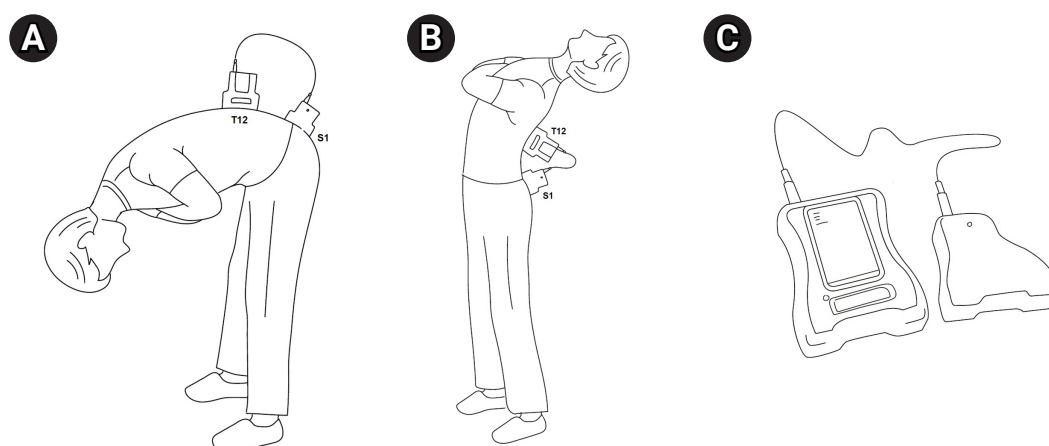


Fig. 2. Range of trunk flexion and extension. (A) Trunk flexion angle. (B) Trunk extension angle. (C) Digital inclinometer.

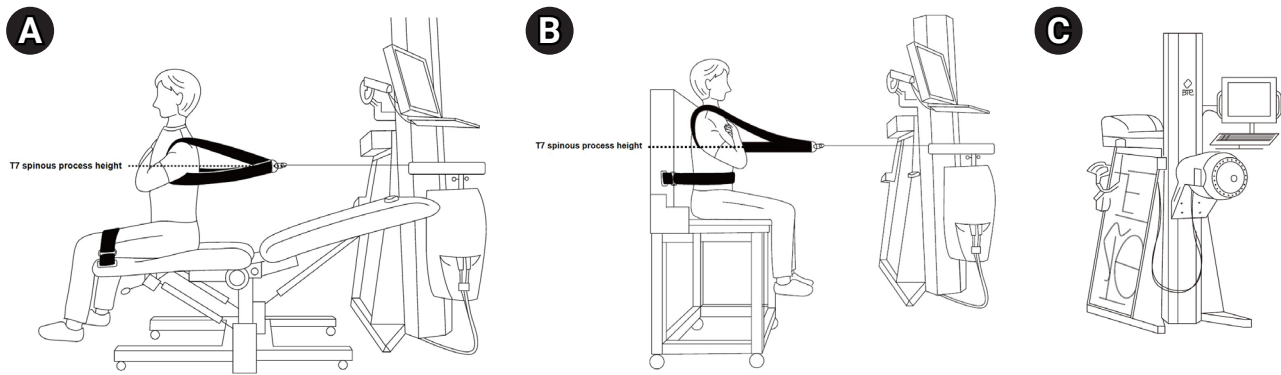


Fig. 3. Isometric strength of trunk flexion and trunk extension. (A) Trunk flexion strength. (B) Trunk extension strength. (C) PrimusRS (BTE Technologies Inc.).

Hence, the initially identified T7 process was compared with this expected location to confirm their correspondence.

During the strength measurements, participants were instructed to fold their arms across their chests and keep their shoulders relaxed. Trunk flexion strength was measured by instructing participants to perform isometric flexion of their trunks. Trunk extension strength was measured by instructing participants to push the square back plate of the instrument as far as possible for a duration of 3 seconds. This measurement procedure was repeated five times, and the mean value was calculated using only the median values, excluding the maximum and minimum values of the five trials.

Leg lifting and back lifting strengths

The evaluation of lifting strength involved two postures: leg lifting and back lifting. Leg lifting, also known as the squat technique, is the recommended lifting technique where the knees are flexed while keeping the back as upright as possible. On the other hand, back lifting, also known as the stoop technique, is a posture where the individual bends forward from the waist, which is considered more strenuous on the lower back.

Isometric lifting strength was measured using a platform called Mobile Lift System (JTECH Medical) in two different horizontal and vertical adjustments. A static force gauge dynamometer (Commander Echo; JTECH Medical) was used for the measurements. The horizontal adjustment refers to the horizontal distance between the midpoint of the hand grasp and the midpoint of the ankle, while the vertical adjustment refers to the vertical distance between the midpoint of the hand grasp and the floor.

In the evaluation of both leg lifting and back lifting, the vertical adjustment was fixed at 15 inches (38.1 cm) (Fig. 4A, B). This vertical distance was maintained consistently for measuring the lifting strength in both postures.

Regarding the horizontal adjustment, there was a distinction between leg lifting and back lifting. For leg lifting, the horizontal adjustment was set at 0 cm, indicating that the midpoint of the hand grasp and the midpoint of the ankle were aligned along the same vertical line.

On the other hand, for back lifting, the horizontal adjustment was set at 38.1 cm. This means that the midpoint of the hand grasp was positioned 38.1 cm horizontally away from the midpoint of the ankle (Fig. 4B). This setting allowed for the assessment of lifting strength specifically in the back lifting posture.

Each measurement was performed three times, and the average value was calculated to obtain a reliable representation of the individual's isometric lifting strength in each posture.

Pushing and pulling strengths

To assess the pushing and pulling strengths, the height of the handle was adjusted to align with the level of the anterior superior iliac spine, as depicted in Fig. 4. The handle was connected to a wireless digital static force gauge dynamometer (JTECH Commander Echo).

Participants were instructed to perform maximal isometric pulling and pushing exercises while standing. For the pushing strength measurement, participants faced a wall and exerted force on the dynamometer, as shown in Fig. 4C. On the other hand, for the pulling strength measurement, the force gauge was connected to the PrimusRS machine, not for utilizing the Pri-

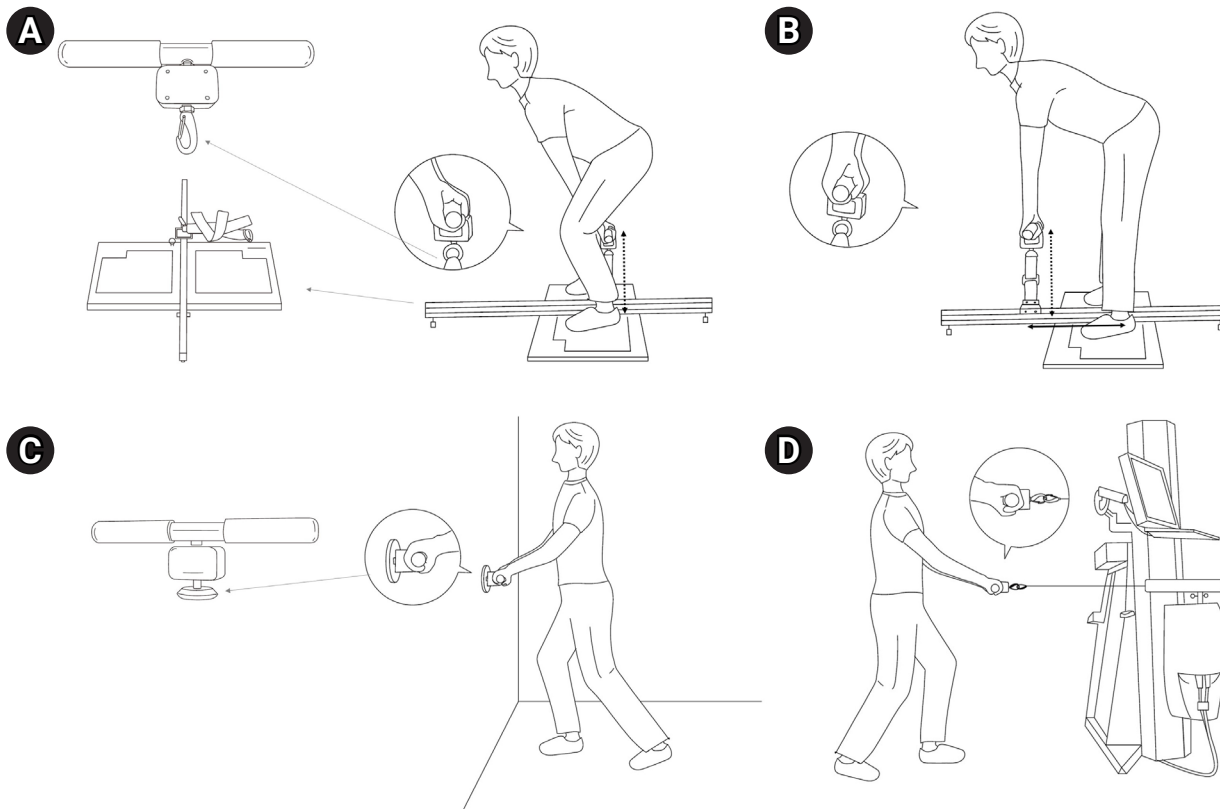


Fig. 4. Isometric strength of leg lifting (A), back lifting (B), pushing (C), and pulling (D) are displayed. (A, B) For lifting strengths, the vertical and horizontal distance of from the hand-held static force gauge dynamometer from the midpoint of the ankle were predetermined. The vertical distance between the midpoint of the hand grasp and the floor was 15 inches (38.1 cm) in both leg lifting (A) and back lifting (B), indicated by the vertical dotted line. The horizontal distance between the midpoint of the hand grasp and the midpoint of the ankle is represented by the horizontal solid line. The horizontal adjustment was set at 0 cm for leg lifting (A), while the horizontal distance was 15 inches (38.1 cm) in back lifting indicated in solid line (B). (C, D) For pushing and pulling strengths, the height of a handle was adjusted to align with the level of the anterior superior iliac spine.

musRS force gauge but for stabilizing the wireless force gauge during the pulling technique (Fig. 4D).

Measurements were conducted three times for each participant, and the average value was calculated to obtain an accurate representation of their pushing and pulling strengths.

Positional tolerance of squat, front, twist, and upward reaching tasks

The positional tolerance test included four types of tasks of manipulating the clothespin in different positions as quickly as possible. The front, twist, and upward tasks were performed in the standing position, whereas the squat task was performed in the squatting position (Fig. 5). Initially, a set of six clothespins was arranged horizontally positioned, each spaced 10 cm

apart from its neighboring clothespin. The starting task height was adjusted differently depending on the specific task being performed: the malleolus level for the squat task (Fig. 5A), the elbow level for the front and twist tasks (Fig. 5B, C), and the eye level for the upward reaching task (Fig. 5D). For each task, participants were instructed to sequentially move and then return the clothespins to their original positions, repeating this process five times. Among these tasks, three required moving the clothespins upward by 30 cm from their initial position (squat, front, and upward tasks), while the twisting task required shifting them horizontally by 90°. The clothespin was gripped with the thumb, index finger, and middle finger of the participant's dominant hand. During the squat, front, and twisting tasks, the thumb was placed on the top, with the index and middle fingers

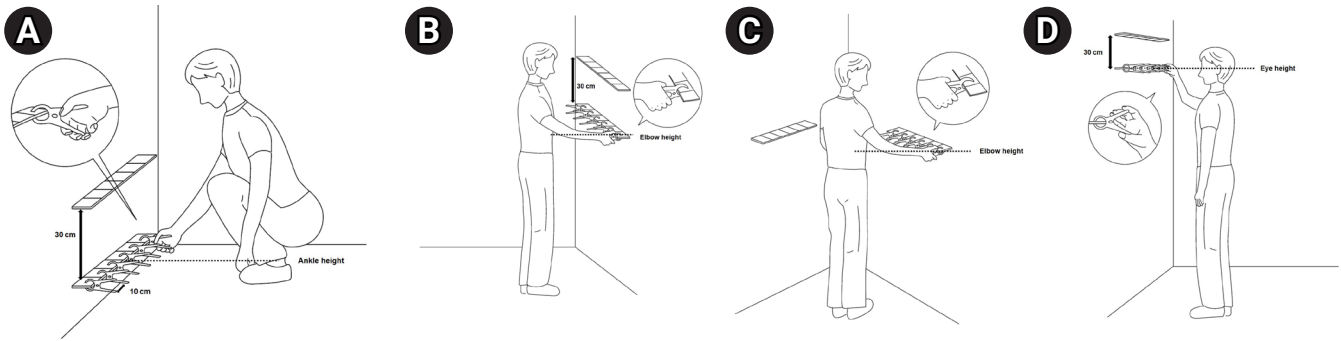


Fig. 5. Positional tolerance of squat, front, twist, and upward reaching tasks. (A) Squat task. (B) Front reaching task. (C) Twist reaching task. (D) Upward reaching task.

located at the bottom. Conversely, during the upward task, the thumb was placed at the bottom, while the index and middle fingers were situated on top.

Test-retest reliability

We analyzed the reliability of the protocols used to determine their reproducibility [21]. All physical work capacity items were re-measured 2 weeks after the first evaluation. Precision measurements, which are usually performed in test-retest studies, are necessary [22]. Classifying the reliability of a protocol involves statistical analysis using indices such as the intraclass correlation coefficient (ICC), which is widely used for this type of analysis [23,24]. This enables the categorization of these measures into indicators relevant to clinical practice [25].

For the isometric trunk extension strength in a seated posture, the test-retest reliability was reported as an ICC of 0.82 with a 95% confidence interval of 0.65 to 0.91 [20]. This indicates a high level of agreement between repeated measurements of isometric trunk extension strength. A mean-rating ($k=3$), absolute-agreement, two-way mixed-effects model was used for strength measurements to calculate ICC estimates and their 95% confidence intervals, except for trunk extension strength measurement [25]. A single-rating ($k=1$), absolute-agreement, two-way mixed-effects model was used for the working speed results [25].

A 95% confidence interval of the ICC estimate was used to determine the reliability level. Values <0.5 indicated poor reliability, between 0.5 and 0.75 indicated moderate reliability, between 0.75 and 0.9 indicated good reliability, and >0.90 indicated excellent reliability.

Trunk body composition

To analyze trunk body composition, the participants underwent

CT scans at the mid-L4 vertebral level using a Philips MX 8000 IDT CT scanner (Philips Medical Systems), with a tube voltage of 120 kV, exposure of 200 mAs, and slice thickness of 1 mm. Images were taken from ten consecutive 1-mm-thick slices (total thickness: 10 mm). Participants maintained their hips in a neutral position during the scan to prevent any effects of hip flexion on the measurement of the cross-sectional area of the muscle. Total muscle mass (TMM, cm^3) and total fat mass (TFM, cm^3) were automatically derived from predefined radiation attenuation ranges using image processing software (Extended Brilliance Workspace version 4.5.3, Philips Healthcare Nederland B.V.). Manual outlining was used to subdivide the TMM into psoas muscle mass (PMM, cm^3) and back muscle mass (BMM, cm^3), and abdominal muscle mass (AMM, cm^3) was calculated by subtracting the PMM and BMM from the TMM. The BMM included the multifidus, iliocostalis lumborum, longissimus, and quadratus lumborum. Visceral fat mass (VFM, cm^3) was determined by manually tracing the inner abdominal wall using TFM. Subcutaneous fat mass (cm^3) was calculated by subtracting the VFM from the TFM. The trunk fat/muscle ratio was calculated by dividing the TFM by the TMM. The scans and image processing were performed by one technician [26].

Statistical analysis

To compare the anthropometric characteristics and trunk body compositions between sex groups, the chi-squared test or independent t-test was employed. This allowed for the examination of any significant differences in variables such as height, weight, BMI, and trunk fat/muscle composition between male and female.

The range of trunk flexion and extension, as well as strength measurements including grip strength, trunk flexion, trunk ex-

tension, lifting, pushing, and pulling, were compared between male and female using independent t-tests. Furthermore, within each sex group, the range of trunk motion, strength measurements, and positional tolerance times were compared among the three age groups using Welch's one-way ANOVA. Post-hoc analysis was performed using the Games–Howell method to determine specific differences between age groups.

Paired t-tests were employed to compare paired variables. This included comparisons of trunk flexion and extension, leg and back lifting strengths, as well as pushing and pulling strengths.

To investigate the association between trunk body composition and physical work capacity evaluation items, such as the range of trunk flexion and extension angles, strength measurements, and positional tolerance times, correlation coefficients were computed. These correlation coefficients quantify the magnitude and direction of the relationship between these variables. By calculating and analyzing the correlation coefficients, the study aimed to assess the extent to which trunk body composition relates to various physical work capacity evaluation items. This information can contribute to a better understanding of the influence of trunk body composition on physical work capacity and performance in tasks related to agricultural work.

RESULTS

Anthropometric characteristics of participants

A total of 124 healthy volunteers participated in this study, including 55 male and 69 female: 60 (48.4%) aged 20–39 years, 51 (41.1%) aged 40–59 years, and 13 (10.5%) aged 60–79 years. Age did not significantly differ between male and female. The mean BMI of the participants was $23.7 \pm 3.4 \text{ kg/m}^2$, with a mean height of $165.4 \pm 9.3 \text{ cm}$ and a mean weight of $63.9 \pm 12.3 \text{ kg}$. The heights of the eye level, waist level, elbow level, and ankle level were 155.4 ± 8.8 , 92.8 ± 5.8 , 106.7 ± 6.0 , and $8.7 \pm 1.0 \text{ cm}$, respectively, in the standing posture. All other height values were significantly higher in male than in female, except for the ankle height. Male had significantly higher values of VFM, TMM, BMM, PMM, and AMM than female ($p < 0.05$; Table 2).

Items of physical work capacity measurement

Dominant hand grip strength

The average grip strength of the dominant hand for all participants was $32.2 \pm 10.5 \text{ kgf}$. In male, the strength was $42.1 \pm 7.1 \text{ kgf}$, which was significantly higher than that in female ($24.3 \pm 4.2 \text{ kgf}$) ($p < 0.01$). Grip strength tended to decrease in the oldest group among female (Table 3).

Table 2. Demographic and anthropometric characteristics of participants

Characteristic	All (n=124)	Male (n=55)	Female (n=69)	p-value
Age group (yr)				
20–39	60 (48.4)	30 (54.5)	30 (43.5)	0.38
40–59	51 (41.1)	21 (38.2)	30 (43.5)	
60–79	13 (10.5)	4 (7.3)	9 (13.0)	
Age (yr)	38.3 ± 15.1	36.4 ± 14.4	39.8 ± 15.5	0.21
Body mass index (kg/m^2)	23.7 ± 3.4	23.9 ± 2.8	23.5 ± 3.9	<0.01
Body weight (kg)	63.9 ± 12.3	72.4 ± 10.0	57.1 ± 9.4	<0.01
Height (cm)	165.4 ± 9.3	173.3 ± 4.9	159.0 ± 6.7	<0.01
Eye height (cm)	155.4 ± 8.8	163.1 ± 5.0	149.2 ± 5.8	<0.01
Waist height (cm)	92.8 ± 5.8	97.3 ± 4.2	89.3 ± 4.2	<0.01
Elbow height (cm)	106.7 ± 6.0	111.6 ± 4.4	102.7 ± 3.8	<0.01
Ankle height (cm)	8.7 ± 1.0	8.9 ± 1.2	8.5 ± 0.7	0.50
Trunk body composition				
Total fat area (cm^3)	232.7 ± 102.9	233.3 ± 88.0	232.3 ± 114.1	0.96
Visceral fat mass (cm^3)	66.2 ± 43.6	75.3 ± 39.5	59.0 ± 45.6	0.04
Subcutaneous fat mass (cm^3)	166.5 ± 75.3	158.0 ± 64.8	173.3 ± 82.7	0.26
Total muscle mass (cm^3)	135.6 ± 34.1	167.4 ± 19.3	110.2 ± 18.3	<0.01
Back muscle mass (cm^3)	58.5 ± 13.8	71.2 ± 8.6	48.4 ± 7.4	<0.01
Psoas muscle mass (cm^3)	23.5 ± 8.8	31.8 ± 6.0	17.0 ± 3.5	<0.01
Abdominal muscle area (cm^3)	53.6 ± 15.2	64.5 ± 9.5	44.8 ± 13.2	<0.01

Values are presented as number (%) or mean \pm standard deviation.

Table 3. Physical work capacity evaluation results of participants

	All (n=124)	All male	Male (n=55)		Female (n=69)		
			20-39 yr	40-59 yr	20-39 yr	40-59 yr	
Hand grip strength (kgf)							
Right hand	31.9±10.4	41.6±7.4	40.8±8.1	42.6±7.0	24.1±4.1	25.4±3.7 ^{§§§}	20.8±4.8 ^{§§§}
Left hand	29.5±10.0	38.9±6.9	38.0±7.3	40.6±6.4	22.3±4.0	22.7±3.4	18.9±4.2
Dominant hand	32.2±10.5	42.1±7.1	41.2±7.9	43.3±6.5	24.3±4.0	25.4±3.7 ^{§§§}	20.8±4.8 ^{§§§}
Range of motion (°)							
Trunk flexion angle	65.3±11.6	65.8±9.4	68.8±10.8 ^{§§§}	62.8±6.0*	69.7±16.4 ^{**}	62.6±8.8	57.2±7.3 ^{**}
Trunk extension angle	29.6±6.6	30.6±6.9	33.3±7.7 ^{§§}	27.7±4.0*	33.1±6.4 ^{***}	26.1±3.0*	23.6±5.1 ^{***}
Isometric strength (N)							
Trunk flexion strength	288.4±119.0	390.1±98.6	397.9±108.3	387.1±80.4	212.2±62.2	199.8±49.7	216.3±32.1
Trunk extension strength	297.3±129.9	385.9±130.5	386.3±126.7	385.9±125.7	252.0±96.5 ^{§§§}	207.3±46.9 [§]	206.6±36.1 ^{§§}
Leg lifting	452.9±233.5	659.0±185.0	660.3±210.6	664.4±137.1	306.5±105.8	271.9±92.7	285.3±93.6
Back lifting	349.2±166.7	467.0±176.0	449.0±135.2	504.4±230.1	272.8±89.1	244.8±58.1	232.0±58.2
Pushing strength	214.7±75.1	276.3±57.2	286.0±64.6 ^{§§}	275.6±37.0	181.0±55.9 [§]	154.2±33.5 [§]	152.6±29.4
Pulling strength	221.7±63.3	264.9±59.8	271.9±71.4	255.9±43.6	195.8±46.3	179.1±33.4	186.6±46.2
Postural tolerance (s)							
Squat-task time	76.8±9.0	76.1±8.4	76.0±8.4	76.3±9.1	77.3±6.9	74.6±5.7	87.4±18.5
Front-task time	73.8±7.7	74.0±7.6	73.4±7.2	74.6±7.9	73.9±5.6	70.8±6.1 ^{§§§}	82.2±13.0 ^{§§§}
Twist-task time	82.2±8.8	82.1±8.8	80.6±8.5	83.2±8.0	82.4±7.8	79.3±6.3 ^{***}	92.8±12.2 ^{***}
Upward-task time	71.9±11.3	71.6±8.3	70.0±7.3	71.8±5.4	70.6±6.4	68.6±6.5	88.3±29.0

Values are presented as mean±standard deviation.

^{a)}Independent t-test between male and female.^{b)}Welch's one-way ANOVA between 3 age groups.

*p<0.05 between 20-39 and 40-59 years in the Games-Howell post-hoc test.

**p<0.05 between 20-39 and 60-79 years in the Games-Howell post-hoc test.

***p<0.05 between 40-59 and 60-79 years in the Games-Howell post-hoc test.

[§]p<0.1 between 20-39 and 40-59 years in the Games-Howell post-hoc test.^{§§}p<0.1 between 20-39 and 60-79 years in the Games-Howell post-hoc test.^{§§§}p<0.1 between 40-59 and 60-79 years in the Games-Howell post-hoc test.

Range of trunk flexion and extension

The ranges of trunk flexion and extension were $65.3^{\circ} \pm 11.6^{\circ}$ and $29.6^{\circ} \pm 6.6^{\circ}$, respectively, and there were no significant differences between male and female ($p=0.70$). Trunk flexion and extension ranges showed a significant tendency to decrease with age ($p<0.05$; Table 3).

Trunk flexion and trunk extension strengths

Trunk flexion and extension strengths were 288.4 ± 119.0 and 297.3 ± 129.9 N, respectively, and were not significantly different using a paired t-test ($p=0.18$). Both trunk flexion and extension strengths significantly differed between males and females (males: 390.1 ± 98.6 and 385.9 ± 130.5 N, females: 207.3 ± 53.6 and 226.6 ± 74.6 N, respectively; $p<0.01$). Trunk flexion and extension strengths did not show significant differences between age groups among male, whereas trunk extension strengths in the older groups were weaker than those in the youngest group among female ($p<0.05$; Table 3).

Leg lifting and back lifting strengths

The strength of leg lifting was 452.9 ± 233.5 N, which was significantly higher than the strength of back lifting (349.2 ± 166.7 N) using a paired t-test ($p<0.01$). Leg and back lifting strengths showed significant differences between male and female ($p<0.01$): 659.0 ± 185.0 and 467.0 ± 176.0 N in male and 288.7 ± 98.7 and 255.3 ± 74.0 N in female for leg and back lifting, respectively. However, there was no significant difference in lifting strength according to age among male and female (Table 3).

Pushing and pulling strengths

The pushing and pulling strengths were 214.7 ± 75.1 N and 221.7 ± 63.3 N, respectively. These strengths were not significant-

ly different using a paired t-test ($p=0.11$). However, pushing and pulling isometric strengths significantly differed between male and female ($p<0.01$): 276.3 ± 57.2 N and 264.9 ± 59.8 N in male and 165.6 ± 45.8 N and 187.3 ± 41.3 N in female for pushing and pulling, respectively. Moreover, only the pushing strength tended to decrease with age in male and female ($p<0.05$; Table 3).

Positional tolerance time

The shortest upward-task time was 71.9 ± 11.3 seconds, followed by front-task (73.8 ± 7.7 seconds) and squat-task (76.8 ± 9.0 seconds) times. The longest time was required for the twist task (82.2 ± 8.8 seconds). There were no significant differences in positional tolerance results between male and female. Positional tolerance did not differ according to age in any of the four positions among male. However, the stand and twist tasks required a longer time in the 60–79 years age group than in the 40–59 years age group among female.

Test-retest reliability

Table 4 shows the ICC for the test-retest reliability. Strength measurements of trunk flexion, pulling, pushing, leg lifting, and back lifting showed excellent test-retest reliability. In contrast, the positional tolerance test showed poorer test-retest reliability than strength measurements. The squat and front tasks, in particular, showed poor reliability, whereas the twist and upward tasks showed moderate reliability.

Association with trunk body composition

Table 5 presents the correlation coefficients between the physical work capacity evaluations and anthropometric factors. The findings indicate the following associations:

- Dominant hand grip strength, trunk flexor and extensor

Table 4. ICC for test-retest reliability of physical work capacity evaluation (n=61)

	Test 1	Test 2	ICC	95% confidence interval	p-value
Strength					
Trunk flexion strength	287.9 ± 107.4	302.7 ± 95.0	0.93	0.88–0.96	<0.01
Leg lifting	443.5 ± 215.6	436.9 ± 190.3	0.95	0.92–0.97	<0.01
Back lifting	356.1 ± 142.0	380.8 ± 147.8	0.95	0.91–0.97	<0.01
Pushing strength	218.6 ± 76.2	215.7 ± 67.1	0.96	0.93–0.97	<0.01
Pulling strength	229.1 ± 65.1	243.3 ± 75.6	0.91	0.84–0.95	<0.01
Positional tolerance					
Squat-task	74.1 ± 7.1	65.6 ± 6.8	0.37	-0.10–0.69	<0.01
Front-task	81.0 ± 6.4	65.9 ± 6.5	0.48	-0.06–0.75	<0.01
Twist-task	80.9 ± 7.9	74.5 ± 7.3	0.55	-0.04–0.80	<0.01
Upward-task	69.3 ± 7.7	62.9 ± 6.3	0.58	-0.09–0.84	<0.01

ICC, intraclass correlation coefficient.

Table 5. Correlation coefficients between physical work capacity evaluations and anthropometric factors

	Body weight	Height	BMI	TFM	VFM	SFM	TMM	BMM	PMM	AMM
Male										
Dominant hand grip strength	0.247	0.143	0.221	0.078	0.072	0.061	0.268*	0.357**	0.150	0.128
Trunk flexion angle	0.082	0.241	-0.003	-0.192	-0.414**	-0.009	0.312*	0.393**	0.222	0.141
Trunk extension angle	-0.056	0.004	-0.072	-0.227	-0.390**	-0.071	0.248	0.223	0.366**	0.073
Trunk flexion strength	0.169	0.280*	0.072	-0.044	-0.075	-0.014	0.239	0.394**	0.277*	-0.043
Trunk extension strength	0.284*	0.338*	0.183	0.011	-0.041	0.039	0.358**	0.457***	0.314*	0.118
Leg lifting	0.070	0.318*	-0.056	-0.070	-0.015	-0.085	0.114	0.212	0.248	-0.116
Back lifting	0.392**	0.214	0.367**	0.316*	0.214	0.299*	0.295*	0.430**	0.142	0.122
Pushing strength	0.391**	0.383**	0.290*	0.139	-0.001	0.189	0.400**	0.442***	0.328*	0.209
Pulling strength	0.435***	0.269*	0.386**	0.312*	0.171	0.320*	0.205	0.333*	0.106	0.050
Squat-task time	-0.071	0.108	-0.131	0.039	-0.018	0.063	-0.242	-0.239	-0.085	-0.225
Front-task time	-0.139	0.174	-0.234	-0.026	0.016	-0.046	-0.338*	-0.290*	-0.261	-0.261
Twist-task time	0.073	0.239	-0.018	0.115	0.094	0.099	-0.176	-0.106	-0.228	-0.119
Upward-task time	0.040	0.067	0.017	0.181	0.206	0.120	-0.256	-0.177	-0.243	-0.207
Female										
Dominant hand grip strength	0.236	0.430***	-0.011	-0.057	-0.136	-0.004	0.310**	0.445***	0.327**	0.097
Trunk flexion angle	-0.084	0.178	-0.178	-0.245*	-0.302*	-0.172	0.251*	0.158	0.182	0.212
Trunk extension angle	-0.358**	0.264*	-0.458***	-0.444***	-0.519***	-0.327**	0.218	-0.021	0.216	0.257*
Trunk flexion strength	0.457***	0.081	0.358**	0.341**	0.157	0.384**	0.495***	0.410***	0.367**	0.362**
Trunk extension strength	0.301*	0.204	0.164	0.094	-0.073	0.170	0.453***	0.381**	0.487***	0.289*
Leg lifting	-0.075	0.099	-0.119	-0.171	-0.238*	-0.105	0.267*	0.168	0.252*	0.211
Back lifting	0.362**	0.166	0.239*	0.122	-0.094	0.220	0.532***	0.546***	0.497***	0.304*
Pushing strength	0.387**	0.074	0.306*	0.227	-0.014	0.321**	0.518***	0.492***	0.464***	0.322**
Pulling strength	0.529***	0.163	0.387**	0.361**	0.115	0.436***	0.294*	0.385**	0.402***	0.088
Squat-task time	0.178	-0.185	0.265*	0.320**	0.380**	0.232	0.040	0.035	-0.160	0.079
Front-task time	0.147	-0.244*	0.264*	0.335**	0.415***	0.234	-0.023	-0.042	-0.180	0.039
Twist-task time	0.197	-0.165	0.277*	0.318**	0.338**	0.253*	-0.042	-0.023	-0.240*	0.017
Upward-task time	0.215	-0.257*	0.328**	0.451***	0.547***	0.321**	-0.044	-0.075	-0.243*	0.045

BMI, body mass index; TFM, total fat mass; VFM, visceral fat mass; SFM, subcutaneous fat mass; TMM, total muscle mass; BMM, back muscle mass; PMM, psoas muscle mass; AMM, abdominal muscle mass.

* $p < 0.05$, ** $p < 0.01$, and *** $p < .001$.

strengths, and trunk flexion and extension angles were positively correlated with TMM in both male and female.

- Leg lifting strength did not show a significant relationship with TMM in both sex.
- Trunk flexion and extension angles were negatively correlated with trunk fat in both male and female.
- Back lifting, pushing, and pulling strengths exhibited positive correlations with factors such as body weight and BMI.
- In male, the time taken to complete the squat, stand, twist, and upward tasks did not show significant associations with body weight and BMI.
- In female, the time required for the squat, stand, twist, and upward tasks increased as BMI, TFM, and VFM increased.

These results shed light on the relationships between physical work capacity evaluations and anthropometric factors, providing valuable insights into the physical work capacities and body

composition of the participants.

DISCUSSION

Our study emphasizes the importance of assessing the physical work capacity of Korean farmers to perform their duties. We examined tasks commonly performed by Korean farmers, including squatting, repetitive wrist movements, shoulder flexion, trunk flexion or twisting, lifting, pushing, and pulling. The evaluation measures included trunk flexion and extension angles, hand grip strength, trunk flexion and extension strengths, lifting strength in two postures, pushing and pulling strengths, and positional tolerance in four working postures. This evaluation provides basic data on the lower limit of normative values of physical work capacity evaluation items in agricultural work. All strength measurements showed excellent agreement

in terms of test-retest reliability. However, the completion time was shorter during the retest for positional tolerance, and the absolute agreement of the test-retest was poor to moderate.

Our results showed that physical work capacity tends to decrease with age among female. Dominant hand grip strength, range of trunk flexion and extension, trunk extension strength, and pushing strength tended to decrease with age. Interestingly, dominant hand grip strength and trunk extension decreased in female but not in male. Furthermore, female in the old age group took longer to complete some of the positional tolerance tests than those in the young age group. On the other hand, in male, the older group did not take longer than the younger group to complete some postural tolerance tests. This result is consistent with that of a previous study on Finnish farmers' self-reported morbidity and physical work capacity [27]. This study revealed that female farmers face higher risks in terms of physical work capacity with increasing age. This may be explained by female having relatively lower muscle strength than male, which reduces their physical work capacity to perform agricultural tasks.

The test-retest reliability of all strength measurements showed excellent agreement, aligning with findings from a previous systematic review [28]. This review, which evaluated 32 studies on strength assessment [28], encompassing both excellent and moderately methodological quality, demonstrated that strength assessment displays good-to-excellent test-retest reliability. This holds true regardless of factors such as participants' history of resistance training, sex, and age.

Furthermore, other high-quality evidence supports the reliability of trunk strength assessment in the seated position. The position is the most reliable protocol for isometric assessment in healthy individuals and individuals with nonspecific non-specific low back pain, for which no anatomical cause can be found [29]. These results are consistent with the findings of this study. Strength measurement is accurate since it is performed through constant mechanical action.

In contrast, the retest for positional tolerance showed poor-to-moderate absolute agreement and a shorter completion time. The low test-retest reliability of time measurement in "positional tasks" is due to its inherent variability. Participants may perform the task slightly differently each time, reducing consistency in time measurement. Moreover, a learning effect in which individuals become more skilled at the task during retesting may occur, resulting in a shorter completion time.

The measured physical strength parameters showed a sig-

nificant relationship with trunk body composition. First, body weight and BMI exhibited a positive correlation with back lifting, pushing, and pulling strength for both male and female and trunk flexion strength in female. This association seems intuitive, suggesting that strength could naturally increase with higher body mass. Second, trunk muscle mass showed significant relationship with most of strength results except for male leg lifting strength. For male, leg lifting strength might be associated other unmeasured muscle mass, such as leg muscle. Third, there were interesting relationship between fat mass, along with BMI, and strength. These positive correlations were particularly apparent in back lifting and pulling strength in male and trunk flexion, pulling and pushing strength in female. This is in accordance with the study of Hulens et al. [30], which studied differences in muscle strength of lean versus obese female. Their research unveiled that obese female with elevated BMI and fat mass demonstrated greater trunk strength when compared to their lean counterparts [30]. This is consistent with that obesity could reasonably possess increased muscle power to mobilize their heavier bodies during exercise [31].

The composition of the trunk body was also found to have a connection with the results of positional tolerance tests. Specifically, the amount of fat mass was associated with an increased in the time of positional tolerance, but this connection was observed only among female. These positional tolerance tests require individuals to maintain a specific posture, which in turn relies on the endurance of their muscles as they repeatedly contract to sustain the posture. This prolonged and repetitive muscle contraction is known as muscle endurance [32]. The proportion of fast-fatigue fibers within the skeletal muscles is elevated in obese individuals [33], which contributes to swift muscle fatigue and an inability to sustain muscle contraction over extended periods, ultimately resulting in decreased muscle endurance. Moreover, the percentage of body fat is a physical trait that tends to be higher in female compared to male, typically by around 10% [34]. This difference places female at a potential disadvantage, as they need to exert more effort in lifting or supporting unnecessary body mass during activities. Second, for the muscle mass, the larger muscle was related with shorter positional tolerance time in front-task in male and twist- and upward-task in female. These results suggest that reducing body fat while maintaining muscle mass may be beneficial for overall physical work capacity, which is consistent with a previous study [35,36]. Excess body fat can lead to a decreased physical work capacity [35], including difficulties with usual and narrow

walk, chair stands, and standing balance [36], whereas maintaining or increasing muscle mass can improve it.

To provide more accurate recommendations for returning to work, Table 3 can be used by clinicians to compare a patient's physical work capacity with that of healthy individuals. However, it's important to note that all normative values should be chosen by clinicians regardless of sex or age. This is because the physical work capacity required for agricultural work must be sufficient to handle the relevant workload, regardless of age or sex [12]. Additionally, a study on the return to work of employees on long-term sick leave showed that one of the obstacles to return to work is that employees struggle to come to terms with their disabilities, and suboptimal thinking patterns and actions can impede the return to work journey [37]. Consequently, the physical work capacity evaluation results can validate their perception of their work capabilities and aid in establishing a course of action for return to work [38].

This study has several limitations that should be acknowledged. Firstly, the lower limit of normative values for physical work capacity evaluation may not capture the work capacity of experienced agricultural workers, as previous researches [38,39] suggest differences between novice and experienced workers. Further research focusing on experienced workers is needed. Secondly, the controlled setting of the physical work capacity evaluation may not fully represent the dynamic and unpredictable nature of actual agricultural work, warranting caution when applying normative values to real-world settings. Lastly, the generalizability of the study's findings to Western agriculture is limited due to the study's reliance on Korean data and the specificities of Korean agricultural practices. Further research considering Western contexts is necessary for broader applicability.

In future studies, it would be beneficial to investigate the concurrent validity between these normative values obtained in this study and results obtained from workplace assessments. This would provide further insight into the usefulness and applicability of the normative values in practical setting. Furthermore, it would be valuable to investigate the normative values of physical work capacity evaluation items in other occupational groups, such as those in forestry, fishing, mining, and manufacturing. This would expand the applicability of the normative values beyond the farming population and provide a more comprehensive understanding of physical demands in various occupational settings. In addition, future studies should continue to investigate the physical strength and positional

tolerance required for various types of farming tasks to provide more detailed and specific normative values for farmers. This would enable more tailored assessments and interventions for individuals in this occupation.

In conclusion, this study establishes normative values for physical work capacity evaluation in agriculture, providing a valuable tool for evaluating workers' suitability. These findings have implications for rehabilitation goals, legal assessments, and work capacity evaluations in the agricultural sector, enhancing accuracy and effectiveness.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Baek S, Kim G, Park H. Methodology: Baek S, Kim G, Park H. Formal analysis: Baek S, Jeong S. Project administration: Baek S. Visualization: Baek S, Jeong S. Writing – original draft: Baek S, Jeong S. Writing – review and editing: Baek S, Jeong S. Approval of final manuscript: all authors.

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Preclinical Study of Dual-Wavelength Light-Emitting Diode Therapy in an Osteoarthritis Rat Model

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Objective: To evaluate the efficacy of light-emitting diode (LED) and their dual-wavelengths as a treatment strategy for osteoarthritis.

Methods: We induced osteoarthritis in male Sprague-Dawley rats by intra-articular injection of sodium iodoacetate into the right rear knee joint. The animals with lesions were divided into an untreated group and an LED-treated group (n=7 each). In the LED-treated group, the lesioned knee was irradiated with lasers (850 and 940 nm) and dose (3.15 J/cm²) for 20 minutes per session, twice a week for 4 weeks. Knee joint tissues were stained and scanned using an in vivo micro-computed tomography (CT) scanner. Serum interleukin (IL)-6 and IL-18 levels were determined using enzyme-linked immuno-sorbent assay. Several functional tests (lines crossed, rotational movement, rearing, and latency to remain rotating rod) were performed 24 hours before LED treatment and at 7, 14, 21, and 28 days after treatment.

Results: LED-treated rats showed improved locomotor function and suppressed matrix-degrading cytokines. Micro-CT images indicated that LED therapy had a preserving effect on cartilage and cortical bone.

Conclusion: LED treatment using wavelengths of 850 and 940 nm resulted in significant functional, anatomical, and histologic improvements without adverse events in a rat model. Further research is required to determine the optimal wavelength, duration, and combination method, which will maximize treatment effectiveness.

Keywords: Knee, Osteoarthritis, Phototherapy, Rats, Inflammation

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INTRODUCTION

Osteoarthritis (OA) is characterized by the loss of degraded articular cartilage, subchondral bone remodeling, osteophyte formation from hypertrophic bone changes, chronic inflammation

including synovial membrane, and normal joint function [1]. The prevalence of symptomatic knee OA varies across countries, but overall, it ranges from 7% to 17% among individuals aged 40 years and older. OA is the fourth leading cause of disability globally, and contributes to medical and indirect costs due to

job loss and early retirement [2].

Treatment options for OA can be broadly categorized into four main groups: (1) non-pharmacologic, (2) pharmacologic, (3) complementary and alternative, and (4) surgical. In general, the least invasive and safest treatment should be tried first before more invasive and expensive therapies are considered [3]. Pharmacologic treatments have the following problems. Patients taking nonsteroidal anti-inflammatory drugs should be aware of potential side effects, including complications related to cardiovascular system, kidney, and gastrointestinal bleeding [4]. And opioids have several problems such as cognitive impairment, delirium, and addiction. Intra-articular injections of corticosteroids, hydrogels, and other materials are another pharmacologic option for treating OA [3,5]. It is difficult to definitively determine which material is the most effective because different formulations have own advantages and disadvantages, and different efficacy [3,6]. While there is evidence supporting the use of these materials to reduce functional limitations, there is a lack of comparison with a placebo or control group [3]. The most effective treatment option is total knee replacement for patients whose symptoms have not responded to other treatments. However, surgical treatment can lead to a variety of complications, including prosthesis infection, venous thromboembolic disease, neurovascular injury, and peri-implant fractures [7]. Even after successful surgery, about 25% of patients report pain and disability for more than a year, requiring additional rehabilitation and reoperation. Consequently, surgical treatment should be withheld as a last resort. These are why new non-pharmacologic treatment options are need to be researched.

Low-level laser therapy can trigger in vitro, in vivo, and in human photobiochemical reactions in multiple conditions of various tissues: neck muscle pain, nerve injury, soft tissue wound healing [8-12]. Light-emitting diodes (LEDs), which are composed of semiconductors, have the ability to convert electrical currents into narrow-spectrum light that its incoherent in nature. LEDs are widely used worldwide due to their relatively low price and high accessibility compared to laser. For this reason, treatment using LED is also being performed in various conditions: oral mucositis, hearing loss, temporomandibular disorder, and traumatic brain injury [10]. Treatments using light reduce pain and inflammation and act like opioids without the side effects of addiction, and toxicity. These treatments also act on tissues to promote cell proliferation, the healing process, and tissue regeneration, prevent cell death, and reduce pain and

inflammation [13]. LED can also trigger in natural intracellular photobiochemical reactions [14].

However, while laser treatment equipment is expensive and has limitations in approach, there have been limited studies examining the effects of LED, and the results reported have been inconsistent. More recently, several chromophores have been studied in relation to the mechanisms by which they produce therapeutic effects on responses called photobiomodulation [15]. Among them, studies have been conducted focused on cytochrome c, an oxidase electron transport system located in the inner mitochondrial membrane that absorbs infrared light in the 760–940 nm region [16]. Inflammatory responses and oxidative stresses were reduced in burn wounds after 850 nm wavelength LED treatment, which promotes wound healing [17]. It has the effect of reducing pro-inflammatory cytokines in mice with colitis after 940 nm wavelength LED treatment [18]. Prior study highlighted that combining LED wavelengths is more effective than using a single wavelength alone in skin lesion [19]. Therefore, the purpose of this study was to determine whether the combination of the 850 nm, and 940 nm wavelengths are effective for OA.

METHODS

Experimental OA models

All animal experiments and surgical procedures conducted in this study were approved by the own Institutional Animal Care and Use Committee (IACUC) of Yonsei University Wonju College of Medicine with an identification code of YWC-211014-1. The procedures were carried out in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Adult male Sprague-Dawley rats (250 g) were obtained and housed under a 12 hours light/12 hours dark cycle at a constant room temperature (20°C–22°C), with free access to food and water. Male Sprague-Dawley rats were anesthetized with a mixture of 3% isoflurane, 80% nitrous oxide (N₂O), and 20% oxygen (O₂). To maintain a constant body temperature of 37°C during the surgical procedure, heating pads were used.

As shown in Fig. 1, for the induction of OA, monosodium iodoacetate (MIA, 30 mg; Sigma-Aldrich) dissolved in 50 μ L of sterile physiological saline solution was injected through the infrapatellar ligament of the right knee joint on day 0 [20]. Seven days after injection, animals that demonstrated gait disturbance during horizontal ladder walking were considered successfully lesioned and used for further experiments. The lesioned ani-

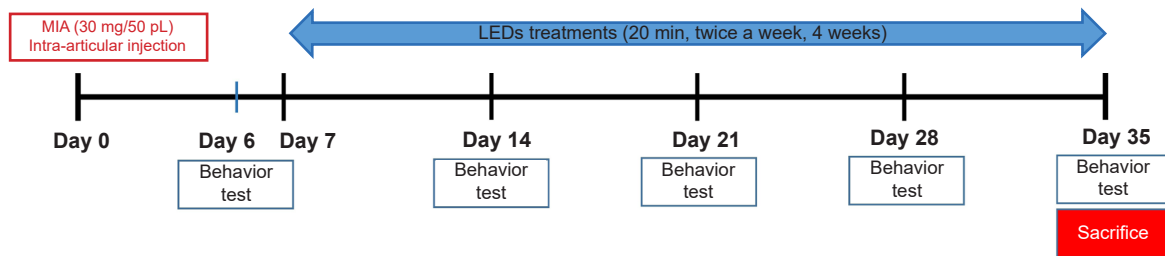


Fig. 1. Schematic overview of the experimental design. MIA, monosodium iodoacetate; LED, light-emitting diode.

mals were divided into two groups. Animals were sacrificed at four weeks after LED treatment. The internal control for this study involved using the contralateral (left) leg as a reference.

LED system and irradiation

The high-density (HD) optical probe and high-power (HP) LED system comprised a HP-LED module, a HD optical probe, and a system controller. The HP-LED module comprised two HP-LED units and two waveguide units. Light outputs were transmitted, mixed through the waveguides, and fed into two custom-made HD optical probes. Each probe, with a diameter of 1.3 mm and a length of 500 mm, consisted of 500 multi-component glass fibers, which are suitable for medical applications. The core and cladding had diameters of $\sim 45\ \mu\text{m}$ and $\sim 50\ \mu\text{m}$, respectively, and the probes were coated and encased in a jacket to protect against mechanical and environmental stresses. Various operational parameters, including the system on/off switch, light output power, irradiation time, and data record, were processed by the system controller with a micro controller unit and an HP-LED driver. The emission wavelengths were 850 ± 20 and 940 ± 20 nm in a 25 mW LED (PT-100; M.I.One). All LED ran intense pulsed light at 100 Hz (duty ratio=21%). The mean energy per unit of the optical fiber was 25 mW for both the 850 and 940 nm LED.

The rats were anesthetized and fixed in an acrylic holder, and the LED probe was attached to the right knee joint (Supplementary Fig. S1). LED stimulation was performed in a $0.5\ \text{cm}^2$ area with the following parameter settings: 20 minutes per session, twice a week for 4 weeks, and LED intensities at 6.25 mW of power for each wave length (850 and 940 nm), which is 25% of the 25 mW machine output [20-23]. The stimulation was then $12.6\ \text{mW}/\text{cm}^2$ for each wave length with 21% of duty ratio in $0.5\ \text{cm}^2$ area. The daily energy dose applied is $3.15\ \text{J}/\text{cm}^2$. The control group did not receive LED irradiation under the same conditions as the experimental group.

Behavioral tests

Functional tests were conducted on all animals at various time points: 24 hours prior to treatment and at 7, 14, 21, and 28 days following LED treatment. Prior to the onset of OA, all rats exhibited normal behavior and were capable of performing the tests. Trained and experienced observers, who were unaware of the treatment groups, administered and scored all behavioral tests. Changes in body weight were determined by subtracting the baseline weight from the weight measured after the injection of MIA. Motor function in rats with OA was evaluated using an open field test and rotarod test. The open field test involved placing the rats in an acrylic box divided into 12 squares (10×10 cm each) with black walls and a white floor. The animals were positioned in the central area of the open field arena and assessed in a quiet room environment. The test consists of placing an animal in an open field arena marked by a grid or lines, and recording the number of times the animal crosses the lines.

The number of lines crossed in line-crossing test (defined as the presence in a quadrant of at least two paws and the nose), amount of rotational movement (unidirectional circling), and amount of rearing (animal standing upright on its hind legs) were recorded for 2 minutes [24-26].

A rotarod apparatus (Panlab rotameter; DL Naturegene Life Sciences, Inc.) was used to assess motor performance. The performance of the animals was assessed by measuring the time it took for them to remain on a levitated rotating rod, which had a diameter of 3 cm. Prior to the actual testing, three acclimation trials were conducted at a constant speed of 5 rpm, each lasting for 3 minutes. To establish a baseline performance, a pretraining session on the rotarod was conducted for three consecutive days, with three trials per day. During the pretraining, the speed of the rod accelerated linearly from 4 to 100 rpm. Each trial had a maximum duration of 5 minutes, with a 3-minute rest interval between trials to prevent fatigue. During each trial, the latency to fall from the rotating rod was measured. If the animal fell, it

was promptly placed back on the rod, and this process could be repeated up to 5 times in a single session. The latency to falling was automatically recorded using photo-cells, and the cumulative latencies on the rod for each day were analyzed. If the animal completed three full revolutions while spinning on the rod, the trial was terminated. Testing was conducted on days 0, 7, 14, 21, and 28.

In vivo micro computed tomography analysis

The collected samples were fixed in 8% formaldehyde and subjected to scanning using a Skyscan 1176 in vivo micro-computed tomography (CT) scanner (Bruker Micro-CT). The scanning parameters included a voltage of 65 kV and a current of 278 μ A. A total of 360 views were obtained at 0.5° angle increments, with each view having an exposure time of 520 ms. This scanning process resulted in a resolution of 18 μ m. The raw data obtained from the tibiae were processed using NRecon software (Bruker Micro-CT) to generate two-dimensional grayscale image slices. Subsequently, a CT analyzer (CT-AN, v1.10.9.0; Bruker Micro-CT) was utilized to assess various structural parameters of the subchondral bone, such as bone volume fraction (BVF), mean polar moment of inertia (MPM), cross-sectional thickness (CST), and bone mineral density (BMD).

Histologic study

The rats underwent transcardial perfusion, in which 100 mL of 0.9% sodium chloride solution was initially infused, followed by 200 mL of 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). By carefully removing the leg muscles, the knee joint, containing parts of the femur and tibia, was removed. Tissues were fixed for 12 hours, decalcified, and embedded in paraffin. Sagittal sections with a thickness of 4 μ m were obtained using a microtome, and these sections were subsequently stained with hematoxylin-eosin-saffron and Safranin O-Fast Green.

Articular cartilage thickness

For all measurements light photo micrographic images were acquired on a Nikon Optiphot microscope (Nikon Inc.) fitted with a Nikon digital camera (DXM1200), using Nikon ACT-1 image capture software (ver. 2.2). The images were imported into Adobe Photoshop (ver. 7.0, Adobe Systems Inc.) and were adjusted for brightness and contrast to optimize photographic representation of the images obtained by the microscope. Acquired cartilage images were divided three regions, anterior, middle and posterior then articular cartilage thickness was

measured at the dividing lines between anterior/middle, and middle/posterior regions [27]. It is presented as the average of the anterior and posterior articular cartilage thickness.

Enzyme-linked immunosorbent assay (ELISA)

At the time of sacrifice, serum was collected from each rat. Serum was spun down, aliquoted, and stored at -80°C until use. The enzyme-linked immunosorbent assay (ELISA; R&D Systems) and commercial kits (MBL-Medical & Biological Laboratories) were used to measure serum levels of interleukin (IL)-6 and IL-18, respectively. A plate reader (Bio-Rad) was used to measure the readings at a wavelength of 450 nm. These readings were compared to a standard curve created using known concentrations of the recombinant mediators. The detection limits for IL-6 and IL-18 were determined to be 0.09 pg/mL and 12.5 pg/mL, respectively.

Statistical analysis

Statistical analysis was conducted using Prism (GraphPad Software) for the t-test and two-way repeated ANOVA. Post-hoc comparisons were performed using the Bonferroni method. Data are presented as the mean \pm standard error of the mean. The significance level was set at $p < 0.05$, unless stated otherwise.

RESULTS

Gross health in OA rat models

To monitor the overall health status of the rats, we measured their body weight weekly for a period of 4 weeks following the LED treatment. Anxiety and depression levels were assessed using the open field test [28]. In the experimental groups receiving LED treatment, there was an approximate 10% reduction in body weight. However, there were no statistically significant differences ($p = 0.053$) observed between the untreated OA group and the LED-treated OA group in terms of body weight (Fig. 2A).

LED therapy improved locomotor function

We assessed locomotor function and weight bearing using the rotarod test and open-field test weekly. The number of line crossings of non-treated rats decreased throughout the treatment period (1.25 ± 1.23), while that of LED-treated rats was maintained at 9.66 ± 1.51 for four weeks post-treatment, implying that LED treatment facilitated motor improvements (Fig. 2B). To evaluate hind limb weight bearing, rearing was assessed. LED-treated rats reared significantly more (6.5 ± 0.85 ,

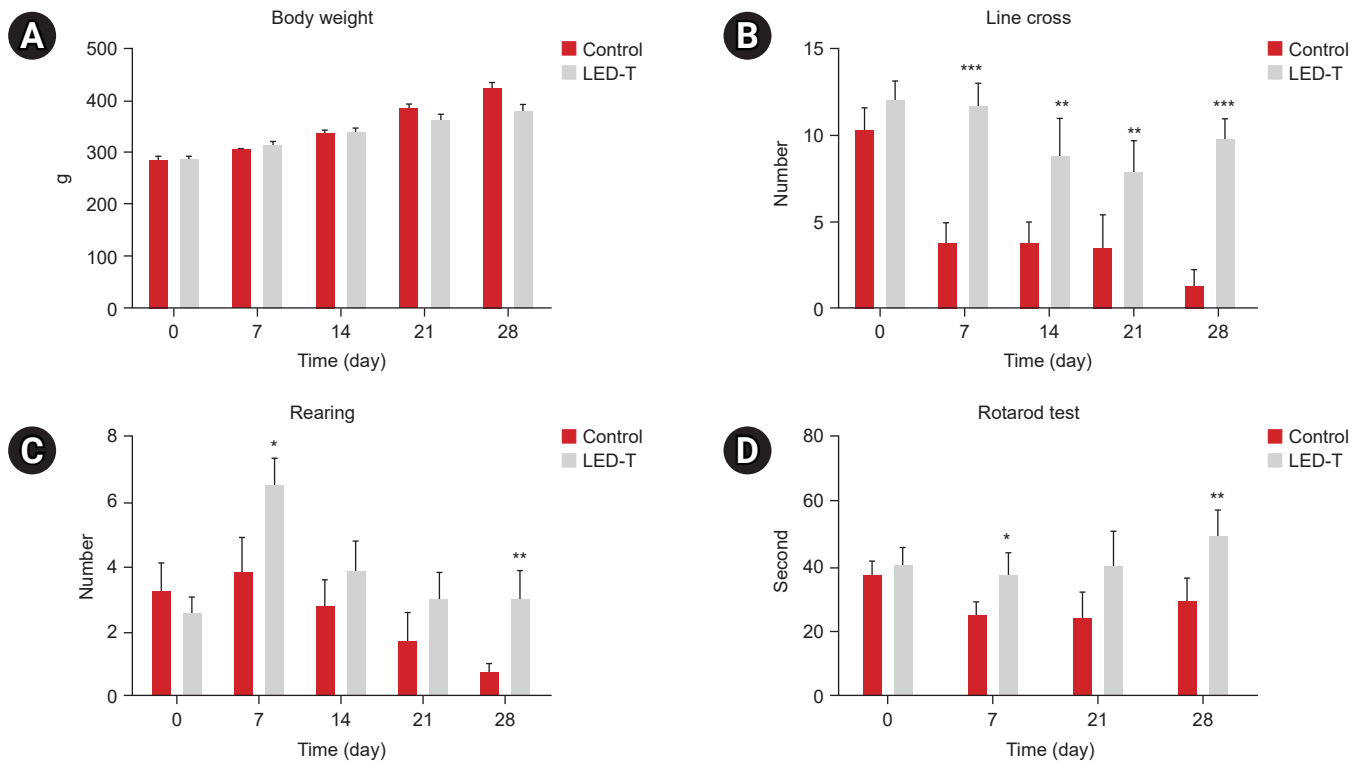


Fig. 2. Improvement of motor function after light-emitting diode (LED) light irradiation treatment in degenerative osteoarthritis model. (A) Change of body weight during LED treatment. LED treatment did not change the general condition including food uptake, depression, anxiety in monosodium iodoacetate-induced osteoarthritis rats. (B) Line cross test. (C) Rearing test. (D) Rotarod test. (B-D) LED treatment significantly increased hind limb motor function. The asterisk (*) denotes a statistically significant difference between un-treated (control) group and LED-treated (LED-T) group at the 0.05 level, ** $p < 0.005$, and *** $p < 0.0005$.

3.0 ± 0.91) than the untreated group (3.75 ± 1.18 , 0.75 ± 0.25) at 7 and 28 days (Fig. 2C). In the rotarod test, the LED-treatment group exhibited significant increases in the time until falling compared to the untreated group. Specifically, at 7 days after LED treatment, the LED-treatment group showed a time until falling of 46.50 ± 4.21 (mean \pm standard deviation), while the untreated group had a time until falling of 25.0 ± 2.65 . Similarly, at 28 days after LED treatment, the LED-treated group had a time until falling of 48.50 ± 5.95 , whereas the untreated group had a time until falling of 29.5 ± 4.82 (Fig. 2D). The LED-treated group demonstrated an improvement in locomotor function compared to the untreated group at both 7 and 28 days after treatment (Fig. 2B-D).

LED therapy attenuated cartilage degradation

To determine the protective effect of LED treatment against OA, we administered LED stimulation to rats 7 days after MIA intra-articular injection, and evaluated cartilage damage after

4 weeks of LED treatment. Safranin O-staining demonstrated proteoglycan loss after MIA injection (Fig. 3). The articular cartilage thickness of normal rat model was 123.0 ± 6.22 μm . It was 41.18 ± 3.00 μm in OA control rat model. Articular cartilage thickness was statistically significantly thicker in the LED-treated OA rat model (61.87 ± 5.66 μm , $p = 0.004$).

Micro-CT images indicated that LED therapy exerted a restorative effect on degenerated cartilage and cortical bone. In the LED-treated group, there was a significant increase in BVF and CST at both the medial and lateral sides compared to the untreated group. BVF represents the total bone volume, while CST reflects the thickness of the subchondral plate. Similarly, BMD and MPM, which represent bone strength and bone stiffness, respectively, also increased significantly in the LED treatment group (Fig. 4).

LED therapy and the IL-6 and IL-18 expression

The levels of IL-6 and IL-18, pro-inflammatory cytokines

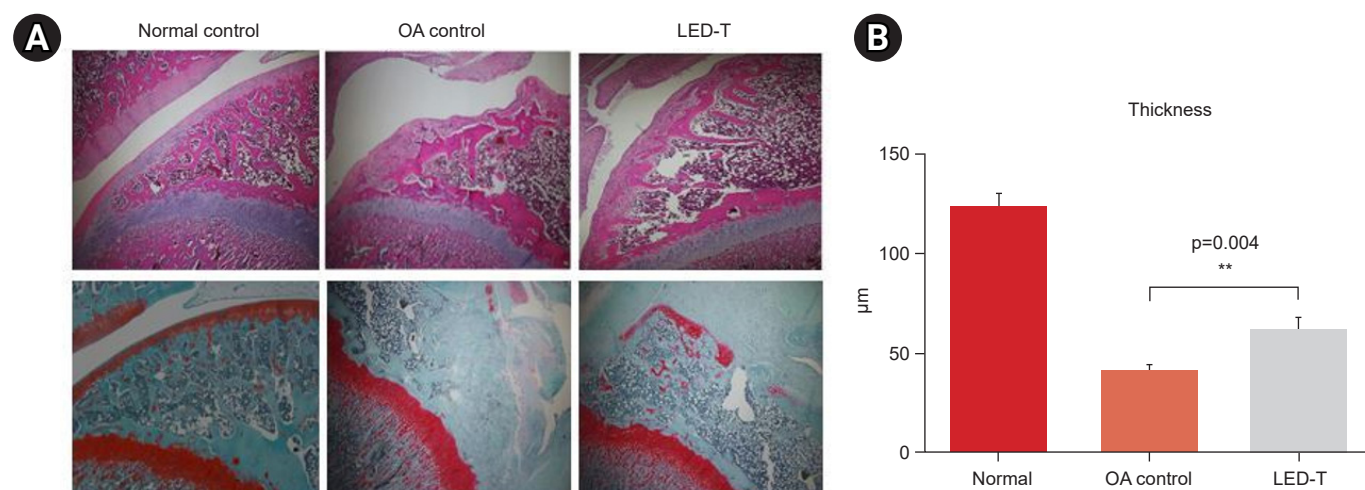


Fig. 3. Articular cartilage thickness differentiation after light-emitting diode (LED) light irradiation treatment in degenerative osteoarthritis (OA) model. (A) Changes in articular cartilage thickness illustrated by hematoxylin and eosin and Safranin O-Fast Green staining after LED light irradiation treatment. Scale bar=50 μ m. (B) Quantification of articular cartilage thickness. LED-T, LED-treated. ** $p<0.005$.

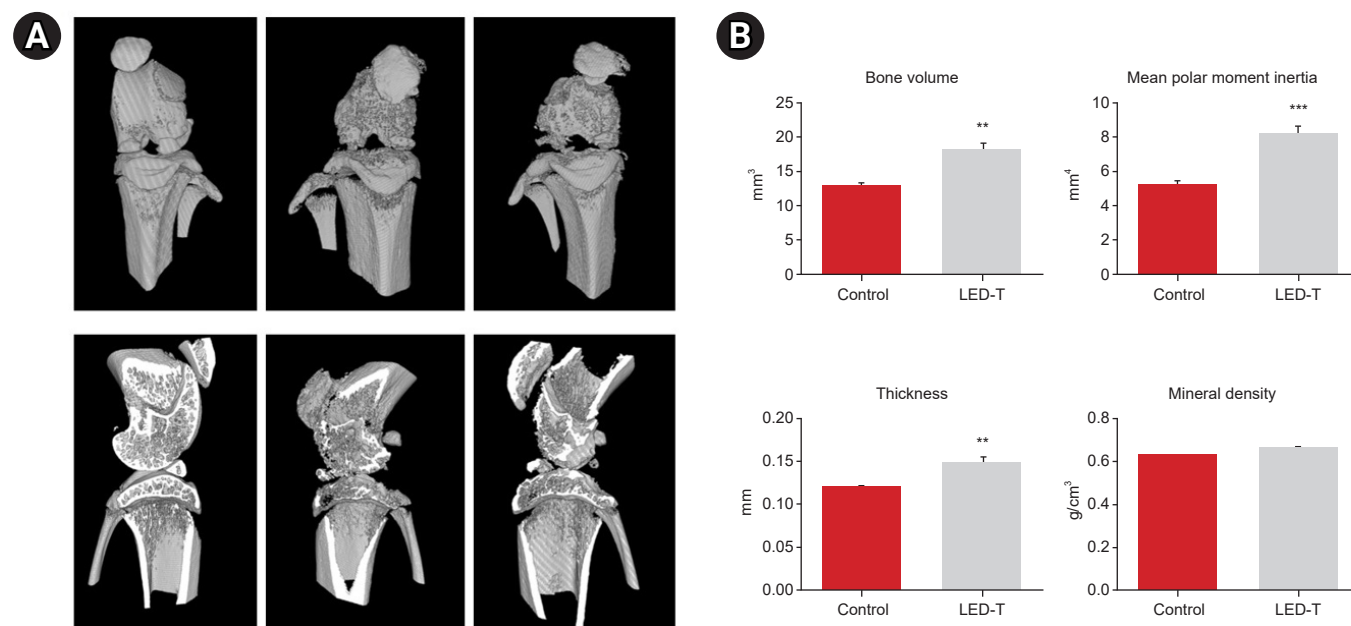


Fig. 4. Micro-computed tomography (CT) images of degenerative changes in articular cartilage following light-emitting diode (LED) light irradiation treatment. (A) Anatomical change in CT image. (B) Analyzing of bone volume, mean polar moment inertia, cross sectional thickness and mineral density. LED-T, LED-treated. ** $p<0.005$, *** $p<0.0005$.

associated with the degradation of articular cartilage, were quantified in the serum using an ELISA. The serum concentrations of IL-6 was significantly decreased in the LED-treated group (103.3 ± 12.38 pg/mL) compared to the untreated group

(259.5 ± 47.74 pg/mL) after LED treatment ($p=0.002$; Fig. 5A). The serum concentrations of IL-18 also decreased in LED treatment group (123.6 ± 13.11 pg/mL), compared to untreated group (218.8 ± 26.97 pg/mL) after LED treatment, but this was not

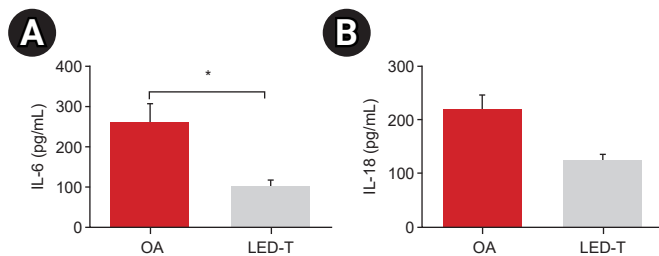


Fig. 5. Changes in interleukin (IL)-6 (A) and IL-18 (B) serum concentration after light-emitting diode (LED) light irradiation treatment. OA, osteoarthritis; LED-T, LED-treated. * $p < 0.05$.

statistically significant ($p = 0.051$; Fig. 5B). Although there was a difference in statistical significance, LED treatment tended to suppress IL-6 and IL-18, which are pro-inflammatory cytokines involved in OA [29].

DISCUSSION

The purpose of this study was to determine whether a combination of the following two wavelengths would be effective for OA: (1) 850 nm, which is the middle wavelength of the two studies (830 and 870 nm) that reported a therapeutic effect for OA, and (2) 940 nm, which is the 900 nm wavelength region that has reported stimulatory effects on osteogenesis and several other conditions such as RA, and colitis [18,20,22,30,31]. We referred to previous studies that examined the interactions between light and tissue, specifically considering the intensity and duration of exposure to light-based devices [15].

For LED-emitted photons to exert an impact on a living biological system, they need to be absorbed by a molecular chromophore or a photoacceptor. Within the mitochondria and cell membranes, there are various light-absorbing entities such as porphyrins, flavins, and other chromophores. When exposed to light of suitable wavelengths and doses, these chromophores absorb the light and initiate biological responses [15]. Increasing evidence suggests that the photobiomodulation mechanism result in the cellular reaction cascade involving the activation of mitochondrial respiratory chain components. Different wavelengths of light are absorbed by different chromophores and have different effects on tissues [15]. The wavelength with high therapeutic effect is different for each disease [32,33]. In addition, the possibility of resulting a synergistic effect by combining wavelengths of different lengths was also reported [22,34].

In this study, the LEDs treated OA rat models exhibited in functional: line crossing, rearing, and rotarod tests (Fig. 2),

histological: cartilage thickness (Fig. 3), and anatomical: BVE, MPM, and CST (Fig. 4) improvements without visible side effects. The LED-treated group demonstrated higher values than the control group for three parameters, in addition, IL-6 and IL-18 serum concentrations significantly decreased (Fig. 5). In the safety evaluation, there were no abnormal findings, such as skin redness, burns, and edema.

Several similar studies evaluated whether LED irradiation could be effective as a non-invasive therapeutic strategy for the treatment of OA. In a particular study, OA was induced in the 24 rats by administering an intra-articular injection of 3 mg of MIA through the patellar ligament of the right knee. To assess the effect of LED irradiation, indomethacin was administered orally, 7 days after MIA injection. Radiographic examination did not reveal any differences between the indomethacin and LED treatment group [35]. In the histological analysis, however, the use of LED irradiation demonstrated a protective effect against cartilage damage and subchondral bone destruction. It also significantly reduced the infiltration of mononuclear inflammatory cells and the formation of pannus. In this study, authors used an LED wavelength of 840 nm, whereas we used a mixed wavelength of 850 and 940 nm. Both studies showed that LED irradiation may be an effective treatment for OA. However, only radiographic and histological analyses were analyzed in 840 nm wavelength study, whereas functional, anatomical, and histological studies were analyzed in this study.

Given the evidence indicating the diverse cellular effects of photobiomodulation, notably its anti-inflammatory properties, the combination of LED therapy with antioxidant treatment emerges as a novel approach for the prevention and treatment of early-stage OA. Wavelength of 635 nm was used to irradiate hydrogen peroxide induced OA like chondrocytes. Pre-treatment with 635 nm of LED light for 2 hours significantly reduced free radical formation (from 100% to 8.25%) and the expression of the inflammatory genes IL-1b and TNF- α in OA-like cells, while the expression of the matrix gene COL-2 was enhanced. Furthermore, a combination of preventative LED treatment with antioxidant treatment exerted synergistic anti-inflammatory effects and a reduction in MMP-13 expression [21]. Another study reported similar results with no significant differences in mRNA expression in cartilage, but there were increased type II collagen expression, and decreased TNF- α expression [20]. According to these study, preventive LED irradiation combined with antioxidant therapy is a novel therapeutic strategy for treating early-stage OA.

OA progression leads to articular cartilage degeneration which is characterized by decreased bone volume, bone density, bone stiffness, and thickness of subchondral bone [36-38]. To observe the morphological changes in subchondral bone, we obtained the parameters such as BVE, MPM, CST, and BMD derived from micro-CT analysis. All relevant parameters were significantly increased in the LED-treatment group. These results show that LED treatment restores the microstructure of subchondral bone and alleviates abnormal bone remodeling caused by osteoarthritis.

Our study had three main limitations. First, the number of rats used in this experiment was not sufficiently large. Second, this study only evaluated short-term therapeutic effects, and long-term therapeutic effects should be assessed in the future. Also, we could not evaluate the score of OA parameters, including articular cartilage destruction (OARSI grading system), because of the severe degradation of articular cartilage. Because different wavelengths can show different effects, it is important to precisely define the disease and condition. In pressure ulcer, 658 nm is more effective than 808 and 940 nm [33], whereas in oral ulcer, 810 nm is more effective than 940 nm [32]. In addition, although each of the wavelengths of 810 and 940 nm did not have a beneficial effect, it is necessary to confirm whether a combination of them has no effects [33]. One of the essential parts is to determine whether they are safe when applied to the human body, even though wavelengths and parameters are discovered that have therapeutic effects.

It is necessary to find the effect of the combination between LED wavelengths as well as between LED wavelengths and non-pharmacologic modality therapy, or between LED wavelengths and invasive procedure [39,40]. Furthermore, more studies should be conducted to verify the efficacy of these treatments in the parameter settings of the device and characteristics of the altered stem cell and cartilage [39,40]. Determining optimal treatment parameters and safety margins is also necessary, as cellular activity depends on wavelength, power density, and irradiation time.

In conclusion, combination of 850 and 940 nm wavelengths LED therapy produced functional, anatomical, and histological improvements without side effects in a rat model of OA.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Choi WW, Kim SH, Lee JY, Yong SY. Methodology: Choi WW, Kim JH, Yong SY. Formal analysis: Kim HS, Lee H. Funding acquisition: Kim SH, Kim JH, Yong SY. Project administration: Choi WW, Yong SY. Visualization: Kim HS, Lee H, Lee JY. Writing – original draft: Choi WW, Kim K, Kim SJ, Kim M, Yong SY. Writing – review and editing: Choi WW, Kim SH, Yong SY. Approval of final whole manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.5535/arm.23138>.

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Changes in Lower Extremity Muscle Quantity and Quality in Patients with Subacute Stroke

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Objective: To analyze the changes in muscle mass and quality with time on the paretic and non-paretic sides in subacute stroke patients and identify correlations between the variation of muscle mass and quality and lower limb functions.

Methods: Thirty hemiplegia patients diagnosed with stroke participated in this study. To evaluate poststroke muscle changes, longitudinal measurement of muscle mass and quality was conducted with bilateral lower limbs. The elastic shear modulus was measured using shear wave elastography and muscle thickness (MT) of rectus femoris, vastus intermedius, vastus lateralis (VL), vastus medialis, tibialis anterior, and gastrocnemius (GCM) muscles. Functional evaluation was performed using Berg Balance Scale (BBS), Five Times Sit to Stand Test (FTSST). Follow-up was performed at discharge. The muscle mass and quality were compared according to time. We analyzed whether muscle quantity and quality were related to function.

Results: MT demonstrated no significant change with time. The elastic shear modulus increased significantly in the paretic VL and GCM muscles and did not change significantly in the muscles on the non-paretic side. Correlation analysis detected that elastic shear modulus in the VL has a cross-sectional negative relationship between BBS and positive relationship between FTSST. There were significant correlation between variation of FTSST and the variation of the elastic shear modulus in VL.

Conclusion: Only paretic VL and GCM muscle quality changed in subacute stroke patients and muscle's property related to lower limb functions. Therefore, the lower extremity requires an approach to muscle quality rather than quantity for subacute stroke patients.

Keywords: Stroke, Muscles, Elasticity imaging techniques, Skeletal muscle, Sarcopenia

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INTRODUCTION

Stroke is a leading cause of disability in adults, and many survivors manifest difficulties in performing the activities of daily living independently [1]. The prevalence of sarcopenia is exten-

sively higher in stroke patients [2,3] and such reduction in muscle mass tends to be more prominent on the paretic than that on the non-paretic side. The causes of this involve multidimensional factors including disuse atrophy due to physical inactivity or altered central neural innervation [4].

In cross-sectional studies on chronic stroke patients, the lean mass of the paretic limb showed a significant reduction. In a computed tomography study, the mid-thigh muscle area showed a 20% reduction [5]. Few studies were conducted to assess the functional alteration in muscle tissues by analyzing the structural changes in muscles in addition to a quantitative analysis of muscle atrophy. In chronic stroke patients, the echo intensity (EI) of ultrasound imaging in lower extremity muscles was higher compared to that in healthy controls [6,7]. In several longitudinal studies on chronic stroke patients, the muscle EI in poststroke patients was shown to increase [8,9]. As the value of EI in skeletal muscle increase, it reflects that the fibrosis and fatty infiltration has progressed. Stroke patients with muscle loss displayed lower levels of function [10] and daily living independence [11] at discharge, which highlighted the need to aim for a better functional outcome through suitable rehabilitation and dietary changes based on an early evaluation of the muscle quantity and quality in stroke patients. Nonetheless, previous studies of muscle loss after stroke was cross-sectional surveys or chronic patient groups. And several studies have focused on the relationships between changes in upper limb muscle quality and functions. But few studies have identified a direct association between lower extremity muscle changes and lower extremity function. Thus, this study aimed to analyze the longitudinal changes in muscle mass and quality on the paretic and non-paretic sides in subacute stroke patients and to identify correlations between muscle mass and quality and lower limb functions.

METHODS

This observational longitudinal study recruited participants who diagnosed with ischemic or hemorrhagic subacute stroke who underwent rehabilitation treatment through admission between September 2022 and March 2023. Measurement of muscle mass, quality and functional evaluation were conducted with bilateral lower limbs at baseline. And follow-up data were collected at discharge. During admission, all patients underwent conventional rehabilitation therapy (twice a day, 30 minutes per session) for six sessions a week.

The inclusion criteria were (1) patients with the first episode of ischemic or hemorrhagic stroke; (2) patients of ≥ 18 years of age; (3) patients with unilateral stroke; (4) patients within six months of stroke; and (5) patients with premorbid independent gait. The exclusion criteria were (1) patients with a limitation

in premorbid gait and balance; (2) patients with a comorbidity that could affect the variables (such as nerve root disease, renal disorder, orthopedic problem, and uncontrolled psychiatric illness); (3) patients with a limitation in the body composition analysis due to a pacemaker or a metal implant in the trunk or limb; (4) patients with cognitive decline and consequent inability to follow simple instructions; and (5) patients with severe visual or auditory impairment. For baseline characteristics, the data on age, sex, body mass index, type of stroke, duration since stroke, comorbidity, serum protein, and albumin level were collected and the nutritional state was divided into oral intake and tube feeding. For the muscle quality and quantity as well as functional evaluation, measurements were recorded at baseline and discharge for comparison. All patients were given explanations of the study flow and submitted a written informed consent before participation. This study was approved by the Institutional Review Board at Samsung Changwon Hospital (IRB No. SCMC 2022-07-003).

Measurement of lower limb muscle mass

Ultrasound images were obtained via B-mode ultrasound imaging (Samsung Medison V8; Samsung Healthcare) with a multi-frequency linear transducer (8–12 MHz). In all measurements, the following settings were applied: a frequency of 45 Hz, gain of 61 dB, and depth of 4.5 cm. The images were obtained for the rectus femoris, vastus intermedius (VI), vastus lateralis (VL), vastus medialis (VM), tibialis anterior (TA), and gastrocnemius (GCM) muscles on the paretic and non-paretic sides. Table 1 shows the ultrasound examination protocols for patient posture and site for each muscle [9,12]. In all measurements, a gel was used to avoid excessive pressure on the skin surface. To assess lower limb muscle mass, electronic calipers were used to measure muscle thickness (MT) at each position. The thigh circumference (TC), calf circumference (CC), and body composition were measured on both paretic and non-paretic sides. For the TC, the records were taken from the midway between the lateral condyle of the femur and the greater trochanter [13]. For the CC, the maximal value upon vertical wrapping of the leg axis with a flexible tape was measured as the patient had the foot and ankle relaxed and the knee at 90° flexion in a supine position [2,14]. For the body composition, a non-invasive multifrequency bioimpedance device (InBody S10; InBody) was used. Four electrodes were each placed at the upper and lower limbs, and measurements were recorded using an identical protocol. The recorded data were fat mass, fat mass index, fat-

Table 1. Measurement positions and sites for the trunk and lower limb muscles

Muscles	Positions	Measurement sites
Rectus femoris	Supine	Midway between the anterior superior iliac supine and the proximal end of the patella
Vastus intermedius	Supine	Midway between the anterior superior iliac supine and the proximal end of the patella
Vastus medialis	Supine	12.5% thigh circumference medially from 20% distal point between the anterior superior iliac supine and the proximal end of the patella
Vastus lateralis	Supine	10% thigh circumference laterally from midway between the anterior superior iliac supine and the proximal end of the patella
Tibialis anterior	Supine	30% proximal between the lateral malleolus of the fibula and lateral condyle of the tibia
Gastrocnemius	Sitting	Lateral head of gastrocnemius at 30% proximal between the lateral malleolus of the fibula and lateral condyle of the tibia
Soleus	Sitting	30% proximal between the lateral malleolus of the fibula and lateral condyle of the tibia

free mass, fat-free mass index, skeletal muscle mass, percentage body fat, and appendicular skeletal muscle mass/height².

Measurement of lower limb muscle quality

As measure lower limb muscle quality, we used shear wave elastography that is a qualitative method to record real-time measurements of the viscoelastic property in soft tissues. The elastic shear modulus (kPa) and shear wave velocity (SWV) are higher in stiffer tissues [15,16]. In this study, we obtained elastic shear modulus (kPa) to evaluate quality of muscles. The probe was positioned longitudinally with respect to the fascicle direction of muscle [17,18], while the measurements were recorded in the circular region of interest (ROI) of 1 mm radius in the muscle (Fig. 1). The mean of eight ROI measurements was estimated for subsequent analysis [19].

Measurement of lower limb function

The Berg Balance Scale (BBS) was used in functional evaluation. As a scale of an objective assessment of balance ability, the BBS consists of 14 items regarding balance movements on a 5-point (0–4) scale [20]. In certain patients whose gait disability was not severe, the Five Times Sit to Stand Test (FTSST) and the 10-Meter walk test (10MWT) were performed and the mean of triplicate measurements were recorded for each test. For the 10MWT, the patient walked 14 m and the time taken to walk middle 10 m excluding the 2 m at the start and the 2 m at the end was measured. All evaluations were performed twice at baseline and follow-up.

Statistical analysis

To analyze the longitudinal changes in MT, elastic shear modulus, and body composition variables, Wilcoxon signed-rank test was used. To identify the correlations across the changes of MT,

elastic shear modulus, and lower limb functions, Spearman's correlation was used. To verify the effects of demographics and clinical data on the significantly changed MT and elastic shear modulus, linear regression analysis was performed. The Stata 14.0 (Stata Corp.) program was used in all analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 36 patients satisfied the inclusion criteria, six of whom were excluded from the follow-up due to other medical problems or early discharge, leaving 30 participants. The data of 30 patients were analyzed (male/female, 14/16; age, 72 [62–80] years). The quantitative variables of demographics were expressed as mean (IQR) (Table 2). The duration from stroke onset to examination was 9.00 (6.00–12.00) days and the follow-up interval was 30 (21–47) days. The MT demonstrated no significant change according to time in all target muscles (Table 3). The elastic shear modulus (kPa) increased significantly in the paretic VL and GCM muscles ($p<0.001$, $p=0.03$, respectively) whereas it did not change significantly in the muscles on the non-paretic side (Table 4).

The lower extremity circumference measurements did not show significant changes, and in the comparison of functional outcome between baseline and follow-up, the BBS, FTSST, and 10MWT showed significant improvements ($p<0.001$, $p=0.005$, and $p=0.01$, respectively). The body composition measurements including the fat mass, skeletal muscle mass, percentage body fat, and appendicular skeletal muscle mass/height² showed no difference between baseline and follow-up (Table 5).

Correlation analysis detected a significant negative correlation between BBS and the elastic shear modulus in the VL at the baseline and follow-up ($p=0.008$ for baseline and $p=0.007$

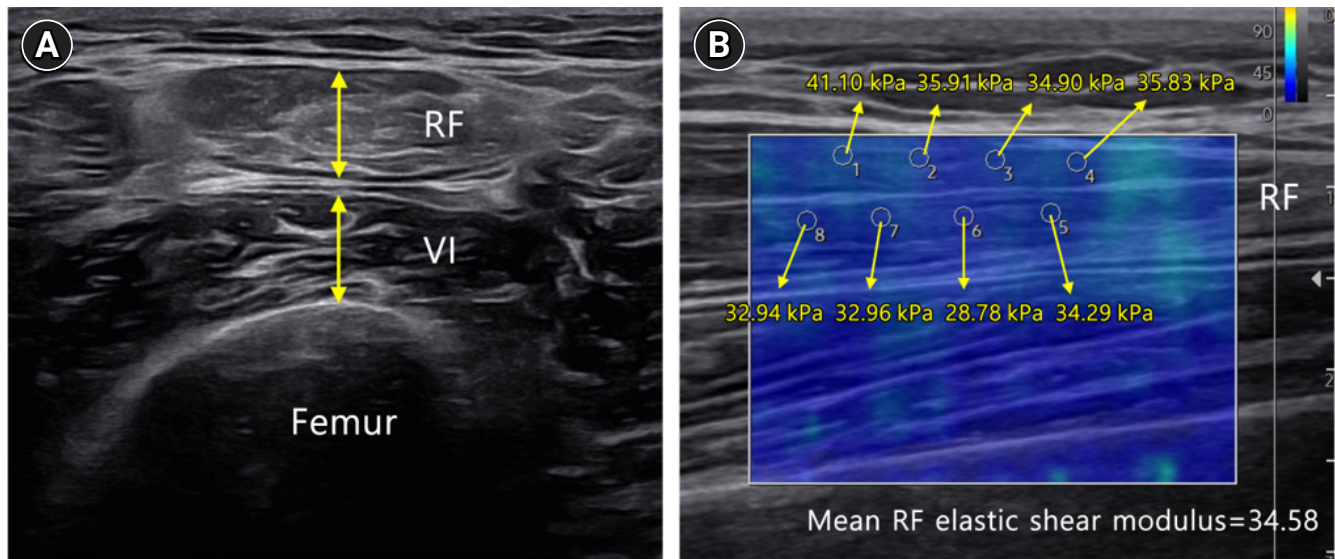


Fig. 1. Measurement of thickness of rectus femoris (RF) and vastus intermedius (VI) muscle (A) and elastic shear modulus (B). The circles represent the region of interest (ROI) from which elastic shear modulus (kPa) was measured. The average of eight ROIs was used for analysis.

Table 2. Demographic and characteristics of patients

Variable	Value (n=30)
Age (yr)	72 (62–80)
Sex (male/female)	14/16
Diagnosis (infarction/hemorrhage)	22/8
Time since stroke (day)	9.00 (6.00–12.00)
Time between baseline and follow-up	30 (21–47)
Serum protein (g/dL)	6.48 (5.95–7.10)
Serum albumin (g/dL)	3.92 (4.27–3.70)
Oral/tube feeding	23/7

Values are presented as mean (IQR) or number only.

for follow-up). A significant positive correlation was found for the FTSST and the elastic shear modulus in the VL ($p=0.002$ for baseline and $p=0.041$ for follow-up). The elastic shear modulus of TA and GCM showed a significant correlation with FTSST only at the follow-up ($p=0.031$ and 0.009 , respectively), not at the baseline (Fig. 2).

An analysis of longitudinal changes in muscles with significant changes between baseline and follow-up was also conducted. There was significant correlation between variation of FTSST and the variation of the elastic shear modulus in VL ($p<0.001$). However, difference of BBS was not significantly correlated with the difference of elastic shear modulus in VL (Fig. 3). Variations in VL and GCM muscle quality according to demographic data did not exhibit a significant correlation.

DISCUSSION

The main findings of this study are that, while the muscle quantity did not significantly change at the time of subacute stroke, the muscle quality showed changes in the paretic VL and GCM muscles. As the elastic shear modulus of VL was high, the lower limb function was low in cross-sectional comparison. In addition, the more elastic shear modulus of the VL changed, the less the improvement in lower extremity function evaluated by the FTSST.

Previous studies have shown that the SWV of the paretic biceps brachii was higher compared to that of the non-paretic side in stroke survivors [17,19,21,22]. The SWV of the GCM muscle was also shown to be higher on the paretic side compared to that on the non-paretic side [15,23]. However, these studies were cross-sectional studies on patients in the chronic stroke stage. In one study conducted for post-acute stage (poststroke duration 8.4 ± 7.6 weeks), SWV of the biceps brachii muscle was higher on the paretic side than that on the non-paretic side [24]. To the best of our knowledge, no study has analyzed the longitudinal muscle quality changes of lower extremity muscles in subacute stroke patients. Thus, this study has revealed that the elastic shear modulus of the paretic VL and GCM muscles increased according to time during the subacute stage in stroke patients.

Table 3. Changes in muscle thickness at baseline and follow-up (n=30)

	Paretic side (cm)			Non-paretic side (cm)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
RF	0.53 (0.40–0.70)	0.52 (0.41–0.76)	0.95	0.59 (0.52–0.75)	0.59 (0.45–0.70)	0.91
VI	0.61 (0.46–0.80)	0.59 (0.47–0.94)	0.36	0.75 (0.61–0.93)	0.68 (0.52–0.95)	0.17
VL	1.22 (0.97–1.54)	1.25 (0.94–1.57)	0.64	1.36 (1.15–1.51)	1.33 (1.13–1.33)	0.83
VM	1.48 (1.25–1.82)	1.44 (1.25–1.78)	0.38	1.51 (1.20–1.68)	1.54 (1.42–1.93)	0.20
TA	2.35 (2.10–2.61)	2.32 (2.10–2.73)	0.05	2.29 (2.16–2.57)	2.42 (2.15–2.63)	0.27
GCM	1.17 (1.08–1.30)	1.07 (0.94–1.35)	0.27	1.12 (1.03–1.32)	1.13 (1.00–1.40)	0.89

Values are presented as mean (IQR).

RF, rectus femoris; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis; TA, tibialis anterior; GCM, gastrocnemius.

Table 4. Changes in elastic shear modulus at baseline and follow-up (n=30)

	Paretic side (kPa)			Non-paretic side (kPa)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
RF	38.66 (28.21–55.27)	43.58 (33.77–58.26)	0.55	41.39 (29.29–55.90)	49.42 (35.38–61.85)	0.41
VI	46.86 (37.19–67.57)	48.03 (32.08–67.15)	0.29	54.89 (40.32–82.59)	57.87 (44.11–74.43)	0.61
VL	20.82 (13.69–32.07)	29.54 (17.11–51.28)	<0.001***	20.26 (13.00–44.10)	18.33 (14.07–37.54)	0.68
VM	16.47 (10.84–22.66)	17.99 (11.17–32.16)	0.89	18.69 (10.78–29.61)	14.06 (10.83–23.73)	0.18
TA	35.11 (26.02–54.85)	44.89 (29.43–55.11)	0.44	41.54 (35.68–51.19)	40.92 (33.70–48.00)	0.76
GCM	19.22 (17.38–25.92)	22.50 (17.05–37.94)	0.03*	23.39 (17.45–33.22)	20.87 (14.85–29.34)	0.50

Values are presented as mean (IQR).

RF, rectus femoris; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis; TA, tibialis anterior; GCM, gastrocnemius.

*p<0.05 and ***p<0.001, Wilcoxon signed-rank test.

Table 5. Functional evaluation and circumferences at baseline and follow-up

	Baseline	Follow-up	p-value
Thigh circumference (cm) (n=30)	37.25 (34.00–39.00)	37.00 (34.00–39.00)	0.24
Calf circumference (cm) (n=30)	30.25 (29.00–34.00)	31.00 (29.00–32.00)	0.86
BBS (point) (n=30)	24.50 (5.00–37.00)	45.00 (24.00–49.00)	<0.001***
FTSST (s) (n=13)	11.32 (9.35–16.00)	10.36 (8.19–13.62)	0.005**
10MWT (s) (n=13)	8.10 (5.80–10.58)	6.38 (5.15–8.10)	0.01*
Fat mass (kg) (n=30)	13.05 (6.20–16.40)	13.10 (7.80–17.30)	0.77
Fat mass index (kg/m ²) (n=30)	5.43 (2.33–6.85)	5.00 (2.83–7.53)	>0.99
Fat-free mass (kg) (n=30)	45.60 (36.60–55.90)	46.50 (36.70–54.30)	0.56
Fat-free mass index (kg/m ²) (n=30)	18.15 (16.07–19.90)	18.36 (16.13–18.80)	0.71
Skeletal muscle mass (kg) (n=30)	24.85 (19.40–31.30)	24.80 (19.50–31.30)	0.77
Percentage body fat (%) (n=30)	19.00 (10.40–27.10)	21.20 (13.20–29.70)	0.53
ASM/height ² (n=30)	8.20 (6.90–9.57)	7.77 (6.76–8.60)	0.21

Values are presented as mean (IQR).

BBS, Berg Balance Scale; FTSST, Five Times Sit to Stand Test; 10MWT, 10-Meter Walk Test; ASM, appendicular skeletal muscle mass.

*p<0.05, **p<0.01, and ***p<0.001, Wilcoxon signed-rank test.

Changes in muscle material properties are identified secondary to neurological injury like stroke [25]. According to muscle biopsy studies, stiff muscles are associated with the increase in the collagen and proteins that constitute the extracellular matrix [26]. Attempts have been made to quantify the alterations of the structure and mechanical properties of skeletal muscles using ultrasound. Various other studies reported an increase in

SWV on the paretic upper limb muscle due to muscle stiffness in stroke patients [17,21,24]. The present study also found an increase in elastic shear modulus in the subacute stage. These changes in muscle quality are predicted to be influenced by the subacute onset muscle stiffness through changes in muscle properties.

The results of this study indicated significant interval changes

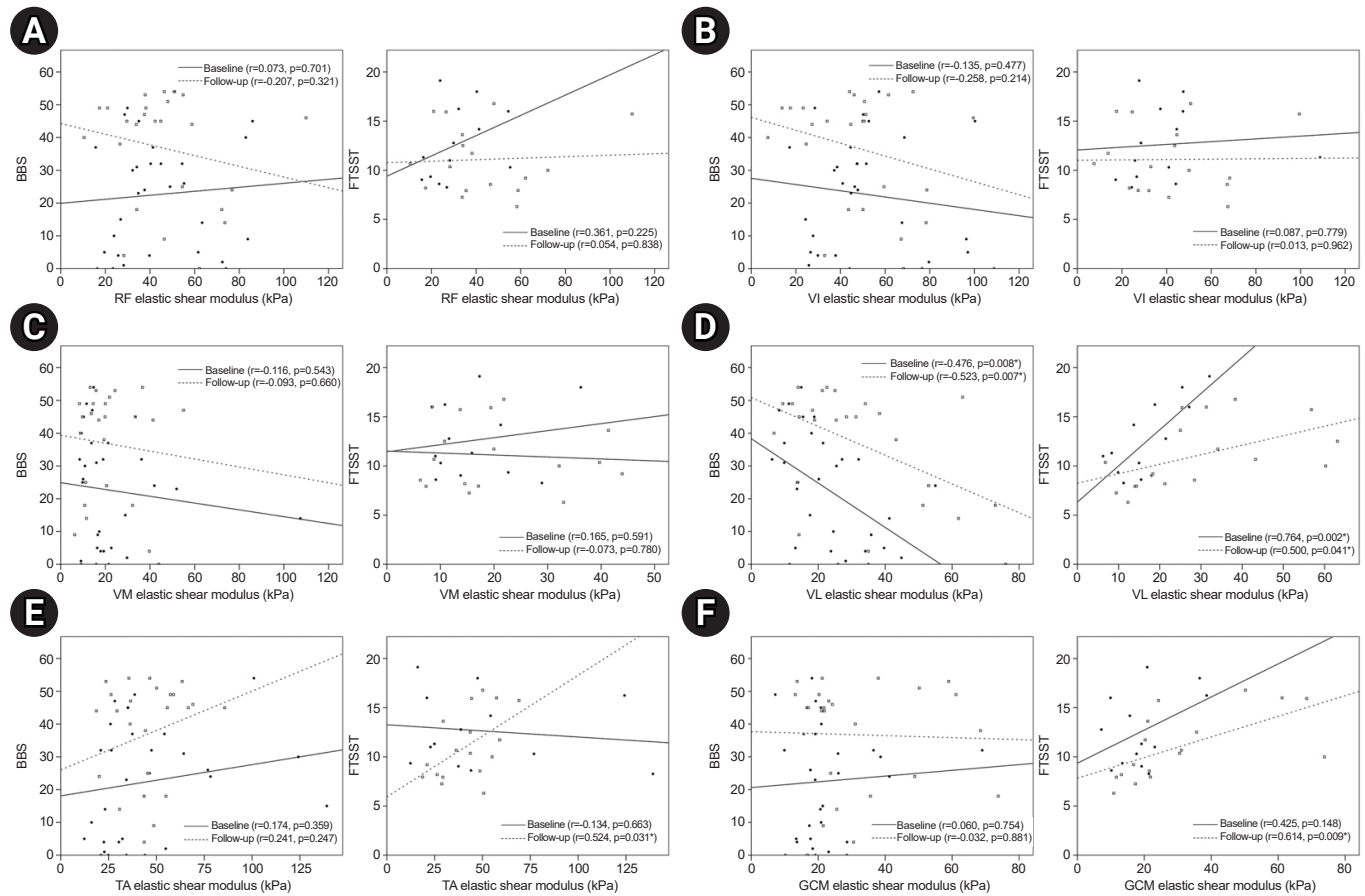


Fig. 2. Cross-sectional correlation between lower limb functions and elastic shear modulus (kPa) of each muscle: rectus femoris (RF) (A), vastus intermedius (VI) (B), vastus medialis (VM) (C), vastus lateralis (VL) (D), tibialis anterior (TA) (E), and gastrocnemius (GCM) (F). BBS, Berg Balance Scale; FTSST, Five Times Sit to Stand Test. * $p<0.05$.

only in the VL and GCM on the paretic side among various lower extremity muscles. In a previous study, the GCM showed a greater difference in SWV between the paretic and non-paretic sides compared to the TA [15]. In another study comparing stroke patients with healthy individuals, the SWV increased in the GCM and soleus muscles [27]. This is presumed to be because the physical adaptation of muscles against neurologic impairment is specific for variable factors as architectural change, anatomical attachment, and fiber type distribution in each muscle [15]. In this study, a similar significant change was found for the elastic shear modulus of GCM, which coincided with that in previous studies. EI is an assessment of muscle quality by quantifying the intramuscular fat and fibrous tissues in the muscles using ultrasound. Meanwhile, in previous study, the EI increased in the paretic VL among the lower extremity muscles at 2-year follow-up of stroke survivors [8]. In a study compar-

ing stroke patients with healthy controls, the EI was higher in the paretic VI, VL, VM, and TA [6]. These findings implied the changes in muscle properties of the quadriceps, which agreed with the increase in elastic shear modulus in VL in this study.

In a study of patients with acute and subacute stroke, it was reported that there was no change in muscle mass measured by two whole-body dual-energy X-ray absorptiometry 6 months after stroke onset [28]. Also, there was no significant change in lean mass in the longitudinal study 1 year after stroke [29]. In a study on chronic stroke patients (1.31 years on average), the lean tissue mass was shown to be significantly lower on the paretic side [30]. In two follow-up studies on chronic stroke patients, the quadriceps muscles showed an increase in EI and a decrease in MT [8,9]. In this study, there were no significant changes in the body composition, thigh and CCs, and MT on the paretic side according to time. Meanwhile, this study

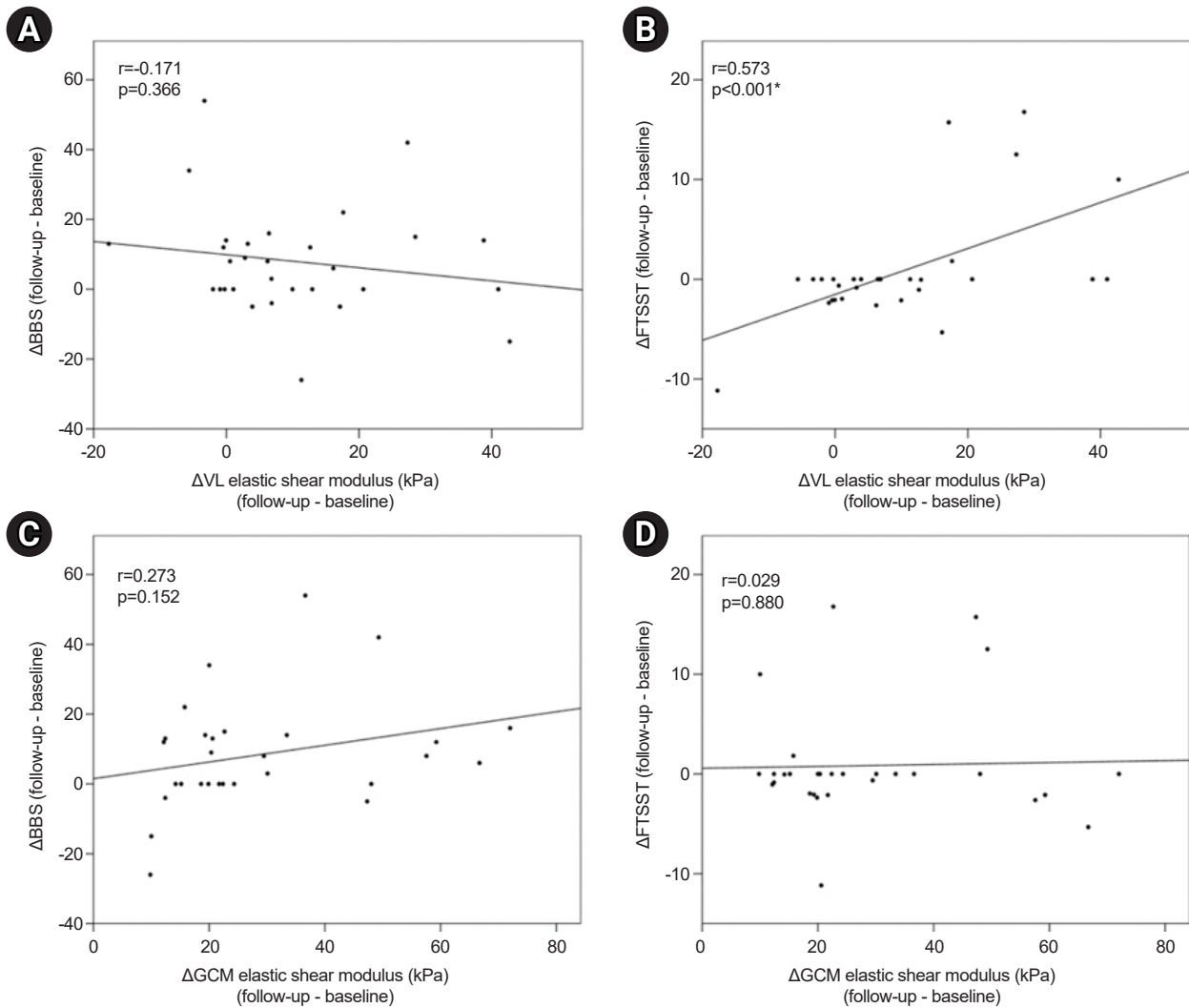


Fig. 3. Relationships between changes in lower limb function and changes in muscle elastic shear modulus. (A, B) vastus lateralis (VL). (C, D) gastrocnemius (GCM). BBS, Berg Balance Scale; FTSST, Five Times Sit to Stand Test. * $p < 0.05$.

showed a significant increase in elastic shear modulus. Thus, for subacute stroke patients, analysis of quality rather than muscle mass is more meaningful approach.

In a study analyzing the correlations between muscle properties and functions in patients, the upper limb functions decreased as the difference in the SWV of the biceps brachii between the paretic and non-paretic sides increased [17]. The upper limb functions assessed by the stroke rehabilitation assessment of movement decreased as the SWV of biceps brachii on the paretic side increased [24]. However, the relationship between lower limb functions and muscle quality remains unclear. The results of this study indicated a significant negative

correlation between lower limb functions and the elastic shear modulus of the paretic VL in a cross-sectional analysis. And there was significant correlation between variation of FTSST and the variation of the elastic shear modulus in VL. An analysis between BBS and elastic shear modulus of VL showed cross-sectional correlation at baseline and follow-up, but the longitudinal change was not significant. It is presumed that various factors such as a small number of participants or a short follow-up period could have limited the results. Nevertheless, these cross-sectional and limited longitudinal correlation suggest that the lower limb functions were reduced as the muscle quality on the paretic VL decreased.

There are several limitations to this study. First, the number of participants was small. The FTSST and 10MWT in functional evaluation could only be tested on a small set of patients (n=13). In the future, the correlations should be analyzed for a larger number of participants. Second, all patients during admission received a conventional rehabilitation treatment (twice a day and 30 minutes per session) so that the natural course of the muscle quality in patients without rehabilitation treatment could not be examined. Third, although the rater was blinded to the site on the paretic side of the patient and diagnosis during measurements, the blinding was not complete as assumptions could be made based on appearance and gait.

In conclusion, the mechanical changes of lower extremity muscles in subacute stroke patients that cannot be evaluated independently by clinical assessments were longitudinally assessed non-invasively. In the subacute stage, the VL and GCM muscle quality on the paretic side exhibited interval changes with a directionality towards increased stiffness. In addition, the stiffness of the paretic VL showed a correlation with lower limb functions within a limited range. To conclude, the lower extremity in subacute stroke patients requires an approach to muscle quality rather than quantity.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

None.

AUTHOR CONTRIBUTION

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A Pulmonary Telerehabilitation Program Improves Exercise Capacity and Quality of Life in Young Females Post-COVID-19 Patients

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Objective: To examine the impact of telerehabilitation training on exercise capacity, lung function, and health-related quality of life (HRQOL) in comparison to no rehabilitation for post-COVID-19 symptoms in adult females.

Methods: A randomized controlled trial of 48 females after mild to moderate COVID-19 survival were equally and randomly assigned to one of two groups: intervention group or control group. Three sessions per week for 6 weeks of a telerehabilitation program provided via a smartphone to the intervention group. Spirometry was used to quantify lung function, a 6-minute walk test (6MWT) measured in meters to measure exercise capacity, and the Short Form Health Survey-36 was used to assess HRQOL.

Results: After treatment, there was no statistically significant difference in forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV₁) between groups ($p>0.05$), but the 6MWT of the intervention group increased significantly more than that of the control group ($p=0.001$). The percent of change in 6MWT for the intervention group and control group was 14.22% and 4.21%, respectively. After therapy, the intervention group's HRQOL significantly improved when compared to the control group's ($p=0.001$).

Conclusion: This study showed that a telerehabilitation programs improved exercise capacity and HRQOL in young females post-COVID-19 compared to no rehabilitation.

Keywords: COVID-19, Telerehabilitation, Pulmonary rehabilitation, Exercise capacity, Quality of life

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INTRODUCTION

In addition to the acute morbidity and mortality of coronavirus disease 2019 (COVID-19) infection, survivors of COVID-19 have also experienced post-acute health complications and re-

percussions. A review found that more than 50 adverse effects were observed, and that up to 80% of COVID-19 patients continue to experience health issues following an acute infection. Several post-acute symptoms still have unclear pathophysiologies. Thought to be a major mediator in the multifactorial devel-

opment of the long-term consequences, ongoing inflammation is still seen as a problem [1].

The term “post-acute sequelae” COVID-19 refers to a broad variety of health issues that follow an acute infection [1-3]. Individuals who have COVID-19 post-acute sequelae experience new, reoccurring, and persistent symptoms four weeks or longer well after the infection [2]. Several guidelines describe the time point for the post-acute stage as ranging between approximately four weeks and three months following the infection [4,5]. The term “long COVID syndrome” generally refers to signs and symptoms that persist or worsen after an initial COVID-19 infection and may take months to resolve completely [6,7]. There are variations in the reported prevalence of long-COVID syndrome across studies and nations [3,8,9]. These manifestations usually include, but are not restricted to, dyspnea, pain, exhaustion, breathing difficulty, compromised lung function, muscle weakness, restricted exercise tolerance, confusion and depressed mood, impaired memory, poor concentration (“brain fog”), neurological problems, taste/smell abnormalities, and poor health-related quality of life (HRQOL) [1-3].

To improve awareness and, particularly, access for those in distant communities or who face transportation challenges, the adoption of telemedicine services has lately been explored as an additional and novel method of providing rehabilitation to patients in their households. An at-home rehabilitation using telemonitoring technology offers considerable potential for preserving and enhancing functional capacity [10].

The burden of long-term COVID is rising rapidly, necessitating the development of interventions to enhance patient long-term outcomes. Presently, policy documents and recommendation statements support both short- and long-term rehabilitation [11,12]. These suggestions, however, are dependent solely on consensus opinion and lack data from specific trials examining the positive impacts of inpatient or outpatient rehabilitation in individuals experiencing long-term health complications following COVID-19.

Others made a significant observation that women and those who had more severe acute infections were more likely than men to experience most manifestations and symptom clusters, and that post-COVID syndrome also impacted younger individuals. Females aged ≥ 20 years were more likely to have long-COVID symptoms than males aged ≥ 20 years (10.6% vs. 5.4%) [13,14]. Therefore, the purpose of this study was to evaluate the outcomes of a home-based pulmonary training program (including aerobic, resistance, and breathing exercises) under the

supervision of telerehabilitation on pulmonary function, exercise tolerance and HRQOL in participants who had COVID-19 manifestations.

METHODS

Study design

The research was carried out between December 2021 and June 2022. All study participants submitted informed consent in writing to participate in this trial. Qassim Regional Research Ethics Committee (No. 784946-1443) approved all study protocols which were carried out in line with the Declaration of Helsinki. The investigation was prospectively listed on ClinicalTrials.gov (NCT05172102).

Participants

After a positive nasopharyngeal or oropharyngeal swab verified the diagnosis of COVID-19, participants were sought out from females at Qassim University in Kingdom of Saudi Arabia via brochures, social media, and online platforms. When the participants expressed willingness to participate, a researcher confirmed their possible candidacy and set up a face-to-face meeting to complete the baseline evaluation. The following in-person appointments were arranged for follow-up evaluations at the baseline assessment. All the testing procedures were performed at cardiopulmonary lab in college of medical rehabilitation, Qassim University. The study included mild to moderate post-COVID-19 survivors, COVID-19 severity was classified into three categories mild to moderate (outpatients with a flu-like condition or probable pneumonia), severe (hospitalized patients treated in hospital wards), and critical (patients treated in an intensive care unit) [15], 18 to 30 years old, not smokers, with a body mass index (BMI) between 18.5 and 24.9 kg/m².

Candidates were excluded if they had any of the following: (1) an identification of progressive neuromuscular, respiratory, or neurological conditions; (2) a contraindication to pulmonary rehabilitation intervention such as angina pectoris, recent myocardial infarction, severe pulmonary hypertension, congestive heart failure, unstable diabetes, inability to do exercise due to orthopedic as intra-articular drug injection or surgical treatment of lower extremities, psychiatric illness and severe exercise-induced hypoxemia [16]; (3) no internet service; or (4) previous participation in a rehab program following a COVID-19 condition. A further exclusion applied to participants who missed more than 15% of therapy sessions.

Sample size calculation was performed using G*Power statistical software (version 3.1.9.2) based on data of 6-minute walk test (6MWT) derived from pilot study conducted on 5 subjects in each group; and revealed that the required sample size for this study was 20 subjects in each group. Calculation is made with $\alpha=0.05$, power=80% and effect size=0.91, For dropout the sample increase to 20%. Participants were randomized and divided into two groups using a simple random approach, and the findings were packed into opaque envelopes to keep the order of group assignment from the investigator who recruited the participants undisclosed. The control group (n=24) received standardized educational instructions and the intervention group received telerehabilitation pulmonary exercise program (n=24) for 6 weeks. It was not possible to blind the treating therapists who participated in the study due to the nature of study procedures. The evaluating therapist was blinded when evaluating the outcomes initially and after the intervention. The treatment and evaluation therapists were different, and the evaluating therapists kept blind of the participants. The participants were instructed not to share their procedures and treatment plan with the therapist who would be evaluating them.

Control group

The participants in the control group got written instructions on an explanatory note and prescribed educational presentations from physiotherapists for 10 minutes. They were instructed to continue with their regular everyday routines, refrain from prolonged bed rest and immobility, engage in light physical activity, such as housework, follow a balanced diet, and get 6 to 8 hours of sleep each night. Also, patients were given instructions on proper facemask use, social distancing, and essential hand hygiene.

Intervention group

In addition to receiving the same instructions and informational materials as the control group, the intervention group also participated in a home exercise routine that was virtually supervised and given via telerehabilitation. The duration of the intervention program was 60 to 80 minutes per session, three sessions per week for 6 weeks.

To ensure safety, proper and correct exercise technique, small groups of 2 to 6 participants underwent the session at a time for education, supervised by specialized physical therapist at college of medical rehabilitation, Qassim University. Telerehabilitation program was guided by a specialized physical therapy

professional through a web platform (by Zoom Video Communications), in live sessions. Participants were asked to connect themselves to the platform in groups of 5 participants, three times a week, for 6 weeks. Each week, the therapist indicated and corroborated individually to each patient the load with which she should train.

Initial exercise types and intensity were determined by the physical therapist based on baseline assessments and in accordance with the American College of Sports Medicine's recommendations for exercise prior to participation [17]. The telerehabilitation pulmonary exercise regime contained (1) breathing exercises and chest expansion, including diaphragmatic breathing exercise, as well as other activities aimed to enhance chest wall muscle strength and chest mobility for 15 minutes. (2) Aerobic activity for 20 to 30 minutes consisted of brisk walking or running outside close to the participant's home or using a treadmill at home (if one was accessible), accompanied by a 3-minute warm-up and 3-minute stretching cool-down. At exercise intensity between 60% and 80% of maximal heart rate, which was defined as 220 minus age [18], the target heart rate for aerobic exercise was determined using the Karvonen formula [19], patients were asked to self-monitor during aerobic exercise and were also trained for reporting Borg scale themselves, and (3) resistance training with weights was proposed to the participants based on an individual's personal evaluation for 30 minutes.

Ten-repetition maximum was used to determine the ideal resistance needed for each muscle group, and the DeLorme method was used to train the muscles [20]. The most weight that a subject can lift repeatedly for ten repetitions is known as the 10-repetition maximum. The main group muscles, including the back, abdominal, shoulder (flexors, extensors, abductors), elbow, hip and knee (flexors, extensors) were exercised. Every muscle group received three sets of 10 repetitions each, with a 60-second rest between sets. In accordance with each person's needs, the resistance was gradually increased.

To maintain clinical safety limits, respiratory rate, heart rate, oxygen saturation (SpO_2), and Borg scale were monitored at each session. Patients were asked to acquire a pulse oximeter to measure their SpO_2 and to self-monitor during the sessions and were also trained for reporting Borg scale themselves. If the SpO_2 value decreased by 4% and if it fell below 95% or registered an increase of three points with respect to the initial value of the Borg scale, the participant had to interrupt the session. Other reasons for interrupting the session were an increase in

heart rate by 20 beats per minute, dizziness, sweating, headache, or chest pressure.

To record compliance, participants were asked to complete a diary at the end of every training session. Adherence to the program was assessed and confirmed by comparing the physiotherapist's notes against each participant's diary notes.

Measurements

Assessment of outcomes for each group was conducted at baseline (pretreatment) and after 6 weeks of intervention (post-treatment). Assessment of functional exercise capacity was conducted using the 6-MWT. According to recommendations from the American Thoracic Society and the European Respiratory Society (ATS/ERS), the 6-MWT was carried out in a 30-meter corridor with standard guidelines. After the 6-MWT, the walking distance was measured [21].

In accordance with the recommendations of ATS/ERS [22], pulmonary function evaluated using spirometry (SpirOx; MED-ITECH). The forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) are the two spirometric tests that will be performed. There will be three successful attempts. The best trial out of the three will be considered.

HRQOL was assessed using the Short Form Health Survey-36 (SF-36) questionnaire, which has been validated. Physical functioning, bodily pain, social functioning, general health, role-physical, role-emotional, vitality, and mental health are the eight scales that make up the SF-36, which consists of 36 items in total. Item scores are recorded, added up, and converted to a scale from 0 (lowest health status) to 100 (best health status) based on these parameters. We used the tool's Arabic version, which has been found to be reliable and accurate [23].

Statistical analysis

The comparison of subject characteristics between groups was done using an unpaired t-test. Shapiro-Wilk test was used to determine whether the data is normally distributed. The homogeneity between groups was examined using Levene's test for homogeneity of variances. Mixed MANOVA was used to examine how the intervention affected the 6MWT, FVC, FEV₁, and SF-36. For further multiple comparisons, post-hoc testing employing the Bonferroni correction were conducted. All statistical tests had a significance threshold of $p < 0.05$. The IBM SPSS version 25 for Windows (IBM Corp.) was used for all statistical analysis.

RESULTS

The flow of subjects through the research is depicted in Fig. 1. In this study, 48 participants took part in this trial and 50 participants were excluded from the study (33 participants do not meet the inclusion criteria of the study and 17 participants declined to participate). The treatment adherence rate for intervention group was 94.21%, with participants completing 16.96 ± 0.86 sessions. The subject characteristics for the intervention group and control group are displayed in Table 1. Age, BMI, and period of rehabilitation following confirmed COVID-19 did not significantly differ between groups ($p > 0.05$).

A significant interaction effect of intervention and time was identified by mixed MANOVA ($F = 413.09$, $p = 0.001$). There was a significant main effect time ($F = 942.28$, $p = 0.001$). There was a significant main effect of intervention ($F = 32.78$, $p = 0.001$).

Before treatment, there was no detectable difference between the groups ($p > 0.05$). Posttreatment comparisons between the groups showed no significant differences in FVC or FEV₁ between the groups ($p > 0.05$), while the intervention group significantly increased its 6MWT compared to the control group ($p = 0.001$; Table 2).

Following treatment, there was a statistically significant difference between the intervention group and the control group in terms of physical functioning, bodily pain, social functioning, general health, role-physical, role-emotional, vitality, and mental health ($p = 0.001$; Table 3, Fig. 2).

In the intervention group, there was a 25.88%, 26.57%, 36.97%, 34.04%, 30.58%, 27.62%, 29.82%, and 29.24% changes in physical functioning, role physical, bodily pain, general health, vitality, social role, emotional role and mental health respectively.

DISCUSSION

In this trial, exercise capacity, pulmonary function, and HRQOL in females with post-COVID-19 symptoms were examined in relation to a home-based pulmonary training program that was videoconference-monitored. The findings of this study demonstrated that the pulmonary training program was successful in enhancing HRQOL and exercise capacity. There were no changes in the parameters of lung function after the pulmonary training program. The intervention protocol was adhered effectively, and there were no significant adverse events.

In this study, a patient-centered, customizable inexpensive

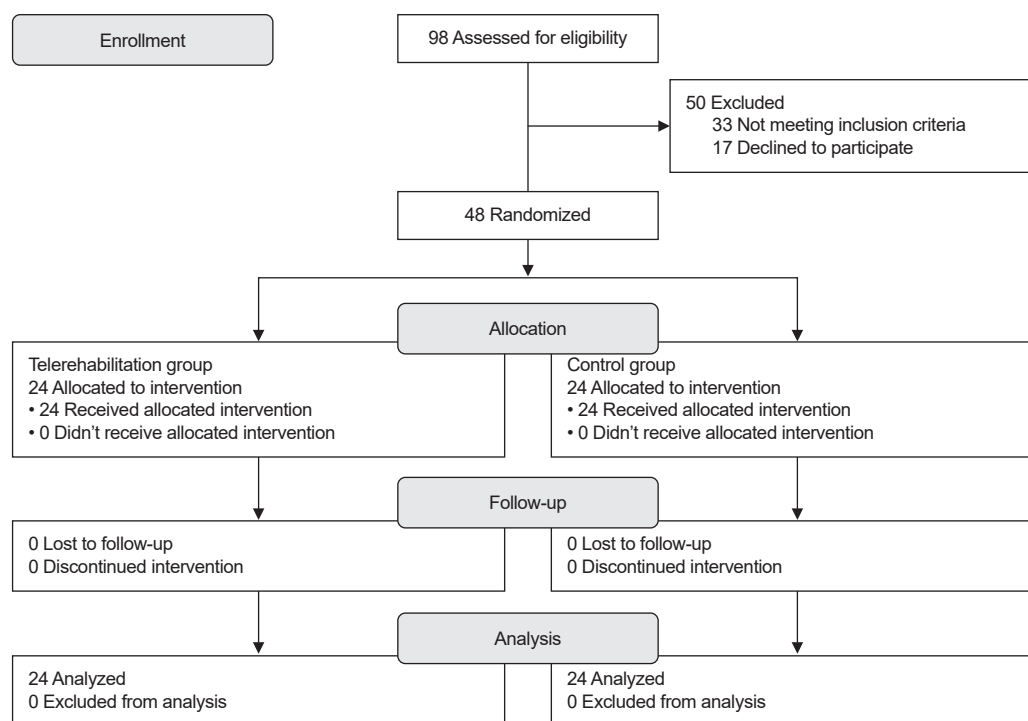


Fig. 1. CONSORT-2010-flow-diagram.

Table 1. Comparison of subject characteristics between intervention group and control group

	Intervention group (n=24)	Control group (n=24)	MD	t-value	p-value
Age (yr)	23.33±2.71	22.58±2.51	0.75	0.99	0.32
BMI (kg/m ²)	22.11±2.66	21.65±2.73	0.46	0.58	0.56
Time to rehabilitation after confirmed COVID-19 (mo)	4.75±1.77	4.33±1.55	0.42	0.86	0.39

Values are presented as mean±standard deviation.

COVID-19, coronavirus disease 2019; MD, mean difference.

Table 2. Mean FVC, FEV₁, and 6MWT pre- and posttreatment of both groups

	Pretreatment (n=24)	Posttreatment (n=24)
FVC (L)		
Intervention group	2.71±0.41	2.92±0.43
Control group	2.72±0.36	2.74±0.37
MD	-0.01	0.18
p-value	0.95	0.12
FEV ₁ (L)		
Intervention group	2.22±0.33	2.39±0.31
Control group	2.26±0.26	2.28±0.25
MD	-0.04	0.11
p-value	0.61	0.19
6MWD (m)		
Intervention group	450.83±40.58	514.95±42.96
Control group	440.58±51.47	459.12±53.71
MD	10.25	55.83
p-value	0.44	0.001

Values are presented as mean±standard deviation.

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; MD, mean difference; 6MWT, 6-minute walk test.

telerehabilitation intervention was assessed using a variety of measures that were pertinent to exercise capacity, lung function, and HRQOL. The availability of therapists for remote supervision and consultations, smartphone access, technological literacy, are all factors supporting the suitability of telerehabilitation programs for large-scale deployment. When a face-to-face program cannot be conducted, telerehabilitation has been suggested as a reasonable alternative. An at-home telerehabilitation program for patients with post-COVID-19 fatigue, which included aerobic and strength training, had positive effects on their persistent symptoms as well as on physical capacity or walking distance measurements [24].

The patients in this study had mild to moderate COVID-19, but they also had significant restrictions. Recovery is frequently incomplete and sluggish. In young adults and people with no or few chronic underlying medical illnesses, mild to moderate

Table 3. Mean Short Form Health Survey-36 pre- and posttreatment of both groups

	Pretreatment (n=24)	Posttreatment (n=24)
Physical functioning		
Intervention group	59.71±4.90	75.16±5.11
Control group	58.08±5.25	63.29±4.92
MD	1.63	11.87
p-value	0.27	0.001
Role physical		
Intervention group	58.33±4.95	73.83±6.46
Control group	57.04±6.05	60.29±5.78
MD	1.29	13.54
p-value	0.42	0.001
Bodily pain		
Intervention group	54.12±3.22	74.13±4.91
Control group	52.92±3.69	56.45±4.04
MD	1.2	17.68
p-value	0.23	0.001
General health		
Intervention group	53.00±4.18	71.04±5.03
Control group	51.2±3.94	54.70±3.67
MD	1.8	16.34
p-value	0.13	0.001
Vitality		
Intervention group	55.17±3.51	72.04±3.86
Control group	53.83±4.25	58.16±3.81
MD	1.34	13.88
p-value	0.24	0.001
Social role		
Intervention group	54.75±3.30	69.87±3.88
Control group	53.17±4.45	56.50±4.17
MD	1.58	13.37
p-value	0.17	0.001
Emotional role		
Intervention group	53.95±4.55	70.04±4.67
Control group	52.83±5.72	54.92±6.46
MD	1.12	15.12
p-value	0.45	0.001
Mental health		
Intervention group	52.87±3.67	68.33±4.38
Control group	52.42±2.94	55.12±3.63
MD	0.45	13.21
p-value	0.63	0.001

Values are presented as mean±standard deviation.
MD, mean difference.

nonhospitalized COVID-19 disease can cause extended sickness and persistent symptoms [25,26].

The physical capacity of post-COVID-19 patients is moderately impaired, which is likely due to muscle deconditioning, according to earlier studies [27,28]. Other contributing factors to the overall symptomatology include physical deconditioning

and decreased exercise tolerance [29-31]. Furthermore, immobility forced by hospital stays and/or enforced quarantine at home worsens the clinical presentation and symptoms in these patients, who may experience symptoms that persist for a long time after having COVID-19 disease [32]. Moreover, the 6MWT was at 76% of the expected capacity among patients who reported physical and psychological consequences in a 5-year follow-up study on 109 acute respiratory distress syndrome survivors [33].

Participants in this trial increased their 6MWT by almost double the minimal clinically important difference, which is about equivalent to rehabilitation outcomes in other COVID-19 patients [34,35]. It appears that referring COVID-19 patients to pulmonary rehabilitation following the acute phase of the disease can facilitate the recovery of exercise capacity. Exercise capacity both in the physical and mental components of HRQL exhibited similar improvement. Like in other studies [34,35], the influence on quality of life was statistically significant when comparing to the control group.

Patients displayed a lower FEV₁ at baseline, which is consistent with another research on post-COVID-19 [36]. Breathing exercises have been shown to have superior effects on lung function measures (FEV₁ and FVC) compared to controls for chronic obstructive pulmonary disease (COPD) in a recent systematic review and meta-analysis [37], but no such effects were observed in the current investigation. In the intervention group, both parameters (i.e., FVC and FEV₁) significantly improved throughout the course of the 6-week rehabilitation period; nevertheless, no significant between-group variation was observed. Additionally, it was determined that the intervention group's mean differences FEV₁ was 0.17 and percentage of change was 7.66% of baseline, and the mean difference of FVC was 0.21 and percentage of change was 7.75% of baseline, did not exceed the clinically meaningful change threshold for patients with COPD that is advised by ATS/ERS (week to week). One possibility is that the workouts used in the intervention program did not substantially target lung function. Further Li et al. [34] findings add evidence to this perspective.

Cardiopulmonary-rehabilitation programs recently emerged to be advised in the treatment of patients following COVID-19 to address the significant disability of people with prolonged COVID-19 and the decline in their quality of life [12,38,39]. Guidelines in this direction were released in 2020 by the Pan American Health Organization, a member of the World Health Organization, for both patients who had COVID-19 in its acute

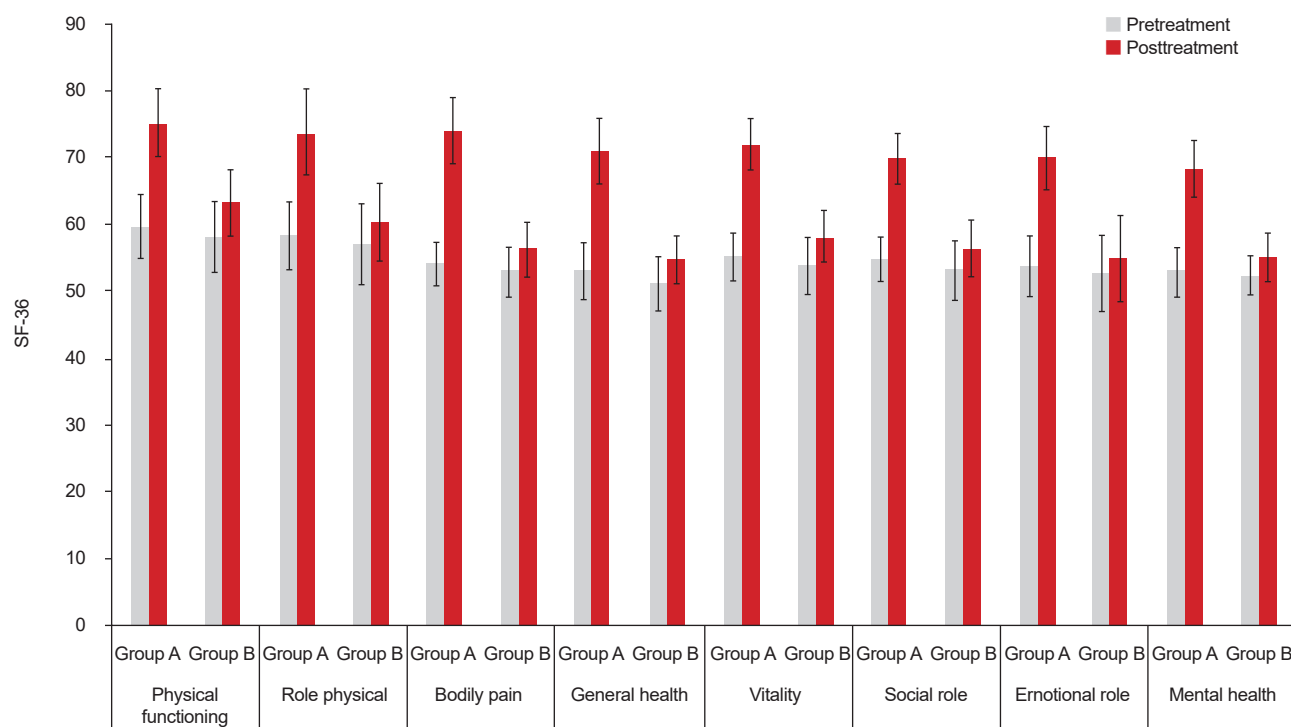


Fig. 2. Mean Short Form Health Survey-36 (SF-36) pre- and posttreatment of group A (intervention group) and B (control group).

phase and those who were still experiencing its long-term effects [40]. Customized rehabilitation-training regimens include cardiopulmonary activities, muscle-strengthening exercises, and focused breathing techniques may improve recovery.

While interpreting the results of our study, it is important to consider many limitations. First, only mild to moderate COVID-19 survivors who had never been hospitalized were included in participant characteristics. The lack of data for some of the secondary outcomes, such as dyspnea, level of fatigue, inspiratory muscle strength, etc., limits the scope of our study. Second, the research cohort was young, highly educated, and most likely had a strong network of healthcare providers, their referrals to rehabilitation without defined protocols at the time cannot be extended to the entire population of COVID-19 survivors. Finally, the small patient population made it difficult to do subgroup analyses to look at variations in illness outcome and progression according to patient variables.

In conclusion, the telerehabilitation pulmonary program is superior to no rehabilitation with regarding to exercise capacity and HRQOL in young females after long COVID-19. The effect of the programs on pulmonary function is otherwise unlikely. In sum, our research affirms the efficacy of integrated customized rehabilitation for COVID-19 young female only. Future

studies should focus on the long-term consequences of rehabilitation and the apparent improvement in pulmonary function in other age and sex.

CONFLICTS OF INTEREST

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

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None.

DATA AVAILABILITY STATEMENT

The authors declare that all relevant data supporting the findings of the study are available within the manuscript.

AUTHOR CONTRIBUTION

Conceptualization: Basha MA, Alrshedi ZO. Data curation: Alanazi AA, Alhawsah EA, Alharbi HK. Formal analysis: Ka-

mel FH, Basha MA. Investigation: Alanazi AA, Alhawsah EA, Alharbi HK, Alrshedi ZO. Methodology: Alsharidah AS, Kamel FH, Basha MA. Project administration: Basha MA. Resources: Alanazi AA, Alhawsah EA, Alharbi HK, Alrshedi ZO. Software: Basha MA. Supervision: Basha MA. Validation: Alsharidah AS, Kamel FH. Visualization: Alsharidah AS, Kamel FH. Writing – original draft: Alanazi AA, Alhawsah EA, Alharbi HK, Alrshedi ZO, Basha MA. Writing – review editing: Alsharidah AS, Kamel FH, Basha MA. Approval of final manuscript: all authors.

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Prognostic Value of Electroneuronography in Severe Cases of Facial Palsy

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Objective: To examine the prognostic value of electroneuronography (ENoG) in predicting functional recovery in severe cases of acute facial palsy.

Methods: Patients with severe degrees of facial palsy (initial House–Brackmann [HB] grades IV to VI) with available electrodiagnostic studies conducted 2–4 weeks after symptom onset were reviewed retrospectively. The patients were categorized into “good recovery” and “poor recovery” groups, with the former showing mild to no dysfunction (HB I to III) and the latter exhibiting moderate to severe dysfunction (HB IV to VI) on follow-up evaluation, 2 months after onset. ENoG amplitudes in four facial muscles (frontalis, nasalis, orbicularis oculi, and orbicularis oris), as well as age, sex, affected side, disease etiology, comorbidities, and laboratory findings, were compared between the two groups.

Results: Thirty-seven patients were included. Twenty-nine of the patients showed “good recovery,” and eight showed “poor recovery” at 2 months after symptom onset. Univariate analysis yielded no significant difference in age, sex, affected side, disease etiology, comorbidities, and laboratory findings between the two groups. Preserved ENoG amplitudes (individual, average, and trimmed means) were significantly higher in the good recovery group than in the poor recovery group ($p < 0.005$). Sex ($p = 0.038$) and the ENoG of the nasalis muscle, acquired 2–4 weeks from symptom onset ($p = 0.004$), showed significant differences in multivariate regression analysis.

Conclusion: This study suggests that the female sex and lower ENoG of the nasalis muscle, acquired 2–4 weeks from symptom onset, have negative prognostic value for the 2-month functional outcome of severe facial palsy cases.

Keywords: Bell palsy, Electroneurography, Facial paralysis, Electrodiagnosis, Prognosis

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INTRODUCTION

Acute facial nerve palsy is one of the most commonly encountered cranial neuropathies characterized by varying degrees of facial muscle paralysis. Bell's palsy, an acute facial neuropathy with idiopathic origins, is the most common etiology of acute

facial nerve palsy. The symptoms can begin suddenly and worsen over a few hours to days, varying from mild difficulty in making facial muscle movements and facial expressions to inability to close the eye or mouth or even social and psychological distress [1]. The neurologic and psychological symptoms are more prominent when the patient cannot voluntarily move their

facial muscles.

Numerous studies have evaluated the degree of nerve degeneration in facial nerve palsy using electroneuronography (ENoG), introduced by Esslen [2] in 1973. The nerve excitability test, maximal stimulation test, ENoG, electromyography, and blink reflex are special tests that can assess the electrophysiological extent of facial nerve damage. In particular, ENoG, by determining action potential amplitude, provides the degree of nerve fiber degeneration with great accuracy [3].

Since it takes about 72 hours for Wallerian degeneration to reach the extratemporal nerve distal to the stylomastoid foramen, which is the area for electrostimulation for ENoG in idiopathic facial palsy, ENoG can be normal in the first 72 hours after symptom onset. The response to ENoG is quickly lost during the next 5–6 days and would not change after 21 days when the nerve degeneration is complete [3,4]. This means that performing ENoG within 14 days after symptom onset may be too early for the test to reflect the full effect of the neurodegeneration. Thus, it seems necessary to determine the predictive usefulness of ENoG performed around 21 days after symptom onset, which is slightly later than the timeframe in traditional studies.

Several factors appear to be related to the prognosis of facial palsy, such as age, sex, and severity of paralysis, and the degree of nerve degeneration obtained by ENoG is the most reliable prognostic factor [5]. However, prior studies on ENoG findings as a prognostic factor did not consider the clinical severity of the paralysis [6,7]. Since facial palsies with more severe axonal damage are associated with longer treatment times and greater variance in treatment results, setting an appropriate treatment duration according to each patient's treatment potential is necessary for severe cases of facial palsy.

This study aimed to evaluate the cutoff values of electroneuronographic data obtained within 2–4 weeks after symptom onset in severe facial palsy cases to provide an objective basis for predicting functional presentation within 2 months post-symptom onset.

METHODS

Patients

The clinical records of patients who underwent electrodiagnostic laboratory tests in Konkuk University Medical Center between January 2005 and August 2021 were reviewed retrospectively. The clinical severity of facial palsy was evaluated us-

ing the House–Brackmann (HB) scale. Patients with HB grades IV to VI were considered to have severe facial palsy since they had obvious facial motor weakness and facial asymmetry [8]. Patients with available electrodiagnostic study data were included 2–4 weeks after symptom onset (Fig. 1, Table 1). The patients were categorized into “good recovery” and “poor recovery” groups. The good recovery group displayed mild to no dysfunction (HB I to III, n=29), while the poor recovery group showed moderate to severe dysfunction (HB IV to VI, n=8) on a follow-up evaluation 2 months after the onset of symptoms.

Our study was approved by KUMC Institution Review Board (approval no. 2022-10-014) on November 7, 2022. This is a retrospective study, and informed consent was not required. Patient data would not be shared with outside parties.

Electrodiagnosis

An electrodiagnostic evaluation was performed using the Nicolet EDX[®] system and Synergy software program (Natus Medical, Inc.). Only patients who underwent electrodiagnosis 2–4 weeks after symptom onset were included because at least 10–15 days are required [9] for electrodiagnosis to adequately reflect the full effect of axonal loss.

ENoG amplitudes for both sides of the four facial muscles (frontalis, nasalis, orbicularis oculi, and orbicularis oris) were collected, along with the average values for the four muscles. The trimmed mean (mean value of conserved ENoG amplitude excluding the maximum and the minimum values) was also considered to minimize the effect of outliers. The preserved amplitudes of ENoG (%) on the affected side compared to the unaffected side were used to assess the degree of nerve fiber degeneration [10] and compare the good and poor recovery groups. The amount of preserved ENoG amplitude was calculated as follows:

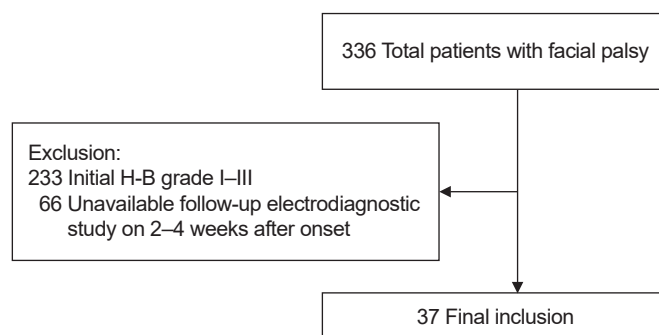


Fig. 1. Patient inclusion flow chart. H-B, House–Brackmann.

$$\text{ENoG value (\%)} = \frac{\text{Amplitude on the affected side}}{\text{Amplitude on the unaffected side}} \times 100$$

During the examinations, the facial nerve was stimulated supramaximally at the stylomastoid foramen, and base-line-to-peak-amplitudes of compound motor action potentials were measured.

Laboratory evaluation

Several previous studies considered a high inflammatory level a poor prognostic factor for facial palsy [11,12]. C-reactive protein (CRP) is a positive acute-phase inflammatory biomarker, and albumin is a negative acute-phase protein. CRP to albumin ratio (CAR) is widely used as a prognostic factor in either short or long-term disease inflammation [10]. Neutrophil to lymphocyte ratio (NLR) has been recommended as a marker for systemic inflammation and facial palsy [13]. This study included CAR, NLR, and white blood cell (WBC) count as prognostic parameters. Serum CRP levels (mg/dL), albumin level (g/dL),

and WBC with differential counts obtained from blood samples collected within 7 days from symptom onset were used.

Statistical analysis

Differences in side-to-side ENoG amplitude percentage, age, and laboratory results between the two groups were assessed using Welch's t-test, considering the unequal variance of variables. Fisher's exact test assessed categorical variables. To identify the discriminatory capability of each ENoG amplitude, we constructed receiver operating characteristic (ROC) curves. Each ROC curve's area under the curve (AUC) was also calculated. The cutoff values of ENoG amplitudes with optimized sensitivity and specificity were evaluated using the Youden Index.

Finally, a logistic regression model was constructed to determine the association between ENoG amplitudes and clinical outcomes. Statistical analysis was performed using R Statistical Software (R-studio version 4.2.1; R Foundation for Statistical Computing). Statistical significance was set at $p < 0.05$.

Table 1. Patient characteristics

Characteristic	Good recovery (n=29)	Poor recovery (n=8)	All patients (n=37)	p-value
Age (yr)	47.0 (25.3)	48.5 (15.5)	45.3 (24.0)	0.89
Sex, male	21 (72.4)	3 (37.5)	24 (64.9)	0.10
Electrodiagnostic study period since onset (day)	16.3 (3.0)	17.1 (4.3)	16.9 (4.2)	0.83
ENoG amplitude (%)				
Average	26.5 (41.6)	7.1 (8.6)	29.9 (36.0)	<0.005
Frontalis	34.5 (40.5)	12.5 (16.0)	32.0 (42.0)	<0.005
Nasalis	34.5 (37.0)	6.5 (13.5)	31.4 (35.0)	<0.005
Orbicularis Oculi	27.0 (36.3)	6.5 (10.3)	30.1 (27.0)	<0.005
Orbicularis Oris	19.5 (45.8)	5.0 (4.0)	26.2 (45.0)	<0.005
Trimmed mean	30.0 (40.6)	6.8 (12.6)	30.4 (31.5)	<0.005
Affected side				0.45
Right	13 (44.8)	5 (62.5)	18 (48.6)	
Left	16 (55.2)	3 (37.5)	19 (51.4)	
Etiology				0.14
Idiopathic	22 (75.9)	5 (62.5)	27 (73.0)	
Ramsay Hunt syndrome	6 (20.7)	1 (12.5)	7 (18.9)	
Traumatic	1 (3.4)	2 (25.0)	3 (8.1)	
Comorbidities				
Diabetes	4 (13.8)	1 (12.5)	5 (13.5)	1.00
Hypertension	4 (13.8)	3 (37.5)	7 (18.9)	0.16
History of facial palsy	1 (3.4)	1 (12.5)	2 (5.4)	0.39
Laboratory				
CAR	0.14 (0.17)	0.11 (0.65)	0.79 (0.38)	0.99
NLR	1.85 (1.65)	1.81 (1.06)	2.52 (1.40)	0.60
WBC count	7.16 (3.60)	7.26 (3.07)	7.89 (2.55)	0.44

Values are presented as mean (IQR) or number (%).

CAR, C-reactive protein to albumin ratio; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell.

RESULTS

Patients' characteristics

A total of 336 patients diagnosed with facial palsy were enrolled, of which 103 patients were considered to have severe facial palsy. Ultimately, 37 patients with available electrodiagnostic study data for the first 2–4 weeks (16.9 ± 4.2 days) after symptom onset were included. Twenty-nine of the patients showed “good recovery,” and the remaining eight showed “poor recovery” at 2 months after symptom onset (Table 1). Idiopathic facial palsy (Bell's palsy) was the predominant etiology in 22 patients (75.9%) in the good recovery group and 5 (62.5%) in the poor recovery group, followed by Ramsay Hunt syndrome (6 patients [20.7%] in the good recovery group and 1 [12.5%] in the poor recovery group). Three patients had a history of head trauma causing the facial palsy (1 patient [3.4%] in the good recovery group and 2 [25.0%] in the poor recovery group). Although all cases of traumatic facial palsy showed mild traumatic subarachnoid hemorrhage on brain computed tomography, the patients were treated conservatively. The patients with traumatic facial palsy were confirmed to have peripheral-type facial palsies by experienced physicians. All (94.6%), except two patients, were diagnosed with facial palsy for the first time. One patient in each group had previously experienced idiopathic facial palsy. One patient in the good recovery group had facial palsy on the ipsilateral side (left) 6 years earlier. The other patient in the poor recovery group had facial palsy on the contralateral side (right) 15 years prior. Neither reported sequelae (such as facial motor weakness or asymmetry) after their first episode of facial palsy.

Electroneuronography

Electrodiagnostic procedures were performed at an average of 16.9 days after symptoms appeared. Preserved ENoG amplitudes of patients in the good recovery group were significantly higher than those of patients in the poor recovery group in terms of individual, average, and trimmed means ($p < 0.005$). The optimal cutoff values of ENoG for each muscle were obtained by plotting ROC curves (Fig. 2). The optimal cutoff, which constrained either the sensitivity or specificity of the test, was 95% for the frontalis, nasalis, and orbicularis oculi muscles. The orbicularis oris muscle had the largest AUC (87.3%; Table 2).

Laboratory analysis

Blood samples were acquired within 7 days from symptom onset. Five patients in the good recovery group were unavailable

for sample collection. The two groups had no significant differences in CAR, NLR, and WBC counts. Patients with a traumatic etiology ($n=2$, the other patient was unavailable for sampling) displayed a marked elevation of CRP level. Nevertheless, there were no significant differences in the results after removing these two patients to exclude inflammatory conditions caused by trauma (CAR, $p=0.78$; NLR, $p=0.42$; and WBC counts, $p=0.57$) [14].

Prognosis prediction model

Logistic regression with backward elimination was conducted to obtain a significant value that can predict prognosis. We found that the lower preserved ENoG amplitude of the nasalis muscle ($p=0.004$) and sex ($p=0.038$) were negative prognostic factors in patients with severe facial palsy (Table 3).

DISCUSSION

It is established that ENoG amplitude has a prognostic value in facial palsy. Our study showed that ENoG amplitude also has predictive value in severe facial palsy. In our study, statistically significant differences were found between patients with severe facial palsy in the good and poor recovery groups concerning the facial nerve degeneration rate of each of the four facial muscles (frontalis, nasalis, orbicularis oculi, and orbicularis oris) and their mean values and trimmed means ($p < 0.005$).

The ENoG amplitudes of the four facial muscles showed significant differences between the two groups; however, only that of the nasalis muscle had prognostic value for severe facial palsy. This finding is concurrent with those of several other studies. Kim et al. [15] studied the prognostic value of ENoG of Bell's palsy at the orbicularis oculi and nasolabial fold in 81 patients and found that the ENoG of the nasolabial fold had more prognostic value than that of the orbicularis oculi. The facial nerve has five extracranial terminal branches: temporal, zygomatic, buccal, marginal mandibular, and cervical. According to most literature and anatomy textbooks, the frontalis muscle is innervated by the temporal branch, the orbicularis oculi muscle is double-innervated by the temporal and zygomatic branches, the buccal branch innervates the nasalis muscle, and the orbicularis oris muscle is double-innervated by the buccal and mandibular branches [16,17]. In our study, we adopted the muscles representative of each branch in standardized settings; temporal-frontalis, zygomatic-orbicularis oculi, buccal-nasalis, and mandibular-orbicularis oris. Martínez Pascual et al. [18] studied

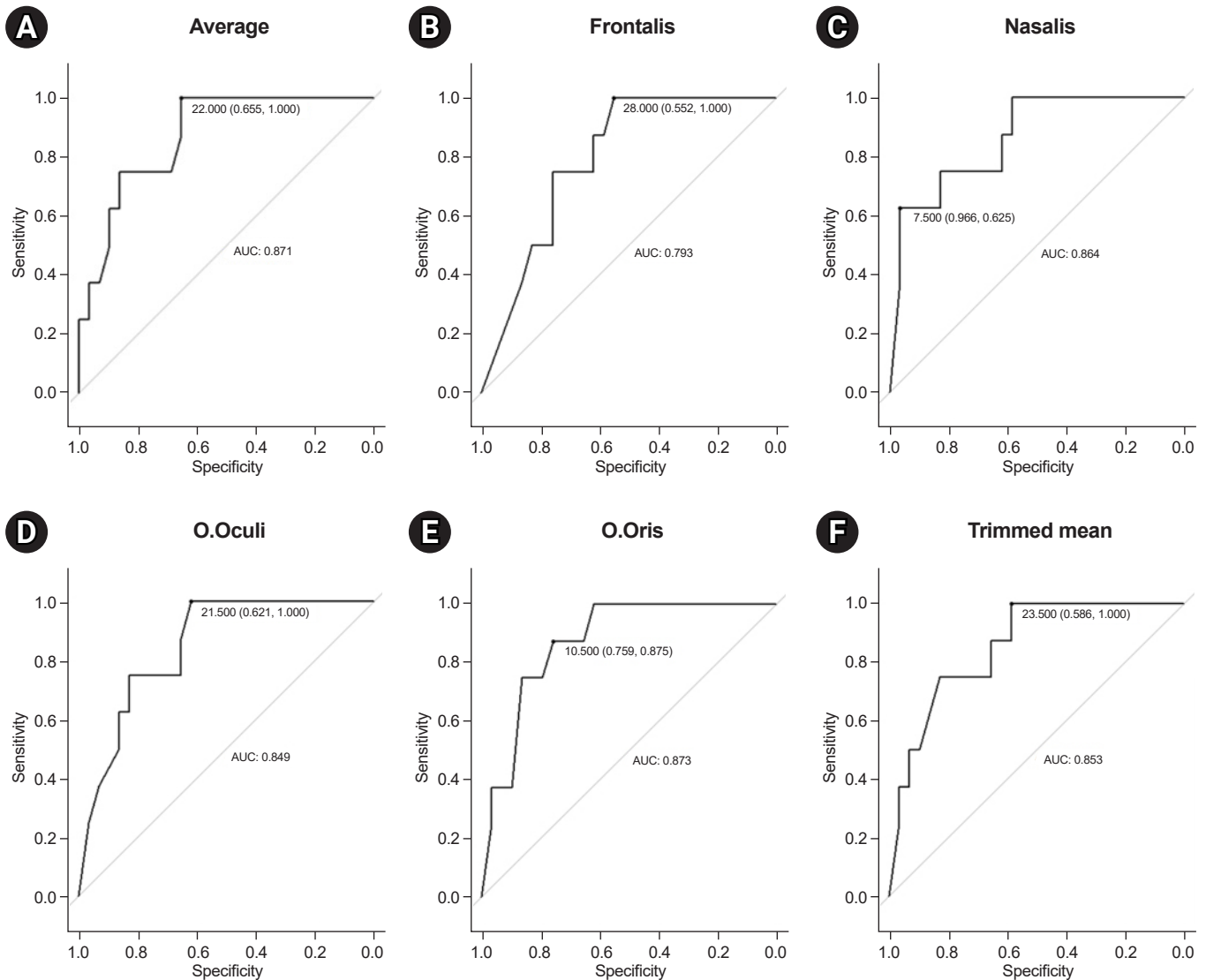


Fig. 2. Receiver operating characteristic (ROC) curves for the discriminatory capability of each muscle. (A) Preserved electroneuronography (ENoG) amplitude averages for all four facial muscles. Preserved ENoG amplitudes of the frontalis (B), nasalis (C), orbicularis oculi (O.Oculi) (D), and orbicularis oris (O.Oris) (E) muscles. (F) Trimmed means of the preserved ENoG amplitude of all four muscles.

Table 2. Optimal cutoff values for each facial muscle

	Cutoff value (%)	Sensitivity (%)	Specificity (%)	Area under the curve (%)
Average	78.0	65.5	100	87.1
Frontalis	72.0	55.2	100	79.3
Nasalis	92.5	96.6	62.5	86.4
Orbicularis oculi	78.5	62.1	100	84.9
Orbicularis oris	89.5	75.9	87.5	87.3
Trimmed mean	76.5	58.6	100	85.3

Table 3. Logistic regression model used to predict poor recovery in severe cases of facial palsy

Predictors	Regression coefficient	Standard error	Odds ratio	95% confidence interval	p-value
Nasalis	0.007	0.002	1.01	1.00–1.01	0.004
Sex, female	0.270	0.125	1.31	1.02–1.67	0.038
Intercept	1.395	0.124			

the extracranial course of the facial nerve in 23 Caucasian adult cadavers and found that the buccal branch has the most varied origin. It can be inferred that muscles located in the central part of the face are more significant since they are dominated by the facial nerve plexus [15]. Since ENoG amplitude reflects nerve fibers reacting to electrical stimulation and their synchronicity [19], the ENoG of muscles that are mostly innervated by the facial nerve plexus, such as central muscles of the face, e.g., the nasalis (or nasolabial fold as in Kim et al. [15]), is more significant than that of their counterparts for predicting recovery from facial nerve insult. Similarly, Engström et al. [20] reported that initial (mean, day 11) ENoG measurements of the nasalis and/or mentalis were the best single recordings for predicting favorable outcomes in patients with Bell's palsy.

Sex has a predictive value for severe facial palsy. Although it seems controversial whether sex is a risk factor for facial palsy, several studies have suggested a male predominance in Bell's palsy. According to the National Health Insurance Service National Sample Cohort data of Korea from 2006 to 2015, the male sex is a significant risk factor for Bell's palsy [21]. Another Korean population-based study reported similar epidemiologic results [22]. In our study, the male sex appeared to have a slight predominance in the overall incidence of severe facial palsy (64.9%). Male patients exhibited better prognoses in the 2-month post-onset period in another previous Korean study. The retrospective cohort study, which aimed to establish whether clinical prognostic factors differ according to H-B grade, found that among patients with severe facial palsy (initial H-B grades, 5–6), male had a more favorable outcome than female (odds ratio, 1.12) [23].

Many prior studies have shown that a <90% degeneration rate of the affected facial nerve has a favorable outcome [5–7]. Our ROC analysis showed that the best cutoff values of preserved ENoG amplitude (%) for sensitivity and specificity were 72.0%, 92.5%, 78.5%, and 89.5% in the frontalis, nasalis, orbicularis oculi, and orbicularis oris muscles, respectively. The nasalis and orbicularis oris muscles displayed similar outcomes to those in previous studies, whereas the frontalis and orbicularis oculi muscles showed stricter cutoff values (72.0% and 78.5%, re-

spectively). It seems that the more severe the nerve damage, the more variable the regenerative potential for each branch of the facial nerve, resulting in heterogeneous regeneration patterns. Since prior studies did not consider facial palsy severity, a 90% prognostic threshold cannot be uniformly applied to severe facial palsy.

The pathophysiology of idiopathic facial palsy remains unclear; it is considered that an inflammatory mechanism is a major contributor to the disease pathogenesis. Cayir et al. [11] reported that higher CAR and NLR levels were associated with poor prognoses in patients with Bell's palsy. Our study did not find significant differences in laboratory data (CAR, NLR, and WBC count) between the two groups in the univariate analysis or logistic regression model. These inflammatory markers can identify levels of inflammation at the acute phase; however, their responses to strong anti-inflammatory medications (such as corticosteroids) vary among individuals. Additionally, there were differences in the time when anti-inflammatory medication was administered, the time when the blood test was performed, and the pathophysiology of the patients. Eliminating this variable response rate could yield a better probability of predicting disease progression; this may be achieved by controlling the blood sampling time before treatment.

This study has some limitations. First, in excluding patients who underwent electrodiagnosis other than 2–4 weeks from symptom onset, 66 patients (64.1%) with missing values were detected, resulting in bias. However, Wallerian degeneration in the peripheral facial nerve takes 72 h after symptom onset to reflect in electrodiagnostic tests and approximately 21 days for complete degeneration [3,4]. Thus, a strength of this study is the inclusion of only electrodiagnostic data collected after this period (at least 2 weeks after the onset of symptoms). Second, the laboratory data of five patients (17.2%) in the good recovery group were unavailable, and the mean imputation method was used to obtain the missing values. Third, the follow-up period was limited to 2 months. In most cases of facial palsy, the complete recovery rate reaches a plateau after 3 months from onset [24]. However, in some cases, recovery occurs after 1 year; therefore, a longer follow-up period would have yielded ENoG

amplitude values that can predict the final recovery state.

In conclusion, this study suggests that the female sex and lower ENoG of the nasalis muscle acquired 2–4 weeks from symptom onset have negative prognostic values for the 2-month functional outcome of severe facial palsy.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Woo M, Lee HH. Methodology: Woo M, Lee HH. Formal analysis: Woo M, Yuk D, Choi SW. Project administration: Woo M, Lee HH. Visualization: Woo M, Yuk D, Choi SW. Writing – original draft: Woo M. Writing – review and editing: Woo M, Lee HH, Lee J. Approval of final manuscript: all authors.

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Association Between Mobilization Level And Activity of Daily Living Independence in Critically Ill Patients

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Objective: To examine the association between the mobilization level during intensive care unit (ICU) admission and independence in activity of daily living (ADL), defined as Barthel Index (BI) ≥ 70.

Methods: This was a post-hoc analysis of the EMPICS study involving nine hospitals. Consecutive patients who spend >48 hours in the ICU were eligible for inclusion. Mobilization was performed at each hospital according to the shared protocol and the highest ICU mobility score (IMS) during the ICU stay, baseline characteristics, and BI at hospital discharge. Multiple logistic regression analysis, adjusted for baseline characteristics, was used to determine the association between the highest IMS (using the receiver operating characteristic [ROC]) and ADL.

Results: Of the 203 patients, 143 were assigned to the ADL independence group and 60 to the ADL dependence group. The highest IMS score was significantly higher in the ADL independence group than in the dependence group and was a predictor of ADL independence at hospital discharge (odds ratio, 1.22; 95% confidence interval, 1.07–1.38; adjusted p=0.002). The ROC cutoff value for the highest IMS was 6 (specificity, 0.67; sensitivity, 0.70; area under the curve, 0.69).

Conclusion: These results indicate that, in patients who were in the ICU for more than 48 hours, that patients with good function in the ICU also exhibit good function upon discharge. However, prospective, multicenter trials are needed to confirm this conclusion.

Keywords: Intensive care units, Rehabilitation, Activities of daily living, Postintensive care syndrome

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INTRODUCTION

Although the short-term prognosis of intensive care unit (ICU) patients has improved recently, long-term dysfunction has become increasingly important [1]. Physical dysfunction after ICU discharge results in the weakening of limbs and limitation of ADL, and it has been reported that 50%–70% of ICU patients develop physical dysfunction [2]. Therefore, improving the functional prognosis of ICU patients has been recognized as an important problem in intensive care medicine [3].

Physical dysfunction after ICU discharge can occur in all patients, but immobility is considered a major risk factor [4,5]. Therefore, early rehabilitation for physical dysfunction should begin immediately after admission to the ICU [6]. The effects of early rehabilitation are widely reported, including the prevention of delirium [7], shortening the length of mechanical ventilation [8] and shortening the length of stay in the ICU [9,10]. Although relatively short-term results have been increasingly reported recently, data on the relationship between the mobilization level in critically ill patients and activity of daily living (ADL) independence at hospital discharge are still lacking [11–13]. Previous studies examined the mobilization level of ICU patients and reported that patients discharged home had higher ICU mobility score (IMS) scores at discharge from the ICU than patients discharged to the facility. However, an analysis of cutoff scores to predict ADL independence in Japan has not yet been performed [14].

Insight into what mobilization level should be targeted during ICU stay for early recovery may help avoid increasing dependence on ADLs during the hospital discharge of critically ill patients. However, the targeted mobilization level during ICU stay for critically ill patients remains unclear. Therefore, this study investigated the relationship between the mobilization level during ICU admission and independence in ADL at hospital discharge. A post-hoc analysis of the EMPICS study [11], a multicenter prospective study of psychiatric symptoms in ICU patients three months after hospital discharge, was performed to investigate the association between the mobilization level during the ICU stay and ADL independence at hospital discharge.

METHODS

Study design, setting, and patients

This was a post-hoc analysis of the EMPICS study (Association between the achievement of Early Mobilization and Psychiatric

symptoms in Japanese Intensive Care Survivors, UMIN ID: 000036503) [11]. This EMPICS study was approved by the Ethics Committee of Nagoya Medical Center (No. 2018093) and eight other participating hospitals. We followed the STROBE guidelines and all methods in this study were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all patients. Consecutive patients, up to 25 in each participating hospital, who stayed in the ICU for more than 48 hours between June and December in 2019, were eligible for enrollment. Patients under 18 years of age, unable to walk independently before admission, with neurological complications, lack of communication skills due to preexisting mental diseases, or in a terminal state were excluded.

Early mobilization protocol

In this study, we sought to mobilize all patients equally and daily under the five-level protocol (level 1, passive range of motion and respiratory physical therapy; level 2, active range of motion; level 3, sitting exercise; level 4, standing exercise; and level 5, walking exercise) tailored to each participating hospital [11,15,16]. At each participating site, ICU physicians or physiotherapists referred to the protocol and decided each patient's rehabilitation level based on the patient's condition. To increase the mobilization level above level 3, it was necessary for the patient to meet the stability criteria listed in [Supplementary Table S1](#). All participating hospitals followed the evidence based expert consensus for early rehabilitation in the ICU of the Japanese society of intensive care medicine regarding the criteria for conducting each mobilization stage of the other five-level protocol [3]. All patients received at least one rehabilitation session per week for 20 minutes. In addition, after ICU discharge, physical or occupational therapists provided rehabilitation, such as muscle strengthening, balance, walking, and stair exercises, for more than 20 minutes on weekdays to each patient according to the rehabilitation policy in the general ward of each hospital. Therefore, in this study, it is difficult to confirm the relationship between the mobilization level after ICU discharge and ADL independence at hospital discharge. Detailed characteristics of the institutions are listed in [Supplementary Table S2](#).

Data collection

The mobilization level during the ICU stay was assessed daily by a physio-therapist using IMS. The IMS is a quick and easy method to measure bedside mobility in a critically ill patient. As a functional endpoint in ICU rehabilitation studies, the IMS

provides a sensitive 11-point ordinal scale, ranging from nothing (lying/passive exercises in bed, score 0), sitting in bed, exercises in bed (any activity in bed, score 1), passively moved to chair (score 2), sitting over edge of bed (score 3), standing (score 4), transferring bed to chair (score 5), marching on spot (at bedside, score 6), walking with assistance of 2 or more people (score 7), walking with assistance of 1 person (score 8), walking independently with a gait aid (score 9), and independent ambulation (score 10) [17]. At the time of ICU admission, the following basic patient information was recorded: age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment (SOFA) score, Charlson Comorbidity Index (CCI), Barthel Index (BI) before hospitalization, ICU admission diagnosis, ICU and hospital length of stay, the incidence of ICU-acquired weakness (ICU-AW) at ICU discharge, EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) at hospital discharge, [18] and in-hospital mortality.

Additionally, BI was measured at discharge. As in previous studies, ADL dependence was defined as BI<70 points [7,11,12,19], and mobilization was defined as being able to sit on the edge of the bed or a higher degree of mobility [9,11,12,19,20]. In this study, early rehabilitation was defined as within the first 72 hours after ICU admission [3]. BI pre-hospitalization was assessed at the time of admission to the ICU based on information from the family or patients if they were conscious. ICU-AW was defined as a Medical Research Council sum score (evaluated by a physical therapist)<48 at ICU discharge [21].

Statistical analysis

We compared patient characteristics by ADL independence at hospital discharge expressed as median (interquartile range) or the number of cases (%) in the data of both groups. For the analysis of continuous variable, the Mann-Whitney U-test was used for nominal variables, the χ^2 test or Fisher's exact test, as appropriate. Before using a non-parametric test, the distribution of each parameter was assessed with the Shapiro-Wilk test. Deaths were excluded from the analysis of ICU and hospital length of stays, as using the ICU and hospital length of stays for early deaths may incorrectly shorten the hospital days in the ADL dependent group.

To assess the association between the highest IMS and independence in ADL at hospital discharge, multivariable logistic regression was performed, adjusting for covariates such as age, BMI, CCI, BI before hospitalization, ICU admission diagnosis (sepsis of non-pulmonary origin status), and SOFA score at

ICU admission. These variables were selected based on the results of previous studies and our clinical interest [9,11,12,15,16]. Results are reported as odds ratio (OR) and 95% confidence interval (95% CI). Receiver operating characteristic (ROC) were constructed for ADL independence at hospital discharge and highest IMS during ICU stay and the area under the curve (AUC) was calculated. To further look for associations between highest IMS during ICU stay and other outcomes, we performed logistic regression analysis with length of ICU (>7 days) and hospital (>28 days) and EQ-5D-5L (>0.5) at discharge as objective variables. Variables were modeled as continuous data when appropriate or were dichotomized using clinically relevant cutoff values.

Next, the patients were divided into two groups for a sensitivity analysis based on changes in the SOFA score, to assess the progress in mobilization. In one group, the SOFA score improved or did not change from the time of ICU admission to the next day (unchanged SOFA score), whereas in the other group, the SOFA score had worsened (worse SOFA score). For sensitivity analysis, we restricted the number of covariates to four: age, BMI, CCI, and BI before hospitalization to prevent model over fitting. Variables in the model with $p<0.05$ from the lack-of-fit test were excluded from the results of this study considering non-fitting [22].

We then performed one subanalysis. We excluded those who died in hospital because the association between ADL independence and mortality is assumed to be bidirectional: ADL dependence may be a consequence of mortality. Covariates in the multivariate analysis included age, BMI, CCI, and prehospital BI.

All analyses were performed using the JMP software (version 13.0; SAS Institute Inc.). Statistical tests were two-sided, and statistical significance was defined as $p<0.05$.

RESULTS

Baseline characteristics

A total of 1,014 patients were admitted to the ICU. After the exclusion of patients younger than 18 years, unable to walk independently before admission, patients with neurological complications, lacking communication skills due to preexisting mental illness, and terminal patients, 203 patients remained. In all patients, the mobilization level activity was assessed by a full-time physiotherapist (Fig. 1). Independent ADL hospital discharge was observed in 143 patients (ADL independence group) but not in 60 patients (ADL dependence group, including death in

the hospital.

Table 1 shows the baseline characteristics of patients in the entire study cohort and in the ADL independence and ADL

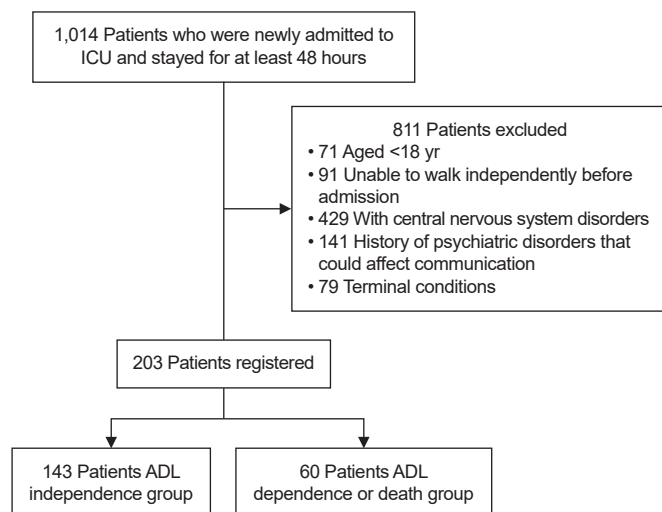


Fig. 1. Flow chart of the patient selection process. ICU, intensive care unit; ADL, activity of daily living.

dependence groups. Intergroup comparisons revealed significant differences (Table 1) in age ($p<0.001$), BMI ($p=0.004$), BI before hospitalization ($p=0.040$), SOFA score at ICU admission ($p=0.001$), highest IMS during ICU admission ($p<0.001$), ICU length of stay ($p<0.001$), incidence of ICU-AW ($p<0.001$) and EQ-5D-5L score at hospital discharge ($p<0.001$). In this study, 25 patients (12.3%) died during hospitalization and were included in the analysis as an ADL dependency group.

Relationship between ADL independence and the highest IMS in the ICU

No multicollinearity was found between the variables highest IMS, age, BMI, BI before hospitalization, sepsis, non-pulmonary status, and SOFA score at ICU admission. Performing multivariable logistic regression analysis using these variables, revealed that the highest IMS (OR, 1.22; 95% CI, 1.07–1.38; $p=0.002$), age (OR, 0.93; 95% CI, 0.89–0.96; $p<0.001$), and SOFA score (OR, 0.91; 95% CI, 0.83–1.01; $p=0.069$) were independent factors for independence in ADL at hospital discharge (Table 2). On performing multivariable logistic regression analysis with ICU (>7 days) and hospital length of stay (>28 days)

Table 1. Comparison of patient characteristics based the ADL independence at hospital discharge

Variable	All patients (n=203)	ADL independence (n=143)	ADL dependence (n=60)	p-value
Age (yr)	71 (61–79)	69 (57–76)	78 (70–85)	<0.001
Sex, male	131 (64.5)	96 (67.1)	35 (58.3)	0.262
Body mass index (kg/m ²)	23 (20–26)	23 (21–26)	22 (19–24)	0.004
Charlson Comorbidity Index	2 (1–3)	2 (1–3)	2 (0–3)	0.783
Barthel Index before hospitalization ^{a)}	100 (100–100)	100 (100–100)	100 (100–100)	0.040
ICU admission diagnosis				
Acute respiratory failure	43 (21.2)	30 (21.0)	22 (36.7)	0.074
Cardiovascular disease	74 (36.5)	48 (33.6)	10 (16.7)	
Gastric or colonic surgery	31 (15.3)	23 (16.1)	8 (13.3)	
Sepsis, non-pulmonary origin status	32 (15.8)	22 (15.4)	12 (20.0)	
Other diagnoses	23 (11.3)	20 (14.0)	8 (13.3)	
APACHE II score	20 (14–25)	18 (13–24)	21 (16–28)	-
SOFA at ICU admission	7 (4–10)	6 (3–9)	8 (6–10)	0.001
Highest IMS during ICU stay	6 (3–8)	7 (4–9)	4 (2–7)	<0.001
ICU length of stay ^{b)}	5 (4–9)	5 (3–7)	8 (4–14)	0.001
Incidence of ICU-acquired weakness	42 (20.7)	20 (14.0)	22 (36.7)	<0.001
Hospital length of stay ^{b)}	18 (10–25)	25 (19–44)	32 (21–67)	0.104
EQ-5D-5L at hospital discharge ^{b)}	0.7 (0.4–0.9)	0.8 (0.7–0.9)	0.4 (0.2–0.6)	<0.001
In-hospital mortality	25 (12.3)	0 (0)	25 (41.7)	-

Values are presented as median (IQR) or number (%).

ADL, activity of daily living; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; IMS, ICU mobility scale; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels.

^{a)}Barthel Index before hospitalization was scored at the time of ICU admission based on the information from the family or the patients if they were conscious.

^{b)}Excluding fatal case.

and EQ-5D-5L (>0.5 point) at discharge as objective variables, we found that EQ-5D-5L at discharge (OR, 1.14; 95% CI, 1.01–1.31; $p=0.039$) was significantly associated with the highest IMS (Table 3). Fig. 2 shows the ROC curve for the highest IMS during ICU stay as a predictor of ADL at discharge. The cutoff value was IMS 6 (specificity, 0.67; sensitivity, 0.70; AUC, 0.69).

Maximum level of activity from day 1 to 7

All patients in this study started rehabilitation within 48 hours. A total of 164 patients (80.8%) were mobilized (sit on the edge of the bed or a higher degree of mobility) within the first seven days of their ICU stay. On day 1 of ICU admission, 128 out of 203 patient (63.1%) underwent rehabilitation at the IMS 0 level, 51 patients (25.1%) at IMS 1–2, 8 patients (3.9%) at IMS 3, 11 patients (5.4%) at IMS 4–6, and 5 patient (2.5%) at IMS 7–10.

The number of patients who underwent rehabilitation with an IMS of zero decreased from 63% to 19% on day 3, and to 7% on day 7. The fraction of patients with IMS 1–2 did not change within seven days of ICU admission. The fraction of patients with IMS or more is low on ICU days 1 (12%) and 2 (26%), increased from day 3 (47%) to 5 (57%), and remained at the same level on ICU days 6 (56%) and 7 (64%) (Supplementary Table S3). All rehabilitation sessions were performed for 20 minutes regardless of intensity.

Sensitivity and subanalysis

Supplementary Fig. S1 and Table 4 show the results of the analysis of the relationship between independence in ADL at hospital discharge and the highest IMS in the ICU in the two

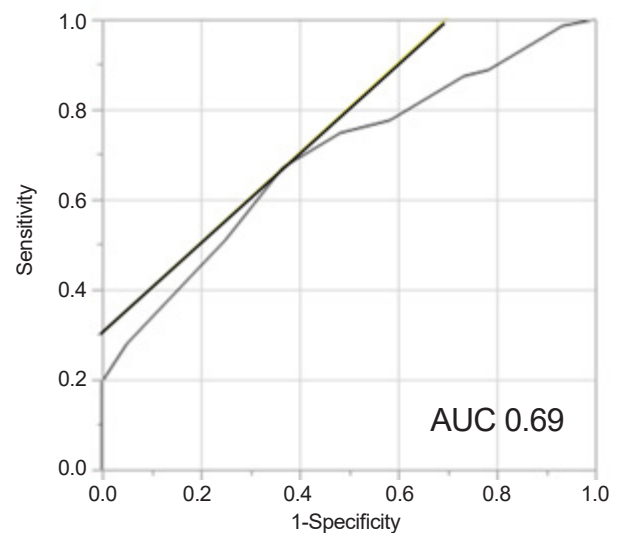


Fig. 2. Receiver operating characteristic curve for highest intensive care unit mobility scale and independence of activity daily living. AUC, area under the curve.

Table 2. Multivariable logistic regression analysis of independent variables for the activity of daily living independence at hospital discharge

Variable	Activity of daily living independence		
	Odds ratio	95% CI	p-value
Highest ICU mobility scale	1.22	1.07–1.38	0.002
Age	0.93	0.89–0.96	<0.001
Body mass index	1.04	0.96–1.14	0.296
Charlson Comorbidity Index	1.11	0.92–1.34	0.264
Barthel Index before hospitalization	1.01	0.97–1.04	0.574
Sepsis, non-pulmonary origin status	0.88	0.34–2.24	0.785
SOFA at ICU admission	0.91	0.83–1.01	0.069

Model χ^2 -test $p<0.01$; AUC, 0.81.

95% CI, 95% confidence interval; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Table 3. Association between highest ICU mobility scale and other outcomes, excluding fatal case

	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio ^{a)} (95% CI)	p-value
ICU length of stay (>7 day)	0.94 (0.84–1.05)	0.271	1.01 (0.89–1.15)	0.837
Hospital length of stay (>28 day)	0.91 (0.82–1.01)	0.068	0.96 (0.86–1.08)	0.526
EQ-5D-5L at hospital discharge (>0.5 point)	1.20 (1.07–1.36)	0.002	1.14 (1.01–1.31)	0.039

ICU, intensive care unit; 95% CI, confidence interval; EQ-5D-5L, Euro Qol-5 Dimensionss-5 Levels.

^{a)}The covariates in the multivariable analysis included age, body mass index, Charlson Comorbidity Index, Barthel Index before hospitalization, sepsis, non-pulmonary origin status, Sequential Organ Failure Assessment score at ICU admission.

Table 4. Multivariate logistic regression analysis of independent variables for activity of daily living independence at hospital discharge with unchanged and worse SOFA score

	ADL independence group with unchanged SOFA score (n=104)			ADL independent group with worse SOFA score (n=39)		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Highest IMS	1.43	1.16–1.76	<0.001	1.17	1.02–1.34	0.020
Odds ratio adjusted with covariates ^{a)}	1.23	1.03–1.46	0.016	1.14	0.95–1.41	0.095

SOFA, Sequential Organ Failure Assessment; ADL, activity of daily living; 95% CI, 95% confidence intervals; IMS, intensive care unit mobility scale.

^{a)}The covariates in the multivariable analysis included age, body mass index, Charlson Comorbidity Index, Barthel Index before hospitalization.

groups of SOFA scores. Logistic regression analysis showed that the highest IMS was significantly correlated with ADL independence at hospital discharge (OR, 1.23; 95% CI, 1.03–1.46; adjusted $p=0.016$) when the SOFA score remained unchanged. In the ROC curve, the cutoff value was IMS 7 (specificity, 0.85; sensitivity, 0.63; AUC, 0.76).

In contact, logistic regression analysis showed that the highest IMS in the worse SOFA score group was not significantly correlated with ADL independence at hospital discharge (OR, 1.14; 95% CI, 0.95–1.41; adjusted $p=0.095$). In the ROC curve, the cutoff value was IMS 5 (specificity, 0.53; sensitivity, 0.63; AUC, 0.65). In the subanalysis, our results remained unchanged even upon excluding those who died in the hospital ([Supplementary Table S4](#)).

DISCUSSION

This study examined the association between ADL independence at the hospital discharge of critically ill patients admitted to the ICU and the mobilization level during their stay in the ICU. The highest IMS during ICU stay was significantly higher in the group with ADL independence at hospital discharge. Multivariate analysis also showed a significant association between ADL independence at hospital discharge and the highest IMS during ICU stay. To our knowledge, this is the first report of the association between independence in ADL at hospital discharge and mobilization level during an ICU stay.

Multivariable analysis showed that the highest IMS score during ICU stay was strongly associated with independence in ADL at hospital discharge. A previous study also reported that IMS during ICU admission was a predictor of home discharge, and our study had similar results [13]. The primary results of this study suggest that good functioning during ICU stay may be significantly related to ADL independence at discharge. The Katz and Barthel Indices used in conventional rehabilitation assessment, do not change significantly in the ICU, and it is difficult to make a difference [3]. On the other hand, recently,

the IMS has been widely used early rehabilitation in the ICU because it can assess baseline function in more detail. Other measures of physical function that have been developed for use in the ICU include the Functional Status Score for the ICU [23], physical function in the ICU test [24], and medical research council scores [25]. However, there are limitations to the generalization in the ICU, such as the lack of reliability or validity evaluation in the ICU, and time-consuming measurements in these evaluation scales [26,27]. IMS has the advantage of being easy to assess, reliable when performed by a nurse or physiotherapist, takes less than a minute, and requires no special equipment. The IMS have demonstrated adequate levels of reliability when applied to diverse patient populations hospitalized in the ICU [13,28]. The advantages of IMS support its use in the ICU to measure a patient's daily mobility level. Furthermore, in this study, highest IMS during ICU stay was significantly associated with EQ-5D-5L at hospital discharge. The EQ-5D-5L primarily measures quality of life, with 3 out of 5 items related to ADL. Therefore, IMS may show an association not only with physical function, but also with physical quality of life at hospital discharge, suggesting that future studies should examine the relationship between mobilization level and other outcomes.

The area under the ROC curve showed similar results to previous studies on home discharge outcomes with 70% sensitivity, 67% specificity, and 69% accuracy [29]. Patients in this study were age older, tended to be more severe than in previous studies, and may have been influenced by the patient's condition (i.e., sedation or hemodynamic instability) in their degree of mobility in the ICU [13,23]. The IMS showed considerable accuracy in predicting independence in ADL with an AUC of 0.76 in the group worse SOFA score had not worsened since the ICU admission (unchanged SOFA group). In the study by Tipping et al. [29], the ROC curve for IMS was not determined. However, the higher the IMS at the time of ICU discharge, the better the discharge prediction by the logistic regression model. This seems logical from a clinical viewpoint, as more functional patients

tend to perform ADL independently after the acute phase.

The IMS rating, which provided the highest accuracy for early determination of whether a patient was independent of ADL at hospital discharge had a strength of six or higher. A Japanese multicenter study investigating the safety of early mobilization reported that the incidence of adverse events increased with the mobilization level beyond standing [15]. Delayed mobilization due to adverse events occurring while the patient is standing may be associated with independence in ADL at hospital discharge. Furthermore, the results of the subanalysis of this study showed that the highest IMS during the ICU stay was not associated with ADL independence at hospital discharge in patients who could not achieve the rehabilitation of $IMS \geq 6$ or worse SOFA score worsened during the ICU stay. Our study suggests that if the rehabilitation of IMS 6 or higher cannot be achieved in the ICU, the time to the first IMS of 6 or higher, including the total length of hospital stay, may predict ADL independence at hospital discharge. In this study, the incidence of ICU-AW was significantly higher in the ADL dependent group. There is a possibility that ICU-AW had a direct impact on the highest mobility level, and future investigation may be necessary the relationship between the incidence of ICU-AW and the highest IMS.

This study had some limitations. First, confounding factors that could not be adjusted for may have had a relatively large impact on the results. Second, the results were limited to short-term follow-up. Third, whether patients could receive rehabilitation at the bedside level or higher depended on the rehabilitation policy of each participating hospital. Fourth, the IMS is itself an assessment tool, consisting of classifications based on functional activity. Factors such as muscle strength, degree of ventilator support, and oxygen demand can cause patients to perceive different intensities during the same mobilization phase. This study may have lacked objectivity as a method for expressing exercise intensity. Future studies should use the variable “amount of rehabilitation” instead of focusing solely on mobilization level. A multicenter randomized controlled trial with more patients is needed to further validate these findings and investigate causality.

For the above reason, good function during ICU stay is significantly related to independence in ADL at hospital discharge. This finding argues with future prospective multicenter trials. In patients whose SOFA score do not show deterioration, the mobilization level achieved during ICU admission could be an important parameter for maximizing the beneficial effect on patient outcomes.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

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SUPPLEMENTARY MATERIALS

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Instructions for authors

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Describe the participants or research materials of the study, and explain in detail the inclusion and exclusion criteria for both the experimental and control groups. Describe the experimental methods in a logical and systematic manner so that they can be reproducible by another investigator. Experimental drugs should be stated in the generic name. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name. When using experimental devices or other products, state the brand name then follow with the name of the manufacturer, in parentheses, e.g., Flow Cytometer (Coulter Electronic Inc.). To ensure anonymity during the peer review process, the authors' affiliations or institutional setting of the study should not be revealed. Statistical analysis and criteria for determining significance should be described in enough detail to allow the knowledgeable reader with access to the original data to verify the reported results. An ethics statement should be placed here when the studies are performed using clinical samples or data, and animals.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

(4) Results

Summarize and describe logically the significant findings and trends observed in the results using text, figures and tables. Avoid extensive repetition of contents of the tables and figures in the text.

In statistical expression, mean and standard deviation should be described as mean \pm SD, and mean and standard error as mean \pm SE. In general, p-values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; p-values smaller than 0.001 should be reported as $p < 0.001$.

(5) Discussion

Interpret the results in respect to the objective of the study, and describe differences with previous studies and significant findings which lead to the deduction of the conclusion. Refrain from excessive review of historic studies, textbook facts, or irrelevant references. Accentuate newly obtained observations from the study, and include significant limitations of the study.

(6) Conflicts of interest

Any potential conflicts of interest relevant to the manuscript should be described. If there are no conflicts of interest, authors should state that none exists.

(7) Funding information

All sources of funding applicable to the study should be stated here explicitly. All original articles, editorials, reviews, and new technology articles must state funding sources for the study.

(8) Author contribution

The individual contributions of the authors to the manuscript should be specified in this section.

(9) Acknowledgments

Persons who have made contributions to the study, but who are not eligible for authorship can be named in this section. Their contribution must be specified, such as data collection, financial support, statistical analysis, or experimentation. The corresponding author must inform the named contributor of the acknowledgment, and acquire consent before manuscript submission.

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- For more on references, refer to the NLM Style Guide for Authors, Editors, and Publishers (<http://www.nlm.nih.gov/citingmedicine>).

Journals

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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 sumatriptan. *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.

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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., * $p < 0.05$, ** $p < 0.01$. *** $p < 0.001$).

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