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Editorial Office
Department of Rehabilitation Medicine, Seoul National University Hospital
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Rehabilitation Strategies for Patients With Spinal Muscular Atrophy in the Era of Disease-Modifying Therapy

Hyung-Ik Shin, MD, PhD

Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, Korea

The impact of disease-modifying therapy ranges from cure to no impact with a wide range of intermediates. In cases where the intermediate group reaches a plateau after the acquisition of some muscle strength, it is necessary to set a functional level appropriate for increased motor power and establish a long-term exercise plan to maintain it. As the disease status stabilizes and the life span increases, early nonsurgical interventions are required, such as using a standing frame to prevent joint contracture, applying a spinal brace at the early stage of scoliosis, and maintaining sitting postures that exaggerate lumbar lordosis. In cases where scoliosis and hip displacement occur and progress even after conservative managements are implemented, early referral to surgery should be considered. Oromotor activity and swallowing function are influenced not only by the effects of disease-modifying drugs, but also by post-birth experience and training. Therefore, although the feeding tube cannot be removed, it is necessary to make efforts to simulate the infant feeding development while maintaining partial oral feeding. Since the application period of non-invasive ventilators has increased, it has become more important to prevent long-term complications such as facial abrasion, skin allergy, orthodontic deformities, and maxillary flattening caused by the interface. Dual ventilator mode or interface can also be utilized.

Keywords: Spinal muscular atrophy, Disease-modifying therapy, Muscle strength, Oromotor activity, Noninvasive ventilation

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Correspondence:
Hyung-Ik Shin
Department of Rehabilitation Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: +82-2-2072-3218
Fax: +82-2-745-2560
E-mail: hyungik1@snu.ac.kr

INTRODUCTION

Spinal muscular atrophy (SMA), an autosomal-recessive disorder characterized by motor neuron degeneration and progressive skeletal muscle weakness, is caused by the deletion of the survival motor neuron 1 (*SMN1*) gene located at chromosome 5q13. The SMN protein is required for motor neuron development and viability. The *SMN2* gene is a homologous gene with variable copy numbers, producing only small amounts of SMN protein. Although SMN2 fails to fully compensate for the loss of SMN1, the SMN2 copy number is the major SMA disease predictor and correlates inversely with disease severity. However, since the SMN2 copy number imperfectly predicts the severity, it is expected that other related genetic factors exist [1].

Since the late 2010s, positive clinical study results using disease-modifying drugs have been reported. The Food and Drug Administration has approved three drugs for SMA: (1) nusinersen (Spinraza®) injected at intervals of 4 months after the implementation of a loading dose through the intrathecal injection route [2,3]; (2) risdiplam (Evrysdi®), orally administered, small-molecule splicing modifier [4]; and (3) onasemnogene abeparvovec-xioi (Zolgensma®) where only a single dose is im-

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plemented through the intravenously administered, adeno-associated virus vector–based gene-transfer mechanism [5].

With the enterprise of drug treatment for SMA, it is mandatory to consider extended survival and enhanced motor function, which are different from the previously known typical trajectories of this disease. These range from remaining asymptomatic—i.e., cure—to having no impact and with a wide range of intermediates; for example, slower than normal acquisition of some motor function skills, such as sitting or assisted walking, reaching a plateau [6].

With regard to rehabilitation strategies for patients within the intermediate drug impact range, experience and scientific evidence remain scarce, and a consensus has not been established. In this review, preexisting rehabilitation strategies are summarized per domain of rehabilitation treatment, and issues to be considered when establishing rehabilitation strategies in the era of disease-modifying treatment are additionally described.

CLINICAL CLASSIFICATION

Traditionally, the severity of this disease is classified into types 0, 1, 2, 3, and 4, depending on the clinical features. Type 3 is divided into types 3A and 3B, depending on the onset of weakness before or after three years. Based on the head control achievement and signs in the neonatal period, type 1 can be divided into types 1A, 1B, and 1C, as shown in Table 1 [7].

With the advent of drug treatments for SMA, alterations from the typical SMA course are expected, resulting in new phenotypes ranging from delayed onset to stopping the progression, reversing, or even curing the disease. The maximal motor function can be sustained as a child grows or may deteriorate more slowly over time. Changes in motor function may or may not correlate with the bulbar function (the ability to handle oral secretions, feeding, and vocalization), respiratory function, or orthopedic issues [6].

These issues are influenced not only by the effects of drugs, but also by experience, rehabilitation therapy, and preventive management during growth.

Validated outcome measurement tools for the SMA motor function include the revised Hammersmith score [8], revised upper limb module [9], 6-minute walk test [10], Hammersmith functional motor scale-expanded [11], and Children's Hospital of Philadelphia infant test of neuromuscular disorders [12].

PREVENTION OF SKELETAL DEFORMITY

Prevention of joint contracture

An active assisted range of motion (ROM) exercise technique can be implemented, where the therapist or equipment helps the patient generate muscle power to achieve ROM, or a passive ROM technique without using one's muscular strength. Since contractures in the major joints of lower extremities, such as the hip, knee, and ankle joints, hinder weight-bearing activity, preventive ROM exercises are necessary even when a contracture

Table 1. Classification of spinal muscular atrophy

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	*SMN* copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..	Four or more copies of *SMN2*

SMN, survival motor neuron. Reprinted from Lancet Neurol 2012 (11) Mercuri E, Bertini E, and Iannaccone ST, Childhood spinal muscular atrophy: controversies and challenges, pp. 443–52, with permission from Elsevier [7].

has not developed.

Using a standing frame not only allows age-appropriate positioning but also effectively prevents lower extremity joint contractures. The joint contracture directions include ankle plantar flexion and, knee, hip, wrist, and elbow flexion. When standing in a standing frame, lower-extremity bracing support (e.g., knee-ankle-foot orthoses or ankle-foot orthoses) can be provided to optimize joint alignment and mitigate excessive valgus forces at the knee and ankle joints [13]. The hip joint should be placed in slight abduction to optimize the hip congruence. Consistent use of 3–7 times per week is usually feasible if use of a stander is tolerated [13].

Unlike the cases of Duchenne muscular dystrophy [14,15], operative interventions to relieve lower extremity joint contractures have not been described in the existing literature. Future research is required on the role of the operative management of joint contractures in the era of disease-modifying treatments. In particular, when the motor function is stabilized in a plateau state and no weight-bearing activity can be implemented owing to joint contractures, it could be required to consider operative intervention.

Scoliosis

Progressive scoliosis due to deteriorating axial muscle strength impairs respiratory function and functional activities, such as maintaining a sitting position. Wijngaarde et al. [16] reported that 60% of patients with SMA type 1 through 4 had scoliosis, and 34% underwent scoliosis surgery in their Dutch cohort. The surgical probability was much higher for SMA types 1C and 2 at 77% and 84%, respectively. These results suggest that periodic radiographic follow-ups are essential. Merlini et al. [17] observed that when children with SMA begin to sit, their backs become kyphotic and between two and four years of age, a scoliotic curve developed. The same was observed in patients with mild SMA when they stopped walking. Kerr et al. [18] reported in their biomechanical study that spinal stability was improved by inducing a lumbar lordosis in patients with Duchenne muscular dystrophy. They speculated that this stability (e.g., tolerance to lateral loading) was associated with locking of the articular facet joints without the contribution of spinal musculature. Therefore, it could be possible to help prevent the development of scoliosis through the application of a seat device that exaggerates and maintains lumbar lordosis by utilizing a biangular backboard, lumbar pad, and shoulder strap. When scoliosis occurs, a spinal orthosis attempts to delay further progression using spinal support at three points of the controlling mechanism. Spine flexibility or reducibility should be maintained to ensure the effectiveness of braces [19]. To evaluate flexibility, the Cobb angle can be compared between the sitting position, where gravity is applied, and the supine position, where gravity is eliminated. Choi et al. [20] reported that scoliosis in patients with Duchenne muscular dystrophy was fully reducible at the early stage and became structural. These results suggest that spinal brace should be applied to scoliosis associated with neuromuscular disease at an early stage after the development of scoliosis.

When attempting a rigid spinal orthosis, poor patient tolerance is a known difficulty in managing neuromuscular scoliosis using a brace [21]. Noble-Jamieson et al. [22] showed that the reduction in forced vital capacity owing to rigid spinal bracing was proportional to the angle of scoliosis. Therefore, they proposed a strategy that applies the spinal brace at an early stage of curve development.

Several researchers have attempted to overcome poor compliance with braces caused by skin pressure problems on the bony prominences and postprandial discomfort due to abdominal flanges. Accordingly, a few researchers have reported improvements in patient tolerance and sitting position in addition to achieving immediate scoliotic curve correction through changes in spinal brace design or materials [23-25]. However, long-term longitudinal studies on the effectiveness of preventing further progression of scoliotic curves are scarce. When conservative methods such as external bracing and spinal casting are not efficient in preventing curve progression, surgical treatment is required. However, definitive spinal fusion could be detrimental in young children with skeletal immaturity, who have a significant potential for growth and pulmonary development. To allow vertebral growth before the end of skeletal maturity, several growing rod lengthening techniques without fusion have been developed [26].

There is no impact on intrathecal drug delivery of nusinersen, even when a surgical operation is performed using such methods since posterior fusion is not performed. To reduce the burden of repeated surgical procedures for rod lengthening in young patients, less invasive or noninvasive rod lengthening techniques have been developed [27-30]. In particular, lengthening can be performed non-surgically at intervals of 3–6 months on an outpatient basis after implanting magnetically controlled growing rods (MCGR). Results regarding curve correction and spinal growth during MCGR treatment are encour-

aging [28,31,32]. Advances in these technologies have enabled early surgical referrals.

Hip instability

Ulusaloglu et al. [33] reported that, in the SMA patient group, the prevalence of hip displacement (HD) was 75.6%, with a mean age of onset of 4.6 years. When stratified by severity (types I, II, and III), the prevalence/mean age (years) of onset was 84%/3.1, 80%/5.8, and 36%/9.0, respectively. The prevalence and clinical characteristics of HD in the presence of disease-modifying drugs remain unclear.

As in the case of the cerebral palsy group, monitoring by pediatric orthopedist or physiatrist is needed when the migration percentage (MP) exceeds 30% [34]. When MP<40%, hip abduction postural management, neuromotor treatment, and spasticity management should be implemented; when 40%<MP<50%, preventive surgery such as soft tissue release or varus de-rotation osteotomy, can be implemented. When MP>50%, reconstructive surgery, including pelvic osteotomy, could be necessary [35]. The same surveillance programs for the early detection of HD that allow timely management can be used in the SMA group as well [33].

However, since the SMA group is not associated with adductor spasticity, the impact of postural management and spasticity treatment on HD will be much lower in comparison with the cerebral palsy group. In this context, early bone surgery may be required instead of soft tissue surgery. In the era of disease-modifying drugs, it is apparent that functional or therapeutic ambulatory patients require early orthopedic intervention.

Traditionally, when HD occurred in patients with non-ambulatory SMA and symptoms such as hip pain and functional difficulties (positioning, skin and perineal care) were not observed, no surgical treatment was performed considering the progressive nature, high rate of recurrent dislocation, and limited life span of the disease [36,37]. However, in a medical environment where the lifespan of SMA patients is substantially extended, orthopedic surgical intervention may also be required due to the following reasons: (1) HD may have an impact on the development and progression of scoliosis. (2) When HD exists, it is difficult to facilitate bone health through passive standing. (3) HD induces pelvic obliquity, making the sitting posture inappropriate. Temporary medial hemi-epiphysiodesis of the proximal femur which is much less invasive and can minimize the possibility of acetabular dysplasia, could be considered [38].

No brace application has been suggested to prevent HD or slow its progression. Exercises facilitating the contraction of the hip abductor muscles (e.g., gait training) could contribute to minimizing HD.

Bone health

Even young children with SMA are at risk of severe bone fragility. Researchers have provided evidence of reduced bone formation [39] and increased bone resorption [40,41], resulting in a negative effect on bone mass over time in patients with SMA. Although Kroksmark et al. [39] reported that bone mineral density was higher in children with better motor function, knowledge gaps still exist regarding the bone mineral density and physical activity in addition to the role of the SMN protein in bone remodeling. The high incidence of osteopenia and fractures in SMA patients may not be simply attributed to muscle weakness and a lower level of physical activity [42,43].

Periodic dual-energy X-ray absorptiometry analysis is necessary to monitor bone density. In case with history of fractures, the administration of bisphosphonates should be considered. Wasserman et al. [43] reported that the femur was the most common fracture location (43.9%).

In an era where the lifespan is extended due to disease-modifying drugs, facilitating weight bearing activities such as standing or gait training and preventing joint contractures, which may hinder such activities, are essential.

EXERCISE

Resistance and aerobic training

Exercise enhanced motor neuron survival in the SMA mouse model [44]. In preclinical studies, exercise is related to a change in the alternative splicing pattern of exon 7 in the *SMN2* gene, leading to increased amounts of exon 7-containing transcripts in the spinal cord of trained mice [44,45].

However, the benefits have not been demonstrated in human studies. Bora et al. [46] reported that when a 12-week arm cycling exercise protocol was implemented in five patients with SMA type 2, the active cycling distance and duration significantly improved. However, these benefits were not associated with SMN2 copy number, SMN protein level, insulin-like growth factor 1, or binding protein 3 levels.

Lewelt et al. [47] reported that a 12-week supervised, home-based, 3 days/week progressive resistance training exercise program is feasible, safe, and well tolerated in children with SMA. In this study, the exercises were performed without weight for

at least one week. Once a participant was able to complete 2 sets of 15 repetitions, resistance was added. A free weight was attached to the distal limbs of the wrist and ankle. Each exercise was progressed by adding a weight in 0.08 kg increments. The weight increased until the participant scored 6/10 (somewhat hard) or 8/10 (hard) on the Children's OMNI-Resistance Exercise Scale of perceived exertion at the end of the second set [47]. To this date, whether exercise has a protective or restorative effect on motor neurons remains unclear. The purpose of muscle strengthening exercises may be just utilizing the available muscle tissue to prevent further muscle deterioration caused by disuse and lower levels of activity.

Although there have been limited studies on aquatic therapy for the SMA, several authors suggest that it has the potential to enhance activities of daily living and muscle strength in both sitters and non-sitters [48-50].

In a study conducted before the era of disease-modifying therapy, therapeutic electrical stimulation was applied to the deltoid and biceps muscles of patients with SMA types 2/3 for 6 months, and based on a comparison with the control group, no improvement in muscle strength was demonstrated [51].

Functional activity

The impact of disease-modifying therapy ranges from cure to having no impact with wide range of intermediates. In cases where the intermediate group reaches a plateau after the acquisition of muscle strength, it is necessary to set a functional level appropriate for increased motor power and establish a long-term exercise plan to maintain it. For example, in cases where the lower extremity strength of sitter patients increases through disease-modifying therapy, therapeutic gait training can be attempted using a body support walker and ankle foot orthosis, although walking with a conventional walker or crutch is still impossible. Each manufacturer provides diverse body support walker designs and components, such as saddles and trunk support modules.

As observed in the cerebral palsy group, hip abductor weakness is one of the mechanisms of HD. This affects the lateral alignment of the proximal femoral growth plate, leading to coxa valga and hip subluxation [52]. In the SMA group, the abnormal physeal alignment could be causally related to weakness of the hip abductor muscles than to spasticity or muscle imbalance between the hip adductor and abductor muscles [38]. Therefore, gait training that activates the hip abductor muscles can be recommended in addition to passive standing exercise on a standing frame.

For non-sitters, a seat device or spinal orthosis should be manufactured to maintain a sitting posture with enhanced lumbar lordosis [53,54]. Di Pede et al. [54] suggested the following methods for manufacturing the spinal orthosis: a plaster cast is taken in a sitting position with a cervical traction at approximately 1/4–1/5 of the body weight. An abdominal opening is made to permit the movement of diaphragm. An elastic strip applied over this opening aids expiration to improve the abdominal wall response. Catteruccia et al. [53] applied an orthosis called the Garches brace not only to prevent the progression of spinal deformities but also to maintain a sitting position with head support.

SWALLOWING AND NUTRITION

McGrattan et al. [55] reported in their 24 months follow-up study that patients with SMA type 1 who received onasemnogene abeparvovec treatment achieved and maintained their swallowing function; 92% (60/65) of patients had a normal swallow, and 75% (49/65) achieved full oral nutrition. This encouraging result is clearly different from the known trajectory: swallowing function deteriorates at an approximate age of 6 months [56]. However, a report also states that, even after the start of nusinersen, impaired feeding and swallowing remain compromized in infants with SMA type 1 [57]. As infants with SMA type 1 grow, it is necessary to record and evaluate the change of swallowing function using tools such as Neuromuscular Disease Swallowing Status Scale (NdSSS) [58] and/or videofluoroscopic swallowing study. As described in the NdSSS staging, there are cases in which partial oral feeding is performed between full oral feeding and tube feeding, and the food texture of partial oral feeding should be escalated to be in line with ordinary weaning food. A small amount of oral feeding challenges may be attempted even with the findings of aspiration in infants/young children with tracheostomy [59]. A partial oral feeding strategy is also necessary for the transition from tube feeding to full oral feeding [60].

Sucking is dependent on both neural maturation and experience; therefore, even infants with SMA type 1 require nutritive/non-nutritive sucking trials immediately after birth in this era of disease- modifying treatment. Once a baby is 6 months or older, it is very difficult to establish bottle feeding for the first time [61]. Furthermore, the oromotor activity depends on maturation and experience. For example, lateral tongue movements

are texture-dependent, and therefore do not emerge unless the child is given a particular texture that requires these skills [62]. If tube-fed children are not exposed to a wide variety of tastes and textures in their first year of life, it may be difficult to achieve oral acceptance at a later age [60]. The second half of the first year is a period of rapid maturation for chewing skills [63].

RESPIRATORY REHABILITATION

Gonski et al. [64] reported that stabilization of respiratory outcomes occurred within 2 years of commencing nusinersen therapy, while some of the SMA type 2/3 cohorts ceased noninvasive ventilation (NIV). Pechmann et al. [65] reported that, when respiratory function improved with nusinersen administration, it was not equivalent to the motor function.

Breathing exercises, such as the active cycle of breathing techniques and autogenic drainage have rarely been implemented in patients with SMA. Even in patients with SMA and relatively preserved respiratory muscle function, the benefits of breathing exercise have not yet been investigated. In the future, it would be necessary to conduct a study to investigate whether inspiratory muscle training has synergistic or additive effects on improving respiratory function induced by disease-modifying drugs [66]. Additionally, modifying traditional breathing exercises would be possible by concurrently implementing active inspiration and passive insufflation using a manual resuscitator or NIV.

Airway clearance techniques should be implemented before the development of respiratory symptoms. These techniques can be classified as cough augmentation, mucus mobilization and postural drainage. Cough augmentation techniques include mechanical insufflation-exsufflation (MI-E), manually assisted cough, lung volume recruitment (breath stacking), and intermittent positive pressure breathing. The manually assisted cough immediately after breath stacking will be effective from the point when the peak cough flow (PCF) drops below 270 $L \cdot min^{-1}$ [67]. The patient receives an assisted inspiration from a manual resuscitator and is instructed not to breathe out. This maneuver is then repeated one to three times. The purpose of this technique is to obtain an augmented inspiratory vital capacity (lung insufflation capacity) beyond the spontaneous vital capacity of a patient. By securing the lung insufflation capacity, atelectasis prevention can be promoted and cough flow can be increased. MI-E delivers positive pressure during inspiration to promote maximal lung inflation, followed by an abrupt change to negative pressure in the upper airway, thereby producing an augmented cough. MI-E can generate a higher PCF than manually assisted cough methods, and patients are more likely to benefit from it if the PCF is <160 $L \cdot min^{-1}$ [68]. MI-E can be used in infants and young children, although it is challenging even for experienced caregivers to synchronize MI-E with the patient's own breaths [69].

Mucus mobilization techniques include intrapulmonary percussive ventilation (IPV), chest oscillations using a vibration vest, and assisted autogenic drainage. Because IPV and chest oscillation techniques are passive therapies that do not require patient compliance, they can be implemented in very young children. The postural drainage technique can be implemented in the side-lying or prone position. It is preferable to focus on a few specific postures to enhance compliance. For example, drainage can be performed comfortably in the prone position if the patient lies face down with a pillow placed diagonally across the thorax and abdomen, with the chest lower than the buttocks.

In patients with SMA, hypoventilation due to respiratory muscle weakness does not cause symptoms in the early stage and has a clinical course of isolated nocturnal alveolar hypoventilation without daytime hypoventilation [70]. Several authors have suggested initiating NIV at this point. In a state where acute respiratory exacerbations are caused by triggers such as upper respiratory infections, the initiation of NIV is psychologically more stressful and difficult than applying it before symptoms occur [71]. To determine when to initiate NIV, nocturnal transcutaneous carbon dioxide tension can be directly measured [70]. However, this is limited as it requires hospitalization and the maintenance of sensitive equipment. Therefore, maximal in/expiratory and sniff nasal pressures are commonly measured to predict the possibility of nocturnal hypoventilation and to decide when to hospitalize [72,73]. Sniffing is a natural maneuver that many children over the age of 3–4 years find much easier to perform [74].

When respiratory muscle weakness progresses, additional ventilator support during the daytime becomes necessary. NIV interfaces may cover the nose (nasal mask), the nose and the mouth (oronasal mask), and the face (full face mask). The nasal pillow-type interface is a minimal contact interface that is also available to children, and there may be a significant preference. As the duration of NIV application has increased owing to the prolonged lifespan caused by disease-modifying drugs, it has

become more important to prevent long-term complications such as facial abrasion, skin allergy, orthodontic deformities, and maxillary flattening in children. To alleviate the complications caused by the interface, two different interfaces can be applied separately during the daytime and nighttime. In particular, the mouthpiece interface can be used during the day as vocalization or feeding may feel more comfortable. Many ventilator manufacturers provide dual mode setting.

Training is essential for both caregivers and patients as they should be familiar with applying and removing the NIV interface and device. In addition, they should be appropriately trained in emergency situations, such as mucus plugging in the tracheal cannula tube that may occur at home to tracheostomized children [75]. It is necessary to check caregivers' skills before discharge. Visits by trained nurses and/or technicians are important factors for the successful implementation of home NIV program.

CONCLUSION

Disease-modifying drugs affect motor performance, respiratory function, swallowing and oromotor function, and skeletal development in children with SMA. These issues are influenced not only by the effects of drugs but also by post-birth experience and multidisciplinary management, which necessitates a comprehensive team approach. A consensus on the changes needed in rehabilitation strategies and techniques has not been established in this era of disease-modifying therapies. Nevertheless, it is clear that rehabilitation interventions are increasingly proactive in terms of extended lifespan and stabilized disease status.

CONFLICTS OF INTEREST

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ORCID

Hyung-Ik Shin, https://orcid.org/0000-0001-8805-3104

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Effect of Pre- and Post-Dialysis Exercise on Functional Capacity Using Portable Ergometer in Chronic Kidney Disease Patients

Tae-Seok Chae, MD[1], Da-Sol Kim, MD, PhD[1,2], Myoung-Hwan Ko, MD, PhD[1,2], Yu Hui Won, MD, PhD[1,2]

[1]*Department of Physical Medicine and Rehabilitation, Jeonbuk National University Medical School, Jeonju, Korea*
[2]*Research Institute of Clinical Medicine of Jeonbuk National University–Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea*

Objective: To assess whether performing exercises during hemodialysis reduces the risk of developing intradialytic hypotension and enhances exercise capacity in patients with chronic kidney disease.
Methods: This study included patients aged ≥18 years undergoing hemodialysis. Participants performed exercises using a portable lower extremity ergometer during hemodialysis sessions for 3 weeks. Data regarding walking distance, knee strength, quality of life, fat-free mass, arterial pressure, blood pressure, heart rate, frequency of intradialytic hypotension, fatigue, and duration of hemodialysis were collected and analyzed.
Results: Significant improvements in walking distance and knee strength were observed following the implementation of exercise training during hemodialysis. Although there was no significant reduction in the frequency of intradialytic hypotension, a decreasing trend was noted. Other parameters such as quality of life and fatigue did not show significant changes.
Conclusion: Using a portable ergometer during hemodialysis improved exercise capacity and knee strength in patients with chronic kidney disease. There was a trend toward reduced intradialytic hypotension, suggesting potential cardiovascular benefits. Further research with larger sample sizes is needed to confirm these findings.

Keywords: Kidney disease, Dialysis, Hypotension, Exercise, Muscle strength

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Correspondence:
Yu Hui Won
Department of Physical Medicine and Rehabilitation, Jeonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju 54907, Korea.
Tel: +82-63-250-1820
Fax: +82-63-254-4145
E-mail: wonyh@jbnu.ac.kr

INTRODUCTION

A reduction in functional ability and quality of life has been observed in patients with chronic kidney disease (CKD) [1,2]. Symptoms associated with CKD, such as nausea, dizziness, and cramps, can adversely affect the quality of life and the ability to tolerate hemodialysis (HD) [3]. Intradialytic hypotension (IDH), which occurs owing to the elimination of plasma fluid via ultrafiltration (UF) exceeding the rate of fluid replenishment, has often been observed in patients undergoing HD [4].

Various strategies, such as accurate dry weight assessment, minimizing excessive weight gain between HD sessions, fasting during HD sessions, appropriate adjustment of antihypertensive agents, sodium and UF profiling, cooling the dialysate, using dialysate with bicarbonate buffering or higher calcium concentration, administration of α1-adrenergic agonists, and convective treatments (hemofiltration and hemodiafiltration) have been implemented for the prevention and management of IDH

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[5-8]. Karmiel [9] reported that cycling exercises performed during HD led to an improvement in energy levels; supported cardiovascular health, muscle strength, and endurance; and a reduction in fatigue after HD sessions. Gołębiowski et al. [10] evaluated the stability of a bicycle-type lower extremity rehabilitation device, and used it to enhance the lower limb function of patients undergoing HD. Anding et al. [11] reported that exercise training during HD could enhance physical function and muscle mass, and improve cardiovascular risk factors, such as blood pressure (BP) and lipid profiles. Previous studies [2,12] have also reported an improvement in mood and overall quality of life following exercise training, in addition to a reduction in feelings of hostility and anxiety.

Many patients continue to face difficulties during treatment owing to the side effects associated with HD treatment, which often persist post-treatment and impact their daily lives, despite the advancements in HD technology. Prevention of these side effects plays a crucial role in ensuring patient compliance, avoiding early treatment termination, and maintaining the efficiency and effectiveness of HD. Frequent incidence of hypotension has been reported in previous studies involving exercise with an ergometer in a seated position, which makes receiving treatment for IDH challenging.

Considering these challenges and the potential for improvement, the primary aim of this study was to assess whether a 3-week exercise program for patients with CKD undergoing regular HD sessions could enhance walking ability as measured using the 6-minute walk distance (6-MWD), improve physical function, and reduce the frequency of IDH during dialysis.

METHODS

Participants

Patients with CKD aged 20–85 years who were undergoing HD at least twice a week between October 2017 to February 2022 were eligible for inclusion in this study. The eligibility criteria were as follows: age ≥18 years, having undergone HD for ≥3 consecutive months, having been undergoing ≥3 HD sessions per week, having at least one non-prosthetic lower limb, ability to walk (with the use of walking aids if necessary), and ability to provide informed consent. Only patients who had not received ergometer treatment previously were included in this study to maintain the integrity of blinding. By including only ergometer-naive patients, the study could better assess the true effects of the exercise intervention without the influence of previous exposure. All participants were evaluated for eligibility based on these criteria.

The exclusion criteria were as follows: having severe untreated cardiovascular diseases, being deemed medically unfit for participation in the clinical trial (e.g., unstable angina, recent myocardial infarction within the past 3 months, uncontrolled hypertension, or any condition that poses a high-risk during exercise), having significant cognitive impairments that hindered adherence to the examiner's instructions, and undergoing lower limb amputations. Furthermore, patients admitted to the hospital for reasons unrelated to the study (e.g., treatment for other acute medical conditions, elective surgeries, or complications from unrelated chronic diseases), as well as those presenting with hypertensive crisis (characterized by systolic BP [SBP] of >180 mmHg or diastolic BP [DBP] of >120 mmHg) [13] or other unfavorable events during the treatment phase, were excluded from the study. This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (CUH 2017-03-021); CRIS number (KCT0002537). Informed consent was obtained from all participants prior to commencing the study.

Sample-size calculation

The hypothesis used to determine the sample size for this study is based on results from previous studies and is defined as follows: The null hypothesis H_0 states that the pre-exercise 6-minute walk test score (μ_{pre}) is equal to the post-exercise score (μ_{post}), versus the alternative hypothesis H_1 which states that μ_{pre} is not equal to μ_{post}. To achieve a 5% significance level and 90% power, the sample size calculation is based on a formula that incorporates a dropout rate of 20%. In previous studies involving similar exercise interventions in kidney dialysis patients, the baseline pre-exercise 6-minute walk test score was 360±132 [11]. If a 10% improvement is clinically significant, the difference score was set at 36, and the standard deviation of the mean change was set at 133. The calculated sample size is 15 participants; considering a 20% dropout rate, the total required sample size is 19 participants (as indicated in the RESULTS section).

Study design

Overview

This study used a pre-post-test crossover single-group design and included 20 participants in the experimental group. It was divided into three phases: Periods (P) 1, 2, and 3 (Fig. 1). HD was conducted for 3 weeks without any additional interventions

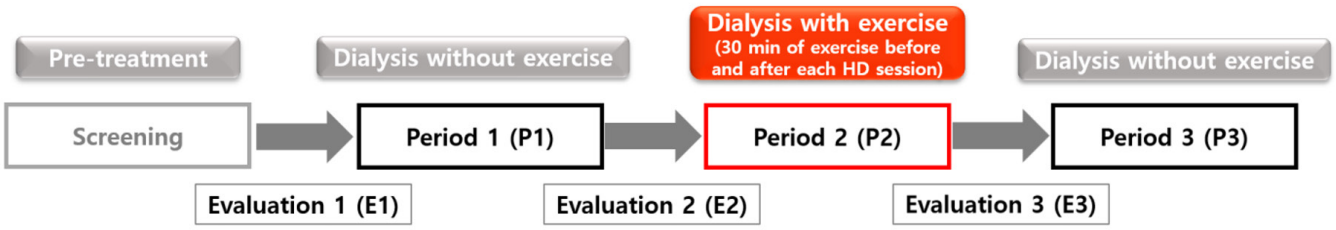

Fig. 1. Flow chart of the study protocol. HD, hemodialysis.

other than the routine medications administered during each period. The study periods were defined as follows. HD P1, P2, and P3 each included a total of 9 sessions, making a total of 27 HD sessions, conducted consecutively within each participant's dialysis cycle, excluding Saturdays and Sundays (HD1–9 for P1, HD10–18 for P2, and HD19–27 for P3). The study was conducted from October 2017 to February 2022.

Screening

During the screening period of the study, participants visited the clinical research facility, where they were provided with detailed explanations of the study. After understanding the study, the participants voluntarily signed written consent forms to participate. The information of age, sex, duration of dialysis, cause of CKD, and laboratory findings related to kidney function was gathered. Participants could withdraw from the clinical study at any time at their own discretion or upon the investigator's decision. Conditions for withdrawal or dropout included the participant no longer wishing to participate, developing a condition or meeting an exclusion criterion that necessitated withdrawal, experiencing adverse effects deemed detrimental to their health, or failing to adhere to scheduled visits and becoming lost to follow-up. Adverse events were defined as any undesirable experience associated with the use of the ergometer, including but not limited to mild dizziness, fatigue, and back pain during dialysis. The withdrawal was managed according to the established criteria, ensuring the integrity and safety of the study.

Study device and intervention

A portable lower extremity exercise device (Q Health PUL; Cybermedic) (Fig. 2) designed to enhance muscle strength and facilitate joint movement recovery was used in this study. A key advantage of this device is that it can be used while the patient is in the supine position on the bed during HD. The device has

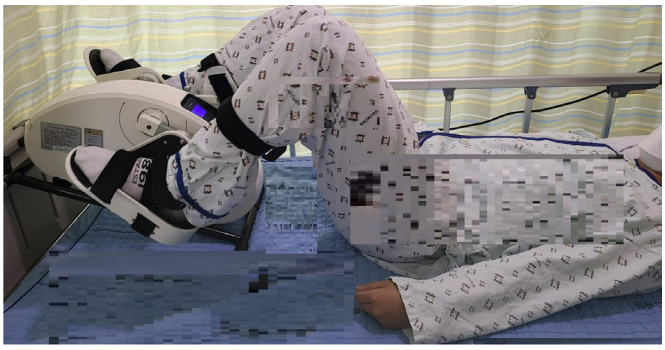

Fig. 2. Image of the study device in action.

two modes, passive and active, which can be selected using the mode button. The default mode is the passive mode, which is especially beneficial for patients with difficulty operating the device independently. The main power switch activates the device and initializes the system. The motor does not run automatically upon pressing the start button. However, resistance is generated when a load is applied to the motor, enabling the patient to perform strength exercises based on controlled resistance. The device's resistance can be adjusted from levels 1 to 20 during strength training.

Intervention protocol

Detailed information on the criteria and extent of the intervention is provided. The passive mode was administered to patients unable to actively participate in the exercises. While the degree of assistance provided by the device in this mode was standardized, specific details on the revolutions per minute (rpm) and the level of assistance were customized based on the patient's initial assessment. The active mode was for patients able to participate actively, resistance levels were individually determined, ranging from level 1 to 20, depending on the patient's capabilities and progress. Exercise intensity was individualized based on target heart rate (HR) and target rate of perceived exertion

(RPE). Exercise intensity was included setting specific target HR and RPE for each patient to ensure exercises were tailored to their fitness levels. Exercise duration, frequency, and progression were also individualized to optimize outcomes. Regular assessments were conducted to modify resistance levels as needed, ensuring a gradual increase in exercise intensity. The rpm in both passive and active modes was monitored and adjusted to ensure safety and effectiveness. Exact rpm values were recorded and modified based on patient tolerance and feedback. By providing these detailed criteria and individualization methods, this study ensures that the exercise intervention can be effectively replicated and tailored for dialysis patients.

Intervention and evaluation

During the initial 3-week phase (P1), participants received standard HD without adjunctive exercise modalities. Hemodynamic indicators, including mean arterial pressure (MAP), SBP, HR, and the presence of IDH-related symptoms and fatigue, were systematically monitored at 30-minute intervals during three weekly HD treatments. IDH was defined as an intradialytic decrease of >20 mmHg in SBP to a level <90 mmHg compared to the baseline BP [14]. When IDH episodes occurred, patients were asked about symptoms like abdominal discomfort, nausea, vomiting, muscle cramps, fatigue, dizziness, and anxiety. The frequency of these symptoms was documented.

During the subsequent 3-week phase (P2), patients exercised in the supine position using a portable ergometer while undergoing HD. The exercise regimen involved 60 minutes of activity during each HD session, split into two segments: 30 minutes at the beginning and another 30 minutes towards the end of the HD session. The exercise intensity for each patient was conducted in passive mode, with speeds ranging from 20 to 25 rpm. For patients unable to perform the exercise actively, the passive mode was utilized, ensuring the exercise was maintained at speeds between 20 and 25 rpm. Most patients performed the exercise at 25 rpm. However, if a patient had low compliance with the intervention, the intervention dose was reduced to 20 rpm. The same parameters, such as MAP, HR, presence of IDH-related symptoms, and fatigue, were measured every 30 minutes during HD.

Throughout the final 3-week phase (P3), patients reverted to standard HD without exercise. The same parameters, such as MAP, HR, the presence of IDH-related symptoms, and fatigue, were measured every 30 minutes during HD, as in P1. Evaluations (E) were conducted two weeks prior to the start of each phase. By comparing these periods, the study assessed the impact of the exercise intervention on hemodynamic stability and the presence of IDH-related symptoms and fatigue. For detailed evaluation timing and processes, refer to Fig. 1.

Assessments

Outcome assessments, including measurement of exercise capacity, such as the 6-MWD, knee extensor strength, fat-free mass (FFM), and the Kidney Disease Quality of Life (KDQOL) questionnaires, were conducted once before each of P1, P2, and P3 (E1, E2, and E3). BP measurements were consistently taken from the brachial artery using either a mercury or aneroid sphygmomanometer to ensure consistency [15].

Primary outcome: 6-MWD

The primary outcome was the 6-MWD [16], which measures a patient's ability to walk within a 6-minute timeframe and assess their exercise capacity. Participants were instructed to walk from one end of a 30-m hallway to the other, covering the maximum distance possible at their own pace within the allotted 6 minutes. The total distance walked during this time was recorded to assess their functional exercise capacity. They were also instructed to report whether they experienced dyspnea, chest pain, or leg pain while walking. This measurement was taken before and after the HD sessions to evaluate the participants' walking endurance at E1, E2, and E3.

Secondary outcomes: cardiovascular parameters (MAP, BP, HR), frequency of IDH, fatigue, KDQOL, knee extensor strength, FFM

The secondary outcomes focused on cardiovascular parameters, all of which were recorded during the HD sessions. MAP was determined using the following equation:

$$MAP=(SBP+2\times DBP)/3 \text{ [17]}$$

Both SBP and DBP were measured, along with HR during the HD sessions. In this study, we documented each occurrence of IDH during the same HD session and measured the frequency of IDH events in each participant. Additionally, we monitored the frequency of IDH and assessed patient fatigue using a visual analogue scale (VAS) [18], along with recording the duration of each HD session. Additional demographic and clinical data were collected separately, including patient age, sex, underlying medical conditions, and mean dialysis duration. The KDQOL-Short Form [19,20], an essential tool used to evaluate

the quality of life of patients with kidney disease, comprises two components: the physical component summary (PCS) and mental component summary (MCS). The PCS and MCS assess the impact of kidney disease on the physical and mental health of a patient, respectively. The handheld dynamometer (Newton, N) was used to assess the thigh muscle strength. The evaluation method for knee extensor strength (N) involved using a dynamometer to measure the maximum voluntary isometric contraction of the quadriceps muscle group. Participants were seated with their hips and knees at a 90-degree angle. They were instructed to exert maximal force against the dynamometer pad positioned just above the ankle. The peak force generated was recorded from three trials, and the highest value was used for analysis. FFM is the total bodyweight measured in kilograms that includes water, muscle protein, carbohydrates, and bone but excludes fat. FFM was measured using the InBody device in the present study.

Statistical analysis

Continuous variables, such as age, height, and weight of the participants, were analyzed using descriptive statistics (mean and standard deviation). Categorical variables, such as sex, were represented as percentages based on frequency. The values for P1, P2, and P3, including all assessments, were determined by averaging the data measured during HD over three weeks. The total number of HD sessions and exercise interventions varied among participants; this variation was accounted for in the descriptive analysis. Comparisons between P1 and P2 and between P2 and P3 were performed using the paired t-test for continuous variables and the Wilcoxon signed-rank test for non-continuous variables. The choice between the paired t-test and the Wilcoxon signed-rank test was made according to the results of a normality test. Potential confounders, such as baseline characteristics, were controlled for by including them as covariates in the analyses where appropriate. Subgroup analyses were conducted based on baseline characteristics such as age, sex, and duration of HD. Interaction terms were included in the regression models to examine potential interactions between the intervention and these baseline characteristics. Missing data were handled using multiple imputation techniques to ensure that the analysis remained robust and unbiased. Sensitivity analyses were conducted to test the robustness of the study findings. These analyses included comparing results from different statistical models, such as using alternative imputation methods for missing data and excluding participants with incomplete data. Loss to follow-up was addressed by analyzing only the data from participants who completed all three periods of the study.

RESULTS

Patient demographics

A total of 20 patients were examined for eligibility, and all 20 were confirmed eligible and included in the study. During the follow-up period, 19 patients completed the study, as one patient dropped out due to personal scheduling conflicts. Ultimately, data from 19 patients were analyzed. The mean age of the participants was 62.1±12.6 years, with an age range of 22 to 78 years. The group consisted of 11 males and 8 females. The following demographic information was gathered (Table 1). The mean dialysis duration was 2,016.0±46.6 days, ranging from 3.5 to 4.2 years. The mean estimated glomerular filtration rate (eGFR) (mL/min/1.73 m2) at the start of dialysis was 5.1±2.2, with a range of 2.5 to 9.5. The causes of CKD among the participants included Type II diabetes mellitus (12 participants), Hypertension (6 participants), and Immunoglobulin A nephropathy (1 participant). Most participants were patients with stage 5 CKD and had underlying conditions of diabetes mellitus.

Effects of exercise during HD on exercise capacity and knee extensor strength

The 6-MWD was measured in 16 of the 19 participants. Data for the 6-MWD in 3 participants were unobtainable due to muscle fatigue, headache, and dizziness. The baseline 6-MWD was 327 m in E1. The 6-MWD increased slightly to 333 m after 3 weeks without exercise in E2. The 6-MWD further increased to 371 m in E3. The p-value for the comparison of values obtained before and after the exercise (E2 and E3) was 0.006,

Table 1. Participant's demographic information

Characteristic	Value (n=19)
Age (yr)	62.1±12.6
Sex (male:female)	11:8
Dialysis duration (day)	2,016.0±46.6
eGFR[a] (mL/min/1.73 m^2)	5.1±2.2
Chronic kidney disease cause	
Type 2 diabetes mellitus	12
Hypertension	6
Immunoglobulin A nephropathy	1

Values are presented as mean±standard deviation or number only.
eGFR, estimated glomerular filtration rate.
[a]Mean eGFR was measured at the start of dialysis.

indicating statistical significance (Table 2). Additionally, the analysis of bilateral knee extensor strength using mean values before and after the exercise intervention revealed a statistically significant p-value (Table 3). This demonstrates that the average muscle strength of the patients increased post-exercise, further supporting the effectiveness of the intervention. Knee extensor strength significantly increased by 11.93 N on left knee extension between pre-exercise E2 and post-exercise E3 (p=0.004). However, no significant difference was observed in the KDQOL score or FFM measured before HD. Thus, exercise training for 30 minutes at the start and end of HD sessions improved exercise capacity and muscle strength (Table 3).

Effects of exercise during HD on hemodynamic parameters

No significant differences were observed between P2 and P3 in terms of fatigue scores, MAP, BP, VAS scores, or duration of HD; however, a trend indicated a reduction in the frequency of IDH following exercise intervention (Table 4). Notably, although the exercise regimen implemented did not result in a significant reduction in the frequency of IDH, an encouraging observation was the decrease in HR post-exercise. For a more meaningful assessment of "resting HR decrease," HR measured during E1–E3 (Table 4, below DBP) should be compared. It is important to note that the HR values in Table 4 are "during dialysis," not exactly the same as resting HR, and P2 shows an

Table 2. Analysis of 6-MWD as the primary outcome

	Evaluation 1 (E1)	Pre-exercise (E2)	Post-exercise (E3)	Δ(E1–E2)	Δ(E2–E3)	p-value (E1–E2)	p-value (E2–E3)
6-MWD (n=16)	327±81	333±97	371±89	-6±66	-37±46	0.697[a]	0.006[a]

Values are presented as mean±standard deviation.
6-MWD, 6-minute walk distance
[a]Paired t-test.

Table 3. Comparative analysis of knee extensor strength, KDQOL, and FFM pre- and post-dialysis sessions

	Evaluation (E1)	Pre-exercise (E2)	Post-exercise (E3)	Δ(E1–E2)	Δ(E2–E3)	p-value (E1–E2)	p-value (E2–E3)
Knee extensor strength (n=18)							
Right	83.8±43.2	90.5±31.1	98.7±30.6	-6.7±34.4	-8.3±17.6	0.076[b]	0.063[b]
Left	82.0±43.7	86.2±31.2	98.1±31.2	-4.2±29.9	-12.0±15.4	0.139[b]	0.004[b]
Mean	82.9±43.0	88.3±30.7	98.4±30.4	-5.4±31.1	-10.1±14.7	0.062[b]	0.010[a]
KDQOL (n=19)							
Physical	38.7±8.0	38.7±10.0	39.0±9.9	-0.0±7.2	-0.3±6.5	0.811[b]	0.523[b]
Mental	42.0±11.2	43.4±10.4	43.4±9.9	-1.4±9.4	0.0±8.7	0.515[a]	0.515[a]
FFM	42.2±11.9	41.7±14.0	42.6±11.3	0.4±4.6	-0.8±4.3	0.486[b]	0.486[b]

Values are presented as mean±standard deviation.
KDQOL, Kidney Disease Quality of Life; FFM, fat free mass.
[a]Paired t-test.
[b]Wilcoxon signed rank test.

Table 4. Assessment of MAP, BP, heart rate, frequency of IDH, and fatigue evaluated using a VAS during dialysis sessions

	Period 1 (P1)	Period 2 (P2)	Period 3 (P3)	Δ(P1–P2)	Δ(P2–P3)	p-value (P1–P2)	p-value (P2–P3)
Blood pressure							
MAP (n=19)	92.8±13.0	94.8±13.5	95.4±13.0	-1.9±5.8	-0.7±7.8	0.231[b]	0.714[a]
SBP (n=19)	127.8±17.1	129.9±17.4	132.6±15.8	-2.1±10.0	-2.7±10.8	0.528[b]	0.291[a]
DBP (n=19)	75.4±12.2	77.1±12.5	77.0±12.7	-1.7±4.1	0.1±6.4	0.133[b]	0.935[a]
Heart rate (n=19)	77.8±11.2	79.4±11.9	75.6±13.2	-1.6±5.3	3.9±5.1	0.192[a]	0.004[a]
Frequency of IDH (n=19)	2.9±2.2	2.4±2.4	2.2±2.1	0.5±1.1	0.2±1.2	0.050[b]	0.717[b]
VAS (n=19)	1.7±2.9	1.6±3.5	1.0±3.0	0.2±1.4	0.6±1.5	0.532[a]	0.123[a]
Dialysis time (min) (n=19)	235.9±8.5	235.9±9.7	237.3±11.0	0.0±6.6	-1.4±8.1	>0.999[b]	0.739[b]

Values are presented as mean±standard deviation.
MAP, mean arterial pressure; BP, blood pressure; IDH, intradialytic hypotension; VAS, visual analogue scale; SBP, systolic BP; DBP, diastolic BP.
[a]Paired t-test.
[b]Wilcoxon signed rank test.

even higher value than P1 (as well as P3). Although this study observed a trend toward a reduction in the frequency of IDH, this was not significant (p=0.05 for comparison between P1 and P2). While analyzing MAP instead of DBP in Table 4 may offer a broader understanding of hemodynamic stability, DBP was used as a representative value for BP due to its relevance in assessing peripheral resistance and cardiovascular risk during dialysis.

Safety events

One patient reported experiencing back, chest, and shoulder pain during exercise training. Another patient reported experiencing dizziness and fatigue. No significant life-threatening adverse events were observed during study.

DISCUSSION

The primary objective of this study was to evaluate the effects of exercise training during HD on exercise capacity, muscle strength, and the prevention of IDH. The key findings of the study include a significant improvement in the 6-MWD and knee extensor strength following the exercise intervention. Despite a non-significant reduction in the frequency of IDH, a notable trend towards improvement was observed. Additionally, a significant decrease in HR post-exercise indicates potential cardiovascular benefits of the exercise regimen. These results align with the study objectives, highlighting the positive impact of exercise during HD on physical function and potential cardiovascular health.

The primary outcome of this study, the 6-MWD, was significantly different before and after exercise. This finding suggests that exercising with an ergometer during HD can enhance muscle strength and functional abilities. The present study also aimed to determine whether exercise training during HD could aid in evaluating lower extremity strength and function and whether it could prevent IDH, the most common side effect of HD. A comparison of the frequency of IDH before and after exercise exhibited no significant difference; however, the decreasing trend remained significant. Gołębiowski et al. [10] and Anding et al. [11] reported that exercise training during HD enhances physical function. However, only a few studies have provided objective statistics to determine whether exercise training during HD can prevent hypotension or evaluate physical function before and during HD.

The 6-MWD exhibited a significant difference before and after exercise training, suggesting that exercising with an ergometer during HD can enhance muscle strength and functional abilities. However, no significant correlation was observed between the fatigue scores assessed using VAS, MAP, BP, and HD duration before and after exercise. Previous studies have demonstrated decreased exercise capacity and quality of life in patients undergoing HD [2,21-23]. This decline can be attributed to factors such as anemia, diminished heart function, weakened musculoskeletal function, and reduced lung capacity resulting from HD [24,25]. Furthermore, the physiological changes and time constraints associated with HD contribute to a reduction in the ability of patients to engage in physical activities [26]. A reduction in physical activity and muscle strength, which can be attributed to exercise-induced fatigue, decreased pulmonary function, chronic pain, other comorbidities, and depression, has been observed in most patients undergoing HD [27,28].

Based on the findings of previous studies, exercise training during HD was hypothesized to be beneficial [29-31]. IDH occurring during HD was managed by adopting the Trendelenburg position to restore the circulating blood volume and administering saline solution while preventing airway aspiration. In addition, bicarbonate can be administered to increase the sodium or ionized calcium concentration in the dialysate and correct anemia and hypoalbuminemia to prevent IDH. We hypothesized that exercise training could help reduce the incidence of IDH-related symptoms. Regarding knee extensor strength, an improvement was observed only in the left side. This may be attributed to the fact that the average muscle strength in the left leg was lower before the exercise intervention. Post-exercise, the muscle strength between the left and right legs equalized, indicating that the initially weaker side had more potential for improvement and that the exercise regimen effectively corrected the muscle imbalance. Alternatively, variations in individual muscle imbalances and usage patterns could have contributed to this discrepancy. Additionally, the analysis of bilateral knee extensor strength using mean values before and after the exercise intervention revealed a statistically significant p-value. This demonstrates that the average muscle strength of the patients increased post-exercise, further supporting the effectiveness of the intervention.

In Anding-Rost et al.'s study [32] involving 917 participants, the group that participated in physical activities exhibited notable improvements compared with the group receiving usual care over 12 months. Specifically, the exercise group demon-

strated a decrease in the Timed-Up-and-Go test by -1.1 seconds (95% confidence interval [CI], -1.9 to -0.3) and an increase in the 6-MWD by 37.5 m (95% CI, 14.7 to 60.4). However, there was no significant difference between the groups in the vitality subscale of the 36-item Short Form Health Survey (SF-36). In parallel, our study also indicated a similar enhancement in the 6-MWD following the exercise intervention. When evaluated using the KDQOL questionnaire, which provides more intricate details than the SF-36, we found no significant differences compared with the previous study.

However, the present study adopted a different approach from that of previous research. We asked patients to use an ergometer to exercise while lying down for 30 minutes at the start and end of their HD sessions. This protocol was established to maximize the benefits of exercise while accommodating the time constraints and physical condition of the patients. Exercising at the start of the HD session aims to improve circulation and prepare the body for the stress of dialysis, while exercising at the end helps in recovery and enhances muscle retention post-dialysis. Additionally, due to the difficulty some patients have in exercising for more than 30 minutes continuously, the exercise was split into two sessions. This approach contrasts with previous studies that often did not specify the timing or structure of exercise sessions during HD, providing a unique insight into the potential benefits of structured exercise regimens during dialysis. The American College of Sports Medicine (ACSM) recommends 150–300 minutes of moderate-intensity exercise per week for individuals with chronic medical conditions [33]. By incorporating exercise within the dialysis sessions, our protocol ensures that patients can achieve these recommended exercise amounts, thereby maximizing potential health benefits while minimizing additional time burdens. References to ACSM guidelines and previous studies were considered to ensure that the protocol not only meets recommended exercise amounts but also optimally fits the patients' dialysis schedules and physical capacities. We also ensured a clear definition of the criteria used to measure the results of the study.

Additionally, a key innovative aspect of our study was the detailed comparison of functional abilities using various assessment tools before and after dialysis, specifically during dialysis. The exercise was conducted during dialysis sessions, ensuring that dialysis times were consistent. To minimize potential confounding variables influenced by time, participants were evaluated within one week of the conclusion of HD P2. We confirmed that variables such as renal function (eGFR) and lab indicators during dialysis remained stable, and a review of patients' medical records indicated that there were no significant changes in dialysis conditions. There were also no vital issues during the study period.

This study provides substantial evidence for the benefits of using an ergometer in improving the 6-MWD and strengthening the lower extremity muscles in patients with CKD undergoing HD. Notably, although the exercise regimen implemented did not significantly reduce the frequency of IDH, an encouraging observation was the decrease in HR post-exercise. This finding suggests a potential cardiovascular benefit of exercise, which may be of clinical significance, particularly in this patient population where cardiovascular concerns are prevalent.

Moreover, the results emphasize the potential of appropriate exercise therapy to enhance muscle strength and cardiovascular health in patients undergoing HD. The observed HR reduction could indicate improved cardiovascular efficiency, which is a crucial factor for patients with CKD, who often experience cardiovascular comorbidities. However, the implications of these findings on long-term cardiovascular health and their translation into clinical practice require further exploration.

Despite the positive outcomes, this study had some limitations. The small sample size and the study's design limit the generalizability of the results. As this study is a clinical trial that is neither controlled nor randomized, there are inherent limitations in establishing causality and ruling out potential confounding factors. Therefore, the results should be interpreted with caution. Future studies should incorporate controlled and randomized designs to strengthen the validity of the findings. Moreover, the lack of significant improvement in the frequency of IDH precludes definitive conclusions about the efficacy of exercise training in preventing this common complication of HD. Also, the inability to correlate changes in functional ability with exercise intensity highlights a gap in our understanding of the dose-response relationship between exercise and its benefits in this patient population. Potential sources of bias include the selection bias due to the non-randomized nature of the study and measurement bias from self-reported data. The magnitude of these biases could potentially overestimate the benefits of exercise interventions.

The generalizability (external validity) of the study results is limited by the small sample size and the specific characteristics of the study population. The findings may not be applicable to all patients undergoing HD, particularly those with different comorbidities or in different healthcare settings. Further research with

larger, more diverse populations is needed to confirm the applicability of these results to the broader CKD patient population.

Recommend a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Overall, while the study provides promising evidence for the benefits of exercise during HD, the findings should be interpreted cautiously due to the noted limitations. The observed improvements in exercise capacity and muscle strength are encouraging, but further research is needed to confirm these benefits and to explore their long-term impacts on cardiovascular health and quality of life in patients with CKD. The consistency of these results with findings from similar studies adds credibility, but the lack of significant changes in IDH frequency and other hemodynamic parameters suggests that exercise alone may not be sufficient to address all complications associated with HD. Future studies should aim to clarify these relationships and determine optimal exercise protocols.

Ultimately, this study makes a significant contribution to the field of nephrology and rehabilitation medicine by highlighting the potential of exercise therapy to enhance the quality of life in patients undergoing HD. The positive effects on exercise capacity and lower limb strength observed in this study underscore the benefits of integrating an exercise regimen during HD sessions. Patients demonstrated significant improvements in the 6-MWD and knee extensor strength, which are indicative of enhanced physical function and muscle strength.

Future research should focus on addressing these limitations. Larger randomized controlled trials with diverse patient populations are essential to validate our findings. Additionally, exploring different exercise intensities and durations could provide insights into the optimal exercise prescription for this patient group. Understanding how exercise impacts various aspects of health in patients with CKD undergoing HD, including cardiovascular function, muscle strength, and quality of life, is vital for developing comprehensive, patient-centered rehabilitation protocols. This paves the way for further research to lead to more effective and personalized rehabilitation strategies for this vulnerable patient population.

CONFLICTS OF INTEREST

Myoung-Hwan Ko is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Won YH. Data curation: Won YH. Investigation: Won YH. Methodology: Won YH. Formal analysis: Chae TS, Won YH. Project administration: Kim DS, Ko MH. Resources: Won YH. Visualization: Chae TS. Supervision: Kim DS, Ko MH, Won YH. Writing – original draft: Chae TS. Writing – review and editing: Chae TS, Won YH. Approval of final manuscript: all authors.

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ORCID

Tae-Seok Chae, https://orcid.org/0009-0007-2833-4087
Da-Sol Kim, https://orcid.org/0000-0002-7745-978X
Myoung-Hwan Ko, https://orcid.org/0000-0002-0566-3677
Yu Hui Won, https://orcid.org/0000-0003-2007-9652

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The Accessibility and Effect of Cardiac Rehabilitation in COVID-19 Pandemic Era

Chul Kim, MD, PhD, Jun Hyeong Song, MD, Seung Hyoun Kim, PT, MS

Department of Rehabilitation Medicine, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Objective: To prospectively compare the efficacy of conventional center-based cardiac rehabilitation (CBCR) and home-based cardiac rehabilitation (HBCR) during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Ninety patients were divided into HBCR and CBCR groups based on cardiovascular risk stratification and individual preference. The CBCR group performed supervised in-hospital exercise training 2–3 times/week and subsequent self-exercise at home. The HBCR group performed self-exercise at home after one or two sessions of exercise education. The cardiopulmonary exercise test results at baseline and those at the 3-, 6-, and 12-month follow-ups were analyzed as primary outcome.

Results: The peak oxygen consumption (peak VO_2, mL/kg/min) in the CBCR group was 20.1 and 24.0 at baseline and 12 months, respectively, showing significant improvement (p=0.006). In the HBCR group, it only increased from 24.4 to 25.5, showing suboptimal improvement. A significant increase in the Korean activity scale/index was confirmed only in the CBCR group (p=0.04). The cardiovascular outcome did not differ between the two groups, nor did the dropout rate or demographic factors.

Conclusion: During the COVID-19 pandemic, only CBCR was associated with a significant improvement in peak VO_2 and physical activity levels, a finding that differs from those of other studies and seems to be affected by COVID-19. Therefore, in situations where the importance of HBCR is emphasized, it is essential to introduce measures to monitor and enhance exercise adherence among participants.

Keywords: Cardiac rehabilitation, COVID-19, Pandemics, Secondary prevention

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Correspondence:
Jun Hyeong Song
Department of Rehabilitation Medicine, Inje University Sanggye Paik Hospital, Inje University College of Medicine, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea.
Tel: +82-2-950-1145
Fax: +82-2-950-1144
E-mail: sjh9233@hanmail.net

INTRODUCTION

Cardiac rehabilitation (CR) is an integral component of the continuum of care for patients with various cardiovascular diseases. However, the global CR participation rate remains low and suboptimal—among eligible candidates, it is approximately 30%–40%. Over 80% of United States (US) patients do not participate in CR and, in South Korea, this figure is much lower at approximately 6% [1-3]. Participation is especially low in female, elderly, and individuals with a lower socioeconomic status who are uninsured [3,4]. Reluctance to participate in group rehabilitation sessions, exercise schedules, occupational issues, transportation and expenses are known barriers to CR participation [5]. Home-based CR (HBCR) was introduced in the 2000s as an alternative strategy to expand participation in CR [5-7]. Theoretically, HBCR could overcome various access-relat-

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ed barriers to center-based CR (CBCR), including geographic, socioeconomic, and logistical factors [3].

Additionally, during the coronavirus disease 2019 (COVID-19) pandemic, safe distancing measures have led to the cessation of CBCR programs [8-10]. According to a global survey, approximately 75% of CR programs were completely or temporarily discontinued, which is about 4,400 programs worldwide [10]. This further increased the need for home-based programs [7]. Along with recent developments in technology, previous research on wearable devices for heart rate monitoring used during exercise has proven their accuracy and validity [10-12], and HRCR programs have demanded a more widespread involvement of such virtual or digital tools [7].

Regarding therapeutic efficacy, most previous clinical trials and systematic reviews have shown comparable improvements in peak oxygen consumption (peak VO_2) in individuals assigned to HBCR and CBCR [3,5,6,13]. The magnitude of improvement in cardiorespiratory fitness (CRF) also appears to be similar for HBCR and CBCR [3].

To the best of our knowledge, this is the first study to compare the efficacy and multifaceted properties of participants in CBCR and HBCR, during COVID-19 pandemic era prospectively. This study was conducted in a single center with one of the most active CR programs in South Korea [1]. Fortunately, this hospital was able to run CR program without any cessation of original CR programs or reduction of CR providing staffs even during COVID-19. The authors intended to identify the influence of COVID-19 pandemic on newly attending CR participants.

METHODS

Ethics statement

The study protocol was approved by the Institutional Review Board of Inje University (No. SGPAIK 2020-12-010). This study was registered with the Clinical Research Information Service (CRIS, KCT0006299). All the participants provided written informed consent.

Sample size calculation

G*Power 3.1.9.7 was used for the sample size calculation. A one-tailed t-test was performed, with a effect size of 0.35, a significance level of α=0.05 and a power of 90% [14,15]. A required total sample size of 63 was determined. Considering a loss-to-follow-up rate of 20%, we recruited more than 76 participants for this study.

Study design and participants

This single-center, prospective, comparative study recruited outpatients from the CR clinic at the Inje University Sanggye Paik Hospital from March 2021 to February 2022. This hospital continued their CR program during the COVID-19 pandemic without any reduction in CR-providing staff. Eligible participants were patients newly diagnosed with stable angina, acute coronary syndrome, heart failure, valvular disease, or aortic disease who visited the CR clinic after discharge. The exclusion criteria were: (1) contraindications to cardiopulmonary exercise testing (CPX) or CR exercise training according to the American Heart Association guidelines [16]; (2) other medical conditions preventing participation in the CPX or CR exercise training.

At the first visit to the CR clinic—usually within a week of discharge for patients undergoing percutaneous coronary intervention or within 4 weeks after coronary artery bypass grafting or valvular surgery—all participants underwent the CPX as a baseline to check cardiorespiratory responses to exercise stress and were administered several questionnaires.

Intervention

For the CPX, a real-time recording 12-channel electrocardiograph (CASE; GE-Marquette), respiratory gas analyzer (Quark CPET; COSMED Co.) with a virus filter attached at the mask–tube interface, automatic blood pressure and pulse monitor (TANGO M2; SunTech Medical Inc.), and treadmill (T-2100; GE Healthcare) were used.

Following the modified Bruce protocol, the CPX was administered in the following order: at rest, during exercise, and during recovery. The test was terminated in accordance with the American Heart Association "Indications for termination of exercise testing" guidelines [16]. To assess changes in CRF, the peak VO_2, maximal metabolic equivalents, rate–pressure product, rating of perceived exertion, heart rate, and blood pressure were measured.

Participants were divided into a CBCR or an HBCR group based on risk stratification for exercise-related adverse cardiovascular events [17] and/or personal circumstances. In detail, participants with low risk were recommended to go through HBCR and participants with moderate/high risk were recommended to go through CBCR initially. However, depending on individual circumstances (where they live, how long it takes

from their house to the hospital, whether they are participating in economic activities) or personal preference on center-based or home-based training, the final group was allocated in line with real-world CR practice.

The CBCR group underwent supervised exercise training in a hospital setting and was subsequently switched to home-based self-exercise. The maximum number of in-hospital exercise sessions was 36, which is the upper limit covered by the Korean National Health Insurance Service. The HBCR group performed home-based exercise training. All the participants were educated on risk factor management and nutrition as well.

The CBCR group attended supervised exercise training while wearing quarantine masks, with real-time electrocardiographic, heart rate, and rating of perceived exertion monitoring. Training sessions were conducted 2–3 times/ week in a hospital setting. Each training session comprised a 10-minute warm-up, 30-minute exercise session, and 10-minute cooldown. The exercise intensity was set based on 60%–85% of the heart rate reserve value. If patients had COVID-19 symptoms, tested positive for COVID-19 using a self-test kit, or their family or partner was infected, the hospital visit was discontinued. After completing the in-hospital training sessions, the participants were instructed to continue aerobic training at home.

In the HBCR group, the exercise prescriptions were the same as those in the CBCR group; however, the participants exercised by themselves at home after one or two sessions of education. They were intermittently contacted to encourage self-exercise.

All participants visited CR clinic for follow-up CPX and appointments with a CR specialist at 3, 6, and 12 months. To enhance patient compliance with home-based training, the attending physician reviewed the previous self-exercise methods and reeducated every participant at each visit.

Outcome parameters

For the primary outcome, a follow-up CPX was performed at 3, 6, and 12 months in the same manner as that at baseline. When the participants were lost to scheduled follow-up CPX, a registered nurse in CR clinic called the patient and asked for the reason of dropping out.

For the secondary outcomes, medical records and other variables, such as demographic (age, sex, body mass index, smoking history [packs per day×year]), geographic (mode of transport, distance and time travelled to hospital visits), and socioeconomic variables (family composition, monthly income, type of insurance), were obtained at baseline.

Questionnaires assessing activity parameters (weekly exercise time in minute), functional status (Korean activity scale/ index, KASI), quality of life (Korean version of 5 level EuroQoL-5 Dimension, EQ-5D-5L) and mood status (Patient Health Questionnaire-9, PHQ-9) were administered at baseline, 3, and 12 months.

The KASI, a Korean version for Duke Activity Status Index, consists of 15 questions about functional capacity with the score ranging from 0 to 79. Depending on the sum of the score, functional classification of KASI is divided into class I, KASI≥46; class II, 46>KASI≥24; class III, 24>KASI≥4; and class IV, KASI<4 respectively [18].

The EQ-5D-5L comprises questions about current health status in the following dimensions; mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Scores for each response are 1, no problems; 2, slight problems; 3, moderate problems; 4, severe problems; and 5, extreme problems. EQ-5D-5L uses preference weights unique to South Korean population and the total score calculated from the 5 digit data set ranges from -0.066 to +1. -0.066 stands for the worst status of health and quality of life and +1 stands for the best [19].

The PHQ-9 is a self-reported questionnaire for screening depressive symptom. It consists of nine items, with the sum of scores ranging from 0–27. The score divides into 5 categories: 0–4, minimal or no depression; 5–9, mild depression; 10–14, moderate depression; 15–19, moderate-severe depression; and 20–27, severe depression [20].

Statistical analysis

All data were analyzed using SPSS statistics version 25.0 (IBM Corp.), and values are presented as mean±standard deviation or numbers and percentages. A t-test and paired t-test were used to compare the averages between groups and paired values within a specific group, respectively. Missing values due to patients who were lost to follow-up were excluded from the analysis. When the number of samples per group did not exceed 30, non-parametric tests were performed using the Mann–Whitney U-test and Wilcoxon signed-rank tests. To analyze the within-group peak VO_2 improvement from baseline, we used peak VO_2 ratio (%), which is calculated as peak VO_2 at follow-up/ peakVO_2 at baseline.

RESULTS

For baseline characteristics, most variables did not differ be-

tween the groups (Table 1). However, the proportion of men, unstable angina, smoking history, and left ventricular ejection fraction showed significant differences—all were higher in the HBCR group, with less proportion of ST-segment elevation myocardial infarction (STEMI).

The mean baseline peak VO_2 in the HBCR and CBCR group was 24.4 and 20.1, respectively, with significantly higher values in the HBCR group (Table 2). During follow-up, both groups showed an improvement in peak VO_2, although only the CBCR group showed a significant improvement from baseline. Furthermore, from 3 to 12 months, the mean peak VO_2 in both the groups did not differ significantly. However, the average peak VO_2 in the HBCR group was consistently higher than that in the CBCR group. The peak VO_2 ratio in the CBCR group showed gradual increases at 116%, 118%, and 120% at 3, 6, and 12 months, respectively; contrastingly, the HBCR group showed peak VO_2 ratios of 103%, 107%, and 107%.

The KASI score was higher in the HBCR than in the CBCR group at baseline and at 3 months; however, at 12 months, the values did not differ significantly (Table 3). The EQ-5D-5L score was higher in the HBCR group at baseline. Similar to the KASI score, the EQ-5D-5L score in the CBCR group increased during the study, and the mean EQ-5D-5L score did not differ significantly at the end of the study. The PHQ-9 showed decrease in CBCR group at 12 month (Table 3).

We recruited 45 participants for each group; however, owing to the COVID-19 pandemic and various other reasons, only 52 participants (CBCR, 27; HBCR, 25) completed the study, surpassing the presumed loss-to-follow-up rate of 20% (Fig. 1). Apart from some subsets of monthly income, no socioeconomic or geographical factors differed between the groups (Table 4), nor did the loss-to-follow-up time points and reasons (Table 5).

Table 1. Baseline characteristics of patients in CBCR group and HBCR group

Characteristic	CBCR (n=45)	HBCR (n=45)	p-value
Age (yr)	60.4±9.5	60.0±7.4	0.77
Sex, male:female	34:11	42:3	0.02
Height (m)	1.65±0.30	1.67±0.57	0.16
Weight (kg)	68.9±14.0	73.8±10.0	0.07
Body mass index (kg/m^2)	25.2±4.4	26.2±2.7	0.19
LVEF (%)	50.7±13.6	58.0±6.5	0.003
Patients with smoking history	31 (68.8)	39 (86.7)	0.04
Smoking history (packs per day×yr)	16.7±18.0	24.3±17.5	0.04
Current diagnosis			
STEMI	14 (31.1)	6 (13.3)	0.04
Non-STEMI	13 (28.9)	9 (20.0)	0.33
UA	4 (8.9)	14 (31.1)	0.008
SA	9 (20.0)	10 (22.2)	0.80
Others[a)]	5 (11.1)	6 (13.3)	0.75
Comorbidity			
HTN	23 (51.1)	22 (48.9)	0.84
DM	16 (35.6)	8 (17.8)	0.06
Dyslipidemia	11 (24.4)	15 (33.3)	0.36
Previous MI	6 (13.3)	4 (8.9)	0.51
PAOD	0 (0)	0 (0)	-
Ischemic stroke	0 (0)	2 (4.4)	0.16
Hemorrhagic stroke	0 (0)	1 (2.2)	0.32
Cancer	2 (4.4)	2 (4.4)	1.00
Management			
PCI	35 (77.8)	36 (80.0)	0.80
CABG	4 (8.9)	2 (4.4)	0.40
No. of diseased vessel	1.3±0.9	1.1±0.8	0.35

Values are presented as mean±standard deviation, number only, or number (%).
CBCR, center-based cardiac rehabilitation; HBCR, home-based cardiac rehabilitation; LVEF, left ventricle ejection fraction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; SA, stable angina; HTN, hypertension; DM, diabetes mellitus; MI, myocardial infarction; PAOD, peripheral artery obstructive disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
[a)]Others: valve disease, tumor, heat failure and others.

Table 2. Changes of cardiopulmonary exercise test results in two groups during 12-month follow-up

CPX result	CBCR	HBCR	p-value
Peak VO_2			
Baseline	20.1±5.3	24.4±4.4	<0.001
3 mo	23.0[a)]±4.6	24.8±4.6	0.10
6 mo	23.6[b)]±5.1	24.6±5.1	0.49
12 mo	24.0[b)]±5.0	25.5±4.8	0.30
Maximal METs			
Baseline	5.7±1.5	7.0±1.3	<0.001
3 mo	6.6[a)]±1.3	7.1±1.3	0.10
6 mo	6.7[b)]±1.5	7.0±1.4	0.49
12 mo	6.9[c)]±1.4	7.3±1.4	0.30
Peak VO_2 ratio (%)			
3 mo	116±15	103±13	<0.001
6 mo	118±22	107±11	0.02
12 mo	120±21	107±13	0.02

Values are presented as mean±standard deviation.
CPX, cardiopulmonary exercise test; CBCR, center-based cardiac rehabilitation; HBCR, home-based cardiac rehabilitation; peak VO_2, peak oxygen consumption (mL/kg/min); METs, metabolic equivalents; peak VO_2 ratio, (follow-up peak VO_2 at each month/baseline peak VO_2)×100.
Significant difference from the baseline, within group: [a)]p=0.008, [b)]p=0.006, [c)]p=0.002.

Table 3. Changes of secondary parameters in two groups during 12-month follow-up

Activity scale and questionnaire	CBCR	HBCR	p-value
KASI			
Baseline	53.6±15.7	63.5±13.3	0.002
3 mo	58.7±13.7	67.5±9.0	0.004
12 mo	61.5[a]±13.5	67.0±10.2	0.12
Exercise time (min/wk)			
Baseline	258±166	227±225	0.46
3 mo	287±167	317±257	0.58
12 mo	291±320	254±188	0.64
EQ-5D-5L			
Baseline	0.815±0.136	0.860±0.047	0.04
3 mo	0.808±0.167	0.869±0.068	0.06
12 mo	0.869±0.040	0.875±0.046	0.62
PHQ-9			
Baseline	4.62±5.06	3.67±4.10	0.33
3 mo	3.23±3.66	3.03±3.64	0.84
12 mo	2.58[b]±2.37	2.04±2.60	0.46

Values are presented as mean±standard deviation.
CBCR, center-based cardiac rehabilitation; HBCR, home-based cardiac rehabilitation; KASI, Korean activity scale/index; EQ-5D-5L, Korean version of 5 level EuroQoL-5 Dimension; PHQ-9, Patient Health Questionnaire-9.
Significant difference from the baseline, within group: [a]p=0.04, [b]p=0.02.

Patients with COVID-19 related issues are provided in Supplementary Table S1.

Concerning clinical outcomes in the CBCR group, one participant was re-hospitalized for coronary artery bypass graft and another died at home, both at the 12-month follow-up. In the HBCR group, one participant at 1 month and three at 3 months were re-hospitalized for two coronary artery and two peripheral artery interventions, respectively.

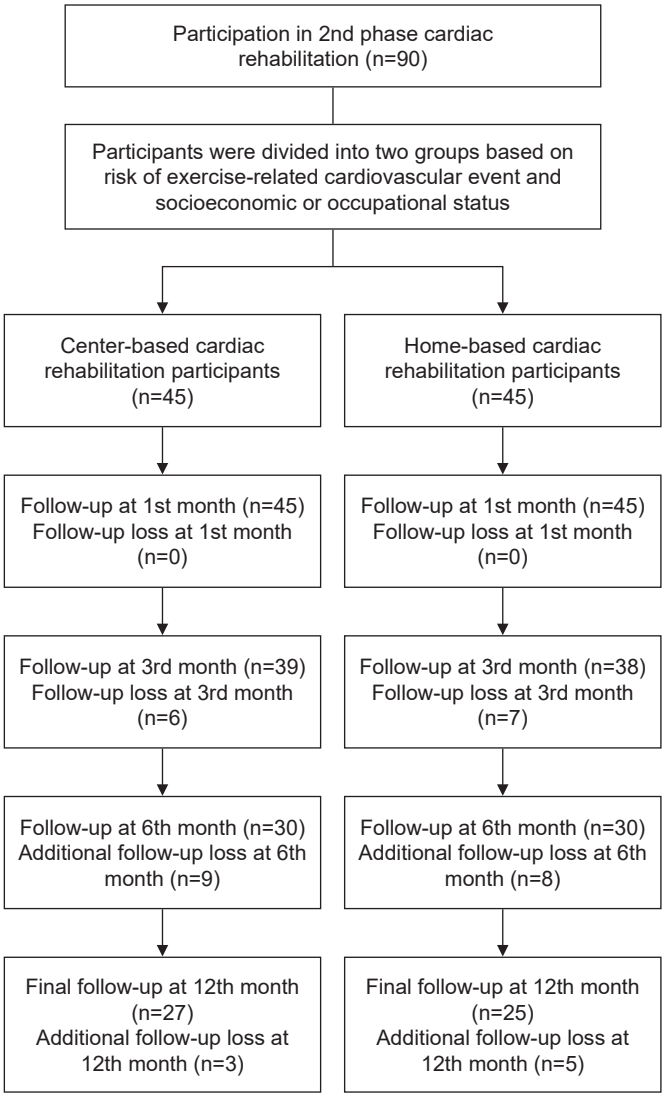

Fig. 1. Flowchart diagram of the participants and loss-to-follow-up during the study period.

DISCUSSION

We aimed to determine the impact of the COVID-19 pandemic on CR behaviors and the therapeutic efficacy of newly attended HBCR and CBCR. The COVID-19 pandemic has influenced CR implementation, necessitating changes in the content and structure of conventional CR to increase its efficiency and effectiveness [21].

At baseline, the proportion of men, unstable angina in acute coronary syndrome, smoking history, and the ejection fraction were higher in the HBCR group with less proportion of STEMI, potentially because this group included participants with a relatively lower risk of exercise-related adverse cardiovascular events and better physical function. Moreover, since unstable angina is the mildest form of acute coronary syndrome progression, more patients with unstable angina and less patients with STEMI could be included in the HBCR group, reflecting a higher baseline peak VO_2 than in the CBCR group.

Both the CBCR and HBCR groups showed an increase in the average peak VO_2 during the 12-month period. However, only the CBCR group showed a significant improvement from baseline. The peak VO_2 and metabolic equivalents in the CBCR group increased by 3.9 mL/kg/min and 1.2, respectively, at 12 months, constituting a 20% increase from baseline. In the HBCR group, these variables increased by 1.1 mL/kg/min and

Table 4. Socioeconomic and geographic factors of patients in CBCR group and HBCR group

Factor	CBCR (n=45)	HBCR (n=45)	p-value
Family composition			
Solitary	6 (13.3)	8 (17.8)	0.57
With spouse	20 (44.4)	16 (35.6)	0.40
With spouse and children	11 (24.4)	17 (37.8)	0.18
With children	2 (4.4)	0 (0.0)	0.16
Others	6 (13.3)	4 (8.9)	0.51
Monthly income (1 million KRW)			
<0.5	10 (22.2)	3 (6.7)	0.04
0.5–1	2 (4.4)	2 (4.4)	1.00
1–2	5 (11.1)	14 (31.1)	0.02
2–3	8 (17.7)	6 (13.3)	0.77
3–5	12 (26.6)	16 (35.6)	0.37
>5	8 (17.7)	4 (8.9)	0.22
Insurance			
National+personal health insurance	28 (62.2)	33 (73.3)	0.26
National health insurance	13 (28.8)	11 (24.4)	0.64
Medical protection	4 (8.8)	1 (2.2)	0.17
Distance (home–center, km)			
<5	24 (53.3)	28 (62.2)	0.40
5–10	12 (26.6)	8 (17.8)	0.32
10–25	7 (15.5)	7 (15.6)	1.00
25–50	2 (4.4)	0 (0)	0.16
50–100	0 (0)	1 (2.2)	0.32
100–200	0 (0)	1 (2.2)	0.32
>200	0 (0)	0 (0)	-
Travel time (min)			
<30	26 (57.7)	23 (51.1)	0.53
30–60	16 (35.5)	17 (37.8)	0.82
60–120	3 (6.6)	5 (11.1)	0.46
>120	0 (0)	0 (0)	-
Mode of transport			
Pedestrian	6 (13.3)	7 (15.6)	0.77
Bicycle	1 (2.2)	4 (8.9)	0.17
Public transport (bus, subway)	20 (44.4)	15 (33.3)	0.29
Taxi	2 (4.4)	0 (0)	0.16
Own car	16 (35.5)	19 (42.2)	0.52

Values are presented as number (%).
CBCR, center-based cardiac rehabilitation; HBCR, home-based cardiac rehabilitation; KRW, the South Korean "Won," which is the official currency of South Korea.

Table 5. Participants lost to follow-up CPX test in CBCR group and HBCR group

	CBCR (n=18)	HBCR (n=20)	p-value
Drop out (mo)			
1	0 (0)	0 (0)	-
3	6 (33.3)	7 (35.0)	0.92
6	9 (50.0)	8 (40.0)	0.55
12	3 (16.7)	5 (25.0)	0.54
Reasons for drop out			
Occupation & busy schedule	1 (5.6)	4 (20.0)	0.20
Distance & travel time	2 (11.1)	4 (20.0)	0.47
Expense	1 (5.6)	1 (5.0)	0.94
Medical issues	3 (16.7)	3 (15.0)	0.89
Musculoskeletal pain	7 (38.9)	4 (20.0)	0.21
Dissatisfaction	4 (22.2)	4 (20.0)	0.87

Values are presented as number (%).
CPX, cardiopulmonary exercise test; CBCR, center-based cardiac rehabilitation; HBCR, home-based cardiac rehabilitation.

0.3 at 12 months, respectively, constituting a mere 7% increase from baseline.

CBCR and HBCR are equally effective in terms of CRF [3,5,6,13] and the magnitude of improvement [3,6]. An average peak VO_2 increase between 2.0 and 3.0 mL/kg/min is reported [3,6,22-24]. Also, although there are discrepancies in the literature, it is generally reported that peak VO_2 improves by about 13% to 35% from the baseline value [25].

However, in our study, only the CBCR group achieved satisfactory peak VO_2 improvement. This can be attributed to several factors. Firstly, there have been reports that greater improvement can be expected from CR if the initial exercise capacity is low [23,25]. Additionally, in studies investigating factors that influence the degree of VO_2 improvement, the number of in-hospital exercise education sessions was identified as an independent factor affecting improvement [25]. In addition, the unsupervised HBCR participants might have performed inappropriate or inadequate exercises. Many studies and interventions in HBCR utilize telephone calls or home visits by healthcare professionals, such as exercise physiologists or nurses, aimed at enhancing adherence and overseeing home exercise [26-28]. In cases involving frequent healthcare provider contact, telephone calls or visits occurred as often as once weekly [27,28]. On the contrary, participants in the HBCR group in this study had minimal contact, limited to follow-up appointments for CPX every few months.

The KASI score was significantly higher in the HBCR than in the CBCR group at baseline and 3 months, indicating that HBCR participants were more physically active from baseline. During the 12 months, the KASI score—reflecting the physical activity level—in the CBCR group significantly increased, al-

though the values did not differ significantly at the end of the study. The average weekly exercise duration gradually increased in the CBCR group. However, in the HBCR group, it only temporarily increased and declined to baseline levels by the end of the study. HBCR participants may have only been physically active in the short-term; in contrast, CBCR participants became more physically active during the study. The HBCR participants may not have shown a significant improvement in CRF since the benefits of aerobic exercise are most significant when performed in the long-term [8].

Regarding quality of life, the EQ-5D-5L score was higher in the HBCR than in the CBCR group at baseline. Similar to the KASI score, the EQ-5D-5L score of the CBCR group increased during the study, as the mean EQ-5D-5L did not differ at 12 months. Additionally, the PHQ-9 score showed a significant decrease at 12 month in the CBCR group. Despite inconsistent results, CR seems to have improved mood and quality of life in both groups, consistent with the findings of previous studies [3,6]. Clinical outcomes, including admission or death due to cardiovascular disease, did not differ between groups, although the number of events was too small for analysis. However, both HBCR and CBCR participation is associated with a markedly reduced risk of readmission and death [3,5,6,29].

Despite the well-known therapeutic effects and benefits, CR has low global participation and maintenance rates [1-5]. There are several barriers to CR participation. A low and high socioeconomic status is linked to low and high referral rates for CR, respectively [30-32]. Moreover, rural inhabitants experience greater barriers to CR, and solitary, old, retired, and poorly educated people with low annual incomes are less willing to participate in CR [32]. These patient groups require special attention to enhance participation rates. In the present study, these non-medical factors were compared between HBCR and CBCR (Table 4). Higher proportion of participants with income lower than 0.5 million KRW/month and between 1.0–2.0 million KRW/month were assigned to CBCR and HBCR respectively. People with a monthly income of less than 0.5 million KRW can be inferred to have irregular or part-time work schedules. Based on this inference, it can be reasoned that they may have more time available to participate in CBCR.

Factors associated with discontinuing CR, which can be categorized into concerns or dissatisfaction with the CR program itself, and logistical, intrapersonal, and clinical reasons are also well reported [33]. These barriers to CR differ depending on the clinical setting. For example, the traveling time between home and hospital is a known cause of CR discontinuation, but not reported in all studies [33]. CR programs are usually funded for a limited number of sessions, or maybe not at all in some countries [21,34]. Participants without CR coverage by the health insurance would be reluctant to participate in CR. Likewise, various barriers may affect CR participation differently in accordance to specific clinical situation in each centers or region. Identifying region- and hospital-specific CR barriers are essential for enhancing CR participation [34].

Although it depends on the circumstances, approximately 25% of participants discontinue CR [6,31,33]. We predicted a 20% dropout rate when designing this study; however, 42% of participants were lost to follow-up. The reasons provided did not significantly differ between the groups (Table 5). Although only two participants reported medical reasons directly associated with COVID-19 (Supplementary Table S1), considering the unusually high dropout rate, other participants who discontinued CR could have been indirectly affected by COVID-19. Moreover, unlike in a previous study [35] in which most dropouts occurred in the first 3 months, in the present study, most occurred at 6 months. The COVID-19 pandemic may have directly or indirectly influenced the participants to consider dropping out, affecting them for a longer duration.

Here, patients in the HBCR group complained that they could not exercise properly for several reasons. Owing to the COVID-19 pandemic, government quarantine authorities strongly advised the public not to go to crowded places and refrain from going out as much as possible, and public sports facilities and health clubs were mostly closed. Additionally, quarantine masks were mandated when leaving the house. Thus, the participants were afraid or reluctant to go out to their community for exercise.

In the US, the COVID-19 pandemic was associated with cessation of CR programs and decline in CR participation which particularly affected socially vulnerable communities [9]. In the United Kingdom, COVID-19 lockdown restrictions were associated with decreased CR participation, leading to almost 30% of participants being reluctant to continue with CR [7].

The psychological and occupational impacts resulting from pandemic also adversely affected the well-being of health care providers [10].

Under these circumstances, digital therapy and telemedicine have become necessary to provide health care to patients and the concept of home-based cardiac tele-rehabilitation (HBCTR) has emerged [36,37]. Here, HBCR participants were unable

to achieve optimal benefits from participating in CR during the COVID-19 pandemic. Furthermore, dropout rates in both the CBCR and HBCR groups were higher than predicted. The COVID-19 pandemic should be considered an opportunity to transform CR by integrating it with recent technologies [7,21,36]. Recent studies in CR have emphasized the importance of such interventions and highlighted the need for future randomized controlled trials to validate the effectiveness of HBCTR [36-39].

However, there are several concerns regarding tele-rehabilitation. Relevant standard treatment guidelines have not yet been developed satisfactorily. High-tech devices may be less accessible to the elderly or low-income groups resulting in digital inequalities. Also, further studies are required to determine its long-term effects [30]. Additionally, it is important that these new programs include the content of traditional CR, which involves individualized treatment plan with nutritional education, psychological evaluation, risk factor control as well as exercise training [36].

This study has several limitations. First, a relatively small number of participants were originally included and various factors, including the COVID-19 pandemic, adversely affected CR maintenance, resulting in a high dropout rate. Second, the participants were divided into HBCR and CBCR group depending on one's risk of exercise related cardiovascular adverse event and socioeconomic or occupational status. Therefore, the randomization of the participants could not have been performed. Finally, this was a prospective observational study conducted at a single center; therefore, the findings cannot be generalized to patients in different settings.

The COVID-19 pandemic and the associated social restrictions may have adversely affected the maintenance of effective CR behaviors [8]. Strategies to supervise the intensity and content of home-based exercises, such as tele-rehabilitation or CR based on digital therapy, are urgently required to improve the outcomes of HBCR and maintain and improve adherence to CR in the case of another pandemic.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Kim C. Data curation: Song JH, Kim SH. Formal analysis: Song JH. Investigation: Song JH, Kim SH. Methodology: Kim C, Kim SH. Funding acquisition: Kim C. Project administration: Kim C. Supervision: Kim C. Validation: Kim C, Song JH. Visualization: Kim C, Song JH. Writing – original draft: Song JH. Writing – review and editing: Kim C, Kim SH. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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ORCID

Chul Kim, https://orcid.org/0000-0001-8223-2945
Jun Hyeong Song, https://orcid.org/0000-0001-9003-0032
Seung Hyoun Kim, https://orcid.org/0000-0003-3051-9287

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Reference Standard of Median Nerve Conduction Study in Korea

Jae Hyun Lee, MD[1,*], Eunkyung Kim, PhD[1,2,3], Hyung-Seok Shim, PhD[4,5], Min-Gu Kang, MD[6], Keewon Kim, MD, PhD[1,3,7], Sang Yoon Lee, MD, PhD[3,7,8], Goo Joo Lee, MD[1,9], Shi-Uk Lee, MD, PhD[3,7,8], Jae-Young Lim, MD, PhD[3,7,10,11], Sun Gun Chung, MD, PhD[1,3,7,11], Byung-Mo Oh, MD, PhD[1,3,7,9,11]

[1]*Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul, Korea*
[2]*Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea*
[3]*Data Center for Korean Reference Nerve Conductions, Seoul National University Hospital, Seoul, Korea*
[4]*National Center for Standard Reference Data, Daejeon, Korea*
[5]*Korea Research Institute of Standards and Science, Daejeon, Korea*
[6]*Department of Rehabilitation Medicine, Daegu Workers' Compensation Hospital, Daegu, Korea*
[7]*Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, Korea*
[8]*Department of Rehabilitation Medicine, SMG-SNU Boramae Medical Center, Seoul, Korea*
[9]*Department of Rehabilitation Medicine, National Traffic Injury Rehabilitation Hospital, Yangpyeong, Korea*
[10]*Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam, Korea*
[11]*Institute on Aging, Seoul National University, Seoul, Korea*

Objective: To establish the reference standard of the median nerve conduction study (NCS) in Korea.

Methods: A total of 648 median motor and 602 median sensory NCSs from 349 Korean healthy volunteers were tested and analyzed prospectively. Equipment calibration, assessment of intra- and inter-rater reliability, and the NCSs per se were conducted according to a predetermined protocol. A reference standard was established from uncertainty components for the following parameters: the onset and peak latencies; the baseline-to-peak and peak-to-peak amplitudes; the area and duration of the negative wave; and the nerve conduction velocity. The effects of sex, age and stimulation intensity were analyzed.

Results: Each measured value of 648 median motor and 602 median sensory nerves were obtained and presented with both mean and expanded uncertainties, as well as mean and standard deviations. The cut-off values with expanded uncertainty were determined for different age and sex groups. After adjusting for anthropometric covariates, all parameters except duration were affected by age, and sex appeared to influence both duration and area. While stimulation intensity significantly affected some parameters including latencies, the effect sizes were negligible.

Conclusion: We propose the median NCS reference standard using the largest Korean dataset ever available. The use of the traceable and reliable reference standard is anticipated to promote more accurate and dependable diagnosis and appropriate management of median neuropathies in Korea.

Keywords: Nerve conduction studies, Reference values, Reference standards, Median nerve, Uncertainty

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Correspondence:
Byung-Mo Oh
Department of Rehabilitation Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel: +82-2-2072-3954
Fax: +82-2-743-7473
E-mail: moya1@snu.ac.kr

*Current affiliation: Jae Hyun Lee (Department of Rehabilitation Medicine, Pusan National University Hospital, Busan, Korea)

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INTRODUCTION

The nerve conduction study (NCS) is a crucial component of electrodiagnosis, evaluating the transmission of electrical signals within nerves in the context of various neuromuscular diseases. This diagnostic procedure analyzes waveform properties, including latencies and amplitudes, to gauge the existence and extent of nerve pathology. Ensuring the accurate assessment of alterations in nerve function between healthy and diseased conditions requires a reliable reference standard. Nevertheless, the range of NCS results can vary due to biological variations and factors related to the environment or the procedure itself [1-5].

Efforts have been undertaken to standardize NCS by establishing normative data and clinical guidelines [6-13]. In the United States, the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) established the Normative Data Task Force (NDTF), which systematically reviewed articles published between 1990 and 2012. They proposed consensus-based methodological criteria, comprising seven key issues and techniques [14]. Additionally, the AANEM provided normative reference data from the literature that met these criteria in a separate publication [15]. Similarly, in Korea, the Korean Association of Electrodiagnostic Medicine (KAEND) is actively working on standardizing NCS by developing guidelines and administering practitioner qualification tests [9].

Previous efforts to standardize NCSs, however, did not take into account measurement uncertainties, a crucial aspect for securing traceability in laboratory medicine. Traceability refers to the ability to link measurement results to recognized references, such as national or international standards, through an unbroken chain of calibrations [16]. To demonstrate traceability, the uncertainty of measurement must be considered and presented along with the results. This requires calibration of NCS instruments and consideration of all uncertainty components [16]. A reference standard produced with these considerations would improve accuracy in diagnosis and increase reliability among electrodiagnostic laboratories.

Measurement uncertainties are well-documented in laboratory medicine and have been studied in clinical biochemistry, encompassing areas such as serum anion calculation, international normalized ratio monitoring, and creatinine clearance evaluations [17-23]. To date, there have been no previous attempts to measure uncertainty in NCS. Since 2018, we have been working on this and have published reference standards for the ulnar nerve and peripheral nerves in the lower extremities [24,25]. Furthermore, there is a dearth of large-scale studies on median nerve NCS within the Korean population. The aim of this study was to produce a reference standard for median NCS, stratified by age and sex, using the most extensive sample of healthy Korean volunteers ever examined, and to investigate the characteristics of the data.

METHODS

Subjects

Before this study, a survey was conducted among experts within KAEND and the field of rehabilitation medicine to gauge the interest in utilizing standardized reference standard data. The findings indicated a strong preference for age and sex-specific average and cut-off data. Consequently, this study is dedicated to establishing age and sex-specific reference standards for nerve conduction, with a specific focus on individuals in their 50s—the most commonly tested age group in Korea based on the 2016 Health and Medical Bigdata Open portal—alongside healthy representative adults in their 20s for comparative analysis [26]. The number of subjects was determined based on previous reports, ensuring accurate estimation and representation of 3rd (97th) percentiles and 2 standard deviation values [6,27].

During 2018–2021, 349 healthy volunteers participated in this study after responding to recruitment ads posted at four hospitals or on the website of the clinical trial center. The following were the criteria for inclusion: (1) reside in Korea, (2) are in good health, and (3) are at the ages of 20–39 or 50–69 years old. The following were the criteria for exclusion: (1) patients on pacemakers, (2) diagnosed with diabetes, (3) having hypothyroidism or hyperthyroidism, (4) having cancer or on chemotherapy or external beam radiation, (5) pregnant or planning to become, (6) significantly reduced cognitive function making communication difficult, (7) numbness or pain in all or part of the upper or lower limbs for more than a month in the last three months, (8) diagnosed with psychiatric or neurological disease or on medications, (9) having other medical conditions or taking medications that affect the peripheral nerve function as judged by the researchers.

NCS was conducted from the left and right upper extremities of each of the 349 subjects according to the predetermined protocol. Out of a total of 349 subjects, 324 subjects conducted median motor NCS, and 301 subjects conducted median sensory NCS. Among the 648 median motor nerves that were analyzed, 13 were excluded as outliers. As a result, a total of 635 median

motor nerves were included in the statistical analysis and reference standard production for distal motor NCS parameters. However, only 629 nerves were analyzed for proximal motor NCS and nerve conduction velocity (NCV) parameters due to the presence of Martin-Gruber anastomosis (MGA) in 6 nerves. Similarly, among the 602 median sensory nerves analyzed, 18 were excluded as outliers, and a total of 584 were included in the analysis. Outliers are determined by more than 1.5 interquartile range from the 3rd quartile or less than 1.5 interquartile range from the 1st quartile according to the distribution characteristics of the parameters from each of the four subgroups by age and sex. All subjects have read and signed an informed consent form and were rewarded after the examination. The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (No. 1804-125-940, 2104-107-1212), Seoul National University Bundang Hospital (No. B-1809-493-301, B-2106-689-402), SMG-SNU Boramae Medical Center (No. 10-2018-82, 10-2021-76), and National Traffic Injury Rehabilitation Hospital (No. NTRH-20017, NTRH-21008).

NCS parameters

The parameters of compound motor action potential (CMAP) were as follows: onset latency (L_{onset}); baseline to negative peak amplitude (Amp_{b-p}); negative peak to positive peak amplitude (Amp_{p-p}); negative spike area (A_{neg}); negative spike duration (D_{neg}). The L_{onset} from CMAP elicited by proximal stimulation was only used in calculating the NCV parameter and is not presented as reference standard. The motor NCV was determined by dividing the distance between the proximal and distal stimulation sites by the time difference between the proximal and distal latencies (Fig. 1A). For the sensory nerve action potential (SNAP), L_{onset}, peak latency (L_{peak}), Amp_{b-p} and Amp_{p-p} were presented as parameters. The NCV, A_{neg}, and D_{neg} were not presented as they were not included in the current reference standard (Fig. 1B).

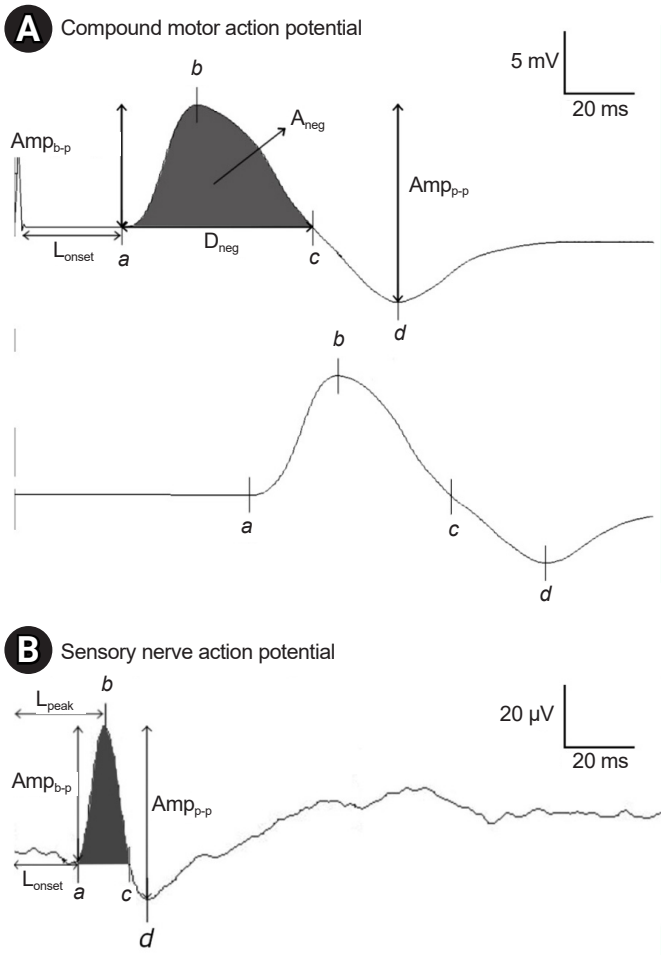

Fig. 1. Demonstration of the waveform of action potentials obtained from median motor (A) and sensory (B) nerves stimulation. *a*, initial point of negative deflection; *b*, peak point of negative deflection: *c*, the point that negative potentials turn into the iso-electrical line; *d*, peak point of positive deflection; L_{onset}, onset latency which is time from initial point to marker *a*; Amp_{b-p}, baseline to negative peak amplitude which is vertical distance from marker *a* to *b*; Amp_{p-p}, negative peak to positive peak amplitude which is vertical distance from marker *b* to *d*; A_{neg}, negative spike area which is shaded; D_{neg}, negative spike duration which is time from marker *a* to *c*; L_{peak}, peak latency which is time from initial point to marker *b*.

NCS instruments and settings

The NCS data were produced using six NCS instruments (Nicolet EDX®; Natus) from four hospitals. Each instrument consisted of a base unit, a hand-held stimulator probe, an amplifier, a control panel, PC and an LCD monitor. The NCS instruments, soft tape measures, thermometers, and indoor thermo-hygrometers had been calibrated annually. The frequency filtration range for motor NCS was 10–10,000 Hz, sweep speed was 2 ms/division, and sensitivity was 2–5 mV/division. The frequency filtration range for sensory nerves was 20–2,000 Hz, sweep speed was 1–2 ms/division, and sensitivity was 5–20 μV/division.

The stimulation intensity was determined by progressively raising the intensity until no further amplitude rise was possible. In order to ensure that the stimulation is supramaximal,

10% to 20% of stimulation intensity was added. If maximal stimulation intensity could not be attained, with stimulation duration of 0.1 ms, even at 100 mA, the process was repeated with the stimulation duration of 0.2 ms.

NCS protocol

First, the surface temperature of both hands was measured to ensure that it is between 33 and 37 degrees Celsius. If necessary, the use of a water bath, a heating lamp, a hot pack, or a hair dryer was permitted prior to beginning NCS. The skin was cleaned with a swab containing 70% isopropyl alcohol to increase electrode contact and decrease impedance. Although the influence of ambient temperature and humidity on NCSs has not yet been precisely established, these variables were likewise kept within tolerable limits of 15 to 25 degrees Celsius and 40 to 60 percent, respectively.

The posture, stimulation locations, and recording sites for median motor NCS were determined according to the predetermined in-house protocol, which is in accordance with widely accepted methodology in Korea and other countries [1,27,28]. In brief, for median motor NCS, the active electrode was attached to the midpoint of the line between the first metacarpophalangeal joint and the median point of the distal wrist crease, on the most prominent belly of the abductor pollicis brevis muscle. It can be moved to obtain maximum negative deflections to get as close to the motor point as possible. The reference electrode was attached to the interphalangeal joint of the thumb. The ground electrode was attached adjacent to the palm or the dorsum of hand. The cathode of the stimulator was placed 8 cm proximal to the active electrode along the following path: (1) from the active electrode to the midpoint of the distal volar wrist crease and (2) upward along the midline between the flexor carpi radialis and palmaris longus tendons. Proximal stimulation was just medial to the brachial artery pulsation on the antecubital fossa (Fig. 2A). The MGA was defined as a nerve where $Amp_{p\text{-}p}$ is 0.3 greater than $Amp_{b\text{-}p}$. Considering that MGA is an anatomical variant occurring in the forearm region, the upper limbs in which MGA was confirmed were only excluded from the analysis of proximal motor NCS parameters and NCV.

For median sensory NCS, the active electrode was attached to the skin over the second proximal phalanx. The reference electrode was attached at least 4cm distal to the active electrode. The ground electrode was attached adjacent to the active electrode between the active electrode and the cathode of the stimulator or on the hand dorsum. The cathode of the stimulator was placed 14 cm proximal to the active electrode between the flexor carpi radialis and palmaris longus tendons (Fig. 2B).

Uncertainty assessment

The evaluation of uncertainty begins with the definition of measurand. In this study, the measurands included all NCS parameters which mentioned in the previous section. The process of evaluating uncertainty is carried out according to the Guide to the expression of uncertainty in measurement (GUM), which is the international standard for uncertainty evaluation [29]. The evaluation of uncertainty followed the steps outlined in the GUM, including the expression of model equation; investigation of uncertainty components and standard uncertainty for each component; calculation of combined standard uncertainty

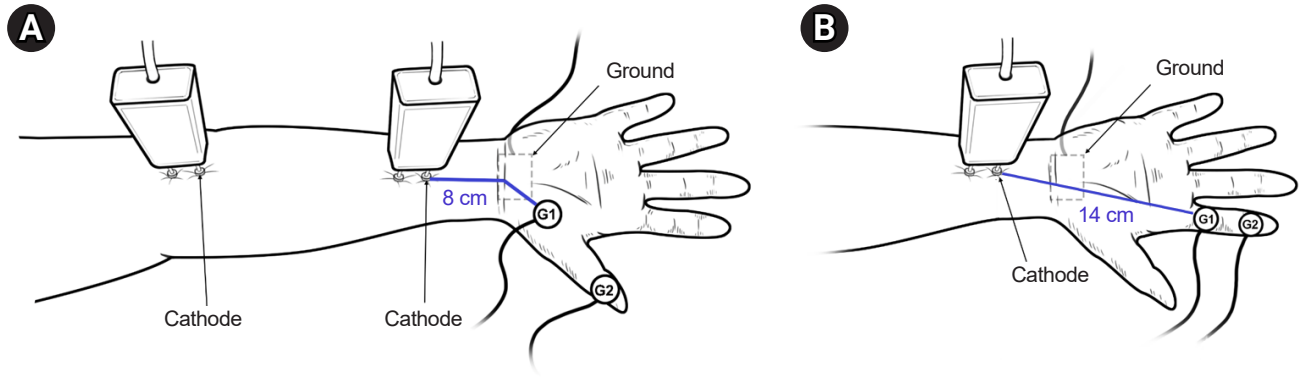

Fig. 2. Schematic illustration of the motor (A) and sensory (B) median nerve conduction studies. (A) Distal and proximal stimulation sites on the median motor nerve and recording electrodes attached to the abductor pollicis brevis muscle. (B) Stimulation site on the median sensory nerve and recording electrodes attached to the index finger. G1, active electrode; G2, reference electrode; Ground, ground electrode; Cathode, cathode of stimulator.

and expanded uncertainty. The entire procedure for evaluating uncertainty is publicly available in Korean at the Data Center for Korean Reference Nerve Conductions website (https://emgreference.org/43) and we attached additional supplement materials with an English translation for international readers (Supplementary Material S1). Additionally, this approach is akin to that employed in the paper on reference standard data for the other nerves, conducted parallelly during 2018–2019 [24,25].

Statistical analysis

Anthropometric data were summarized by age and sex, then compared using the student-t test. To assess the impact of age and sex on NCS parameters, both univariable and multivariable linear mixed models (LMMs) were employed to effectively address the data gathered from two separate instances within both extremities. The univariable LMM was adjusted only for the side (left or right), while the multivariable LMM accounted for height, weight, soft lean mass, body fat mass, and skeletal muscle mass. Additionally, the effect of stimulation intensity on NCS parameters was also analyzed using a multivariable LMM that accounted for the aforementioned anthropometric factors, as well as sex and age. Normality was confirmed in each model through residual plots, with no models failing to meet this criterion. Statistical significance was established at p-value<0.05. All statistical analyses were conducted using R statistical software (version 3.5.3; R Foundation for Statistical Computing).

RESULTS

Anthropometric data

The anthropometric data, detailed in Table 1, reveal significant differences in measured parameters based on sex within the same age group or age within the same sex group. Specifically, obesity rates, defined as a body mass index exceeding 25, demonstrate notable disparities. In the 20s–30s age group, 51.0% of male and 6.8% of female are classified as obese. In the 50s–60s age group, these rates shift to 46.2% for male and 27.2% for female. Notably, only one subject required an increased stimulation duration of 0.2 ms for supramaximal stimulation.

Reference standards for the NCS parameters

Tables 2 and 3 comprehensively summarize the NCS parameters, with Table 2 summarizes the upper limits of latency parameters and Table 3 summarizes the lower limits of the rest parameters. All parameters are presented as mean with expanded uncertainty and mean with two standard deviations.

Due to the vast amount of data, this section will present the cut-off values with expanded uncertainty on L_{onset} and NCV

Table 2. Latency variables stratified by sex and age of median nerve conduction studies

		Latency variable		
		Distal motor	Distal sensory	
		L_{onset} (ms)	L_{onset} (ms)	L_{peak} (ms)
Male				
20–30s	Mean+EU	4.20	3.13	3.98
	Mean+2SD	4.04	2.95	3.78
50–60s	Mean+EU	4.57	3.45	4.34
	Mean+2SD	4.42	3.23	4.07
Female				
20–30s	Mean+EU	4.06	3.20	4.11
	Mean+2SD	3.89	3.00	3.86
50–60s	Mean+EU	4.41	3.33	4.17
	Mean+2SD	4.27	3.13	3.88

648 for motor nerves, 602 for sensory nerves.
L_{onset}, onset latency; L_{peak}, peak latency; EU, expanded uncertainty; SD, standard deviation.

Table 1. Anthropometric data stratified by age and sex

	Young adults (20–30s)		Middle-aged (50–60s)		p-value			
					Male vs. Female		20s vs. 50s	
	Male (N=98)	Female (N=103)	Male (N=74)	Female (N=74)	20s	50s	Male	Female
Height (cm)	174.46±5.55	160.26±4.81	169.18±5.67	156.70±4.74	<0.001	<0.001	<0.001	<0.001
Weight (kg)	77.01±10.52	55.30±7.11	70.68±9.79	58.28±7.15	<0.001	<0.001	<0.001	0.007
SLM (kg)	55.02±6.33	35.62±4.16	50.36±6.02	36.18±3.35	<0.001	<0.001	<0.001	0.338
BFM (kg)	18.92±7.53	17.33±4.55	17.23±5.30	19.83±5.41	0.073	0.004	0.085	0.001
SMM (kg)	33.01±4.13	20.37±2.70	29.81±3.80	20.62±2.10	<0.001	<0.001	<0.001	0.454
BMI (kg/m^2)	25.27±3.02	21.51±2.38	24.65±2.86	23.64±2.58	<0.001	0.04	0.172	<0.001

Values are presented as mean±standard deviation.
N, number of subjects with at least one nerve examined; SLM, soft lean mass; BFM, body fat mass; SMM, skeletal muscle mass; BMI, body mass index.

Table 3. The variables except latencies, stratified by sex and age of median nerve conduction studies

		Parameters except latency										
		Distal motor				Proximal motor				Proximal to distal	Distal sensory	
		Amp_{b-p} (mV)	Amp_{p-p} (mV)	A_{neg} (mVms)	D_{neg} (ms)	Amp_{b-p} (mV)	Amp_{p-p} (mV)	A_{neg} (mVms)	D_{neg} (ms)	NCV (m/s)	Amp_{b-p} (μV)	Amp_{p-p} (μV)
Male												
20–30s	Mean-EU	6.97	10.49	19.47	4.39	6.63	10.08	18.39	4.52	46.34	27.08	34.40
	Mean-2SD	7.01	10.50	19.47	4.39	6.67	10.09	18.39	4.52	53.45	27.43	34.72
50–60s	Mean-EU	6.47	9.78	15.83	4.12	6.19	9.23	15.34	4.33	43.71	16.17	19.75
	Mean-2SD	6.52	9.79	15.83	4.12	6.24	9.24	15.34	4.33	50.17	15.94	17.71
Female												
20–30s	Mean-EU	7.72	11.61	21.48	4.27	7.22	10.91	19.94	4.37	43.97	34.06	37.30
	Mean-2SD	7.76	11.62	21.48	4.27	7.27	10.92	19.94	4.37	51.85	35.23	38.42
50–60s	Mean-EU	6.35	9.31	15.35	3.93	6.12	8.90	15.04	4.13	41.85	23.85	31.42
	Mean-2SD	6.40	9.32	15.35	3.93	6.17	8.92	15.04	4.13	49.26	26.42	35.61

648 for motor nerves, 602 for sensory nerves.
Amp_{b-p}, baseline to negative peak amplitude; Amp_{p-p}, negative peak to positive peak amplitude; A_{neg}, negative spike area; D_{neg}, negative spike duration; NCV, nerve conduction velocity; EU, expanded uncertainty; SD, standard deviation.

which hold clinical significance in the diagnosis of carpal tunnel syndrome. In case of L_{onset} of SNAP, the cut-off value was 3.13 ms for male in their 20s–30s and 3.45 ms for those in their 50s–60s. For female, these values were 3.20 and 3.33 ms for the respective age groups. Regarding CMAP, the cut-off values were 4.20 ms for male in their 20s–30s and 4.57 ms for those in their 50s–60s. For female, these values were 4.06 and 4.41 ms for the respective age groups. As for the cut-off values for NCV, the values were 46.34 and 43.71 m/s for male in their 20s–30s and 50s–60s, respectively. For female, these values were 43.97 and 41.85 m/s for the respective age groups.

The effects of age and sex on NCS parameters

In the CMAP parameters, such as L_{onset}, Amp_{b-p}, Amp_{p-p}, A_{neg}, and NCV showed significant age effects in both univariable and multivariable analyses, with p-values less than 0.001. However, D_{neg} did not exhibit a significant age effect in either analysis. In the SNAP parameters, L_{onset}, L_{peak}, Amp_{b-p}, and Amp_{p-p} showed significant age effects in both analyses. In particular, SNAP amplitude parameters exhibited significant effect sizes, presenting -18.49 ($p<0.001$) for Amp_{b-p} and -27.86 ($p<0.001$) for Amp_{p-p}.

Regarding the effect of sex on all NCS parameters, there were no parameters that showed the sex effect, except for A_{neg} and D_{neg}, which were observed as significant in both types of analyses. In case of L_{onset} of CMAP and Amp_{b-p} and Amp_{p-p} of SNAP, they displayed statistical significance in the univariable analysis. However, these effects did not persist in the multivariable analysis once anthropometric factors were controlled for. These findings are summarized in Table 4.

The effects of stimulation intensity on NCS parameters

When exploring the effects of stimulation intensity on CMAP parameters, L_{onset} showed a negative effect size of -0.002. Amp_{b-p} demonstrated a effect in both distal and proximal CMAPs with effect sizes of -0.011 and -0.018, respectively. D_{neg} also showed significant differences with effect sizes of 0.004 in distal and 0.003 in proximal CMAP. These parameters show p-values indicating statistical significance. However, Amp_{p-p} in the distal CMAP did not reach statistical significance (-0.015, $p=0.077$), contrasting with its significant effect in the proximal CMAP (-0.028, $p<0.001$). In the SNAP parameters, L_{onset} showed a significant effect size of -0.003 ($p=0.004$), and L_{peak} was also significant with an effect size of -0.003 ($p=0.032$).

The remaining parameters did not show significant differences, and the results are summarized in Table 5.

DISCUSSION

We conducted median motor and sensory NCSs, producing the largest reference standard for the Korean population to date. We comprehensively evaluated the effect of age, sex and stimulation intensity on median NCS in Koreans, while considering as many uncertainty components as possible, encompassing subject characteristics and testing procedures.

The significance of developing a reliable new reference standard for the Korean population

In this study, we produced the NCS dataset comprising 648 median motor nerves and 602 sensory nerves, along with 14 NCS

Table 4. Effects of age and sex for nerve conduction study parameters on univariable and multivariable linear mixed model analysis

	Age effect				Sex effect			
	Univariable		Multivariable		Univariable		Multivariable	
	b	p-value	b	p-value	b	p-value	b	p-value
Distal motor								
L_{onset} (ms)	0.25	<0.001***	0.23	<0.001***	-0.16	<0.001***	0.03	0.728
Amp_{b-p} (mV)	-1.60	<0.001***	-1.53	<0.001***	-0.16	0.519	-0.51	0.290
Amp_{p-p} (mV)	-3.16	<0.001***	-2.85	<0.001***	-0.61	0.156	-1.37	0.083
A_{neg} (mVms)	-6.42	<0.001***	-5.42	<0.001***	-2.76	0.002**	-4.03	0.013*
D_{neg} (ms)	-0.09	0.188	0.01	0.850	-0.32	<0.001***	-0.33	0.007**
Proximal motor								
Amp_{b-p} (mV)	-1.57	<0.001***	-1.53	<0.001***	-0.23	0.360	-0.56	0.234
Amp_{p-p} (mV)	-3.08	<0.001***	-2.82	<0.001***	-0.71	0.091	-1.40	0.069
A_{neg} (mVms)	-5.98	<0.001***	-5.12	<0.001***	-2.63	0.002**	-3.94	0.012*
D_{neg} (ms)	-0.05	0.468	0.06	0.391	-0.30	<0.001***	-0.26	0.040*
Proximal-to-distal								
NCV (m/s)	-2.29	<0.001***	-2.09	<0.001***	0.02	0.952	-0.91	0.175
Distal sensory								
L_{onset} (ms)	0.08	0.003**	0.10	0.0015**	-0.05	0.075	0.03	0.527
L_{peak} (ms)	0.07	0.029*	0.09	0.0052**	-0.04	0.211	0.04	0.512
Amp_{b-p} (μV)	-18.20	<0.001***	-18.49	<0.001***	11.99	<0.001***	4.51	0.152
Amp_{p-p} (μV)	-27.17	<0.001***	-27.86	<0.001***	19.32	<0.001***	9.00	0.102

b, estimate; L_{onset}, onset latency; Amp_{b-p}, baseline to negative peak amplitude; Amp_{p-p}, negative peak to positive peak amplitude; A_{neg}, negative spike area; D_{neg}, negative spike duration; NCV, nerve conduction velocity; L_{peak}, peak latency.
*p<0.05, **p<0.01, ***p<0.001.

Table 5. Effect of stimulation intensity on nerve conduction study parameters

	Effect of stimulation intensity	
	Effect size	p-value
Distal motor		
L_{onset} (ms)	-0.002	0.016*
Amp_{b-p} (mV)	-0.011	0.042*
Amp_{p-p} (mV)	-0.015	0.077
A_{neg} (mVms)	-0.001	0.964
D_{neg} (ms)	0.004	0.012*
Proximal motor		
Amp_{b-p} (mV)	-0.018	<0.001***
Amp_{p-p} (mV)	-0.028	<0.001***
A_{neg} (mVms)	-0.027	0.083
D_{neg} (ms)	0.003	0.021*
Proximal-to-distal		
NCV (m/s)	-0.012	0.145
Distal sensory		
L_{onset} (ms)	-0.003	0.004**
L_{peak} (ms)	-0.003	0.032*
Amp_{b-p} (μV)	-0.023	0.675
Amp_{p-p} (μV)	0.031	0.751

L_{onset}, onset latency; Amp_{b-p}, baseline to negative peak amplitude; Amp_{p-p}, negative peak to positive peak amplitude; A_{neg}, negative spike area; D_{neg}, negative spike duration; NCV, nerve conduction velocity, L_{peak}, peak latency.
*p<0.05, **p<0.01, ***p<0.001.

parameters and 6 anthropometric factors, making it the largest normative dataset currently available. A few previous studies in Korea have presented normative data for the median nerve, however they were subject to certain limitations.

For example, in 1982, Hahn and Chang [30] reported normative data on distal latency, Amp_{b-p}, and conduction velocity for both motor and sensory median nerves. However, their study was limited by a small sample size of only 120 subjects, with some subgroups containing as few as 10 subjects. Later, in 1998, Lee et al. [31] reported the terminal latency and amplitudes of median motor and sensory nerves in 242 normal Korean subjects. Yet, their study did not provide normative data segmented by age and sex, nor did it examine the effects of these factors. In 2002, a meta-analysis conducted by Lee and Ra [32] reviewed data from 36 articles, with subject populations ranging from 296 to 500. However, only one of these articles focused on the Korean population, which was the study conducted by Hahn and Chang [30]. Our study addresses these gaps by providing a more extensive and detailed dataset, featuring over 100 nerves in each groups, categorized by sex and age. This extensive dataset could enriches the understanding of median nerve characteristics in the Korean population.

Furthermore, this study not only establishes the largest refer-

ence standard for median NCS but also introduces the concept of "expanded uncertainty," a value commonly used in other medical fields [17-23], yet novel in the context of NCS. Previous attempts by physicians, researchers, and electrodiagnostic societies to create normative data involved skilled practitioners and standardized procedures [6-15]. However, achieving "metrological traceability" remains. Metrological traceability can be achieved by developing measurement standards that include measurement uncertainty and by establishing an unbroken calibration chain to the international unit system through collaboration with the National Metrology Institute in Korea. For instance, we have developed a standard signal generator that mimics neural waveforms, used for calibrating electrodiagnosis machines. This signal generator undergoes yearly calibration by a nationally certified institution and is accompanied by calibration certificates. In our pursuit of robust NCS reference data, we calculated the expanded uncertainty by considering a wide range of comprehensive uncertainty components. These components were meticulously integrated and presented in a formula that encompasses each standard uncertainty. Considering these various potential variabilities could enhance reliability across different laboratories. Electrodiagnostic laboratories not only refer to these standards for clinical tests but also have the flexibility to adapt this reference data to various laboratory environments by adjusting the standard uncertainty with their specific uncertainty components from our openly disclosed protocol. Consequently, reference data presented with expanded uncertainty becomes versatile, making it applicable to diverse situations. To achieve this goal, more hospitals must actively participate, labs must become proficient in evaluating nerves with uncertainties, and international collaboration is necessary to establish international reference standards.

The effect of aging

Our study was conducted on adult populations with two age groups: those in their 20–30's and those in their 50–60s. The latter group is commonly tested for NCS in Korea, and we sought to examine the impact of age by comparing them with the younger group. Thus, the age effects reported in our study are based on the comparison between these distinct adult groups. Although direct comparisons with studies from other age populations are limited, discovering similar trends could still hold significant implications. Our data could be compared with two previous studies, due to the appropriateness of the study populations and the methodological completeness. The first study, conducted by Hahn and Chang [30], was the only one that attempted to produce the reference of median NCS for a healthy Korean population. The second study, conducted by Buschbacher [27], was the only study to meet the NDTF criteria set by AANEM for the median motor nerve. Hahn and Chang [30] compared NCS parameters of individuals in their 10–40s with those in their 50–60s, while Buschbacher [27] compared individuals in their 20–40s with those in their 50–70s.

In our study, the effect of aging on all NCS parameters, except D_{neg}, was significant in the univariable analysis. Upon further multivariable analysis, all parameters remained statistically significant, but the effect sizes of CMAP parameters were slightly reduced, and the effect sizes of SNAP parameters were slightly increased.

At first, all latency parameters and NCV had an aging effects that delayed and slowing down. Previously, NORRIS et al. [33] have explained the aging changes of conduction velocity in terms of changes in the endoneurial permeability because of vascular changes and local ischemia, WAGMAN and LESSE [34] have explained it in terms of changes in metabolism and circulation. The previous Korean study showed a similar trend but reported sensory NCV, which was not included in our study and was not statistically significant. It is possibly due to the smaller sample size [30].

All amplitudes parameters and A_{neg} are larger in younger group. This age effect on Amp_{b-p} are previously reported and appear to be relevant [15]. However, reports regarding Amp_{p-p} and A_{neg} are scarce. The previous Korean data, which only reported statistically significant aging effects on the Amp_{b-p} of SNAP, contrasts with our study [30]. Nevertheless, our findings, with its sufficient sample size and inclusion of various covariates, demonstrated aging effects on all amplitude parameters, corroborating with Buschbacher's [27] data.

The absence of an age effect in D_{neg} suggests a relatively consistent aging process in nerve fibers, because inhomogeneous aging in either the fastest or slowest fibers could conceivably result in a decrease or increase in D_{neg}. Additionally, the observed decrease in amplitudes with aging suggests that it is primarily attributable to a reduction in the source of action potentials, rather than dispersion of conduction duration. Previous findings revealed that aging, including in adults ranging from their 40s to 70s, had no impact on D_{neg}, further reinforcing the idea of a homogeneous aging process in nerves post-adulthood [27,30]. Conversely, some studies have shown that children have shorter durations compared to adults, which suggests that

immature nerves may conduct electrical signals more synchronously [30,35].

The effect of sex

In the previous studies, sex effects have been inconsistent. Notably, when considering anthropometric covariates comprehensively, the apparent effect of sex tends to vanished [3,36]. There have been reports of minor morphological and certain electrophysiological variations based on sex [5,37,38]. A particular study on cadavers focusing on sexual dimorphism in morphometric characteristics found no significant differences in the total count, average cross-sectional area, and circularity ratio of myelinated axons [37]. Gøransson et al. [38] noted a higher density of epidermal nerve fibers in females, while Meh and Denišlič [39] observed a heightened sensitivity to minor temperature shifts in females. Some researchers have hypothesized that these differences might be attributable to environmental factors, such as higher rates of alcohol consumption, occupational neurotoxic exposure, and physical trauma, which are more common in males [5,38]. In our study, all six examined anthropometric parameters showed substantial sex-based differences, necessitating multivariate analysis in assessing the impact of sex on NCS data, to adequately account for physical disparities between the sexes.

Initially, multivariable analysis, accounting for anthropometric factors, revealed no sex differences in all latency parameters of motor and sensory nerves. This suggests that median nerve fibers transmit electrical signals at equivalent speeds in both sexes, given similar physical traits. There was no sex effect in NCV, as it is calculated based on latency. These findings align with previous Korean data, however, contrast with the study by Buschbacher [27], which reported sex differences in L_{onset} and NCV [30]. This inconsistency could stem from different racial backgrounds of subjects. However, Buschbaher's [27] study only considered height as a covariate, overlooking other sex-specific anthropometric variables like lean muscle mass, body fat mass, and appendicular muscle mass.

Among all amplitude parameters, only SNAP amplitudes were significantly larger in female in univariable analysis. However, this significance vanished after adjusting for anthropometric factors in multivariable analysis. A_{neg} was significantly small in females. Although A_{neg} decreases in both females and the aging group, the result in females is due to shorter durations without a difference in amplitude, while in the aging group, it is due to smaller amplitudes without a difference in duration, presenting a contrasting appearance. In case of D_{neg}, it was the only parameter displaying no aging effect but a significant sex effect, even after adjusting for anthropometric factors. This implies that besides the physique differences, other neuromuscular physiologic factors such as dimorphic neurotransmitter release at the neuromuscular junction [40] might contribute to the observed disparities between sexes.

In summary, latencies and NCV were faster, and amplitudes and A_{neg} were higher at the subjects in their 20–30's. The smaller A_{neg} and shorter D_{neg} of female subjects show the statistical significance but the difference of other parameters were vanished after adjusting for anthropometric factors.

The effect of stimulation intensity

In our previous study, we firstly describe supramaximal stimulus intensity on Asian populations, and stimulation intensity show correlation with body fat mass and faster L_{onset} [25]. The present study also found statistical significance between stimulation intensity and NCS parameters such as all latency parameters, all duration parameters, and CMAP amplitude parameters, although the effect sizes were small. A_{neg} were same on both distal and proximal stimulations, so that whole median nerve fibers are depolarized and supramaximal stimulus are appropriately achieved. Interestingly, at higher stimulation intensities, durations were longer and amplitudes were smaller. This could be due to the requirement for higher intensity to achieve supramaximal stimulation, indicating the presence of more conducting soft tissue between the stimulator and the median nerve, leading to slight but definite unsynchronized excitation. Furthermore, even after achieving supramaximal stimulation, higher intensity shortened all latency parameters. Nevertheless, the effect size is notably small, amounting to less than one percent compare to age effects, suggesting that the clinical significance may be limited. Therefore, while these results are intriguing, further comprehensive research is necessary to fully understand their clinical implications.

Uncertainty components

There are several dominant uncertainty components. The most dominant source of uncertainty came from the "difference between subjects including repeated observation on a subject." For example, the expanded uncertainties of distal motor L_{onset} ranged from 0.89 to 1.03 according to groups, and the uncertainty components from "difference between subjects" accounted for 45.04% to 50.03%.

Meanwhile, the second most dominant source of uncertainty, the "selection of points on the waveform," accounted for 23.93% to 26.32%. Notably, in NCV parameter where these components are calculated twice, the expanded uncertainty becomes enlarged compared to other parameters. This outcome could be an inherent aspect of the current practice, where practitioners manually identify the inflection points of each L_{onset}. Factors such as using a consistent scale of sensitivity and sweep speed, as well as ensuring similar skill levels among practitioners could help mitigate these uncertainty components.

The uncertainty components of "measurements from skin temperature" accounted for 12.39%–13.63%. To address this aspect, the conversion coefficients were adopted to convert surface temperature and distance into milliseconds, as reference in existing literatures [1,4]. For example, Kouyoumdjian et al.'s [4] study stated that a 1°C difference in skin temperature corresponds to a 0.2-millisecond change in motor latency. To aid in comprehension, the uncertainty components of input quantities for each measurand of the median motor nerve are presented as an example (Supplementary Table S1).

Limitations

This study faces several limitations. Firstly, it examines non-continuous adult age groups, omitting data for individuals in their 40s, those over 70, and those under 20. However, through preliminary expert surveys, the study primarily presented data comparing standards for individuals aged 50 to 60, where median nerve conduction studies are most prevalent, to those in the 20 to 30 age group. Secondly, the actual distance and composition of the conducting soft tissue between the stimulator and the median nerve are not directly measured. However, this component was at least indirectly reflected in the differences between subjects, and while direct measurement using imaging technique such as ultrasonography is feasible, it is time-intensive and thus hinders clinical application. In the future, such detailed measurement standards might be considered for specialized research situations requiring precise data. Lastly, employing a single device type suggests the potential for variability in uncertainty components when using devices from other manufacturers. Nevertheless, the overall resemblance in the setup of NCS machines implies that these disparities may be insignificant. If necessary, the expanded uncertainties using other NCS devices could be determined by substituting their specific uncertainty components and standard uncertainties, given that reference standard have traceability. Future research could expand to include NCS devices from multiple manufacturers. Additionally, it is feasible to develop a model formula that accounts for the uncertainties of each separate element of NCS machines.

Conclusions

In conclusion, this study produced the measurement and reference standards for median NCS in the Korean population, considering appropriate uncertainty components. It also revealed effects of age, sex and stimulation intensity among Korean population beside physique difference from the produced reference standard data. All measurement tools are connected to the calibration chain, the protocol is reproducible, and the data is traceable to the international measurement standard. The resulting data has been approved as the national standard reference data of Korea, and it is expected to improve reliability among laboratories, decrease the need for redundant re-tests, reduce medical costs, and be utilized in various clinical situations.

CONFLICTS OF INTEREST

Byung-Mo Oh is the Editor-in-Chief, Jae-Young Lim is a Section Editor, and Sang Yoon Lee and Shi-Uk Lee are Editorial Board members of Annals of Rehabilitation Medicine. The authors did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Kim K, Lee SY, Lee SU, Lim JY, Chung SG, Oh BM. Data curation: Lee JH, Kim E, Shim HS. Formal analysis: Lee JH, Kim E, Shim HS. Funding acquisition: Oh BM, Kim K. Methodology: Lee JH, Kim E, Shim HS, Kim K, Lee SY, Lee GJ, Lee SU, Lim JY, Chung SG, Oh BM. Project administration: Oh BM, Kim K. Investigation: Lee JH, Oh BM, Kang MG. Writing – original draft: Lee JH, Shim HS. Writing – review and

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SUPPLEMENTARY MATERIALS

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ORCID

Jae Hyun Lee, https://orcid.org/0000-0002-4927-9722
Eunkyung Kim, https://orcid.org/0000-0001-6264-722X
Hyung-Seok Shim, https://orcid.org/0000-0003-3438-1721
Min-Gu Kang, https://orcid.org/0000-0002-0680-9607
Keewon Kim, https://orcid.org/0000-0001-6597-578X
Sang Yoon Lee, https://orcid.org/0000-0002-2906-3094
Goo Joo Lee, https://orcid.org/0000-0002-8436-4463
Shi-Uk Lee, https://orcid.org/0000-0003-0850-5217
Jae-Young Lim, https://orcid.org/0000-0002-9454-0344
Sun Gun Chung, https://orcid.org/0000-0001-5785-8110
Byung-Mo Oh, https://orcid.org/0000-0001-9353-7541

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Extensive Multilabel Classification of Brain MRI Scans for Infarcts Using the Swin UNETR Architecture in Deep Learning Applications

Jaeho Oh, MD[1], Hyunchul An, MD[2]

[1]*Department of Physical Medicine and Rehabilitation, Seoul Daehyo Rehabilitation Hospital, Yangju, Korea*
[2]*Department of Emergency Medicine, Pohang SeMyeong Christianity Hospital, Pohang, Korea*

Objective: To distinguish infarct location and type with the utmost precision using the advantages of the Swin UNEt TRansformers (Swin UNETR) architecture.
Methods: The research employed a two-phase training approach. In the first phase, the Swin UNETR model was trained using the Ischemic Stroke Lesion Segmentation Challenge (ISLES) 2022 dataset, which included cases of acute and subacute infarcts. The second phase involved training with data from 309 patients. The 110 categories result from classifying infarcts based on 22 specific brain regions. Each region is divided into right and left sides, and each side includes four types of infarcts (acute, acute lacunar, subacute, subacute lacunar). The unique architecture of Swin UNETR, integrating elements of both the transformer and u-net designs with a hierarchical transformer computed with shifted windows, played a crucial role in the study.
Results: During Swin UNETR training with the ISLES 2022 dataset, batch loss decreased to 0.8885±0.1897, with training and validation dice scores reaching 0.4224±0.0710 and 0.4827±0.0607, respectively. The optimal model weight had a validation dice score of 0.5747. In the patient data model, batch loss decreased to 0.0565±0.0427, with final training and validation accuracies of 0.9842±0.0005 and 0.9837±0.0010.
Conclusion: The results of this study surpass the accuracy of similar studies, but they involve the issue of overfitting, highlighting the need for future efforts to improve generalizability. Such detailed classifications could significantly aid physicians in diagnosing infarcts in clinical settings.

Keywords: Deep learning, Infarction, Classification, Rehabilitation

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Correspondence:
Jaeho Oh
Department of Physical Medicine and Rehabilitation, Seoul Daehyo Rehabilitation Hospital, 36 Goeumnam-ro, Yangju 11492, Korea.
Tel: +82-31-894-1000
Fax: +82-31-894-1077
E-mail: bibliother@naver.com

INTRODUCTION

Evolution of deep learning architectures-from perceptrons to Swin UNEt TRansformers

Artificial neurons are designed to mimic the way biological neurons fire signals when they receive a sufficient number of inputs from other neurons [1]. In 1943, McCulloch and Pitts [1] introduced an early artificial neuron model, known as threshold logic units (TLUs). This model compares a weighted sum of input signals to a threshold to determine the neuron's output, marking the beginning of artificial neural networks [1]. In 1957, Rosenblatt [2] invented the perceptron using a modified TLU

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that applies a step function to the weighted sum of the inputs. To address the limitations of perceptron highlighted by Minsky and Papert [3], particularly their inability to solve exclusive classification problems, a multilayer perceptron (MLP) were developed by stacking multiple perceptrons [4]. Rumelhart et al. [4] developed the groundbreaking backpropagation algorithm, and convolutional neural networks (CNNs) were developed, inspired by the consecutive layered structure of neurons, the optic nerve's local receptive fields [5]. For years, deep CNNs have led in various visual recognition tasks [6]. However, they have limitations in learning long-range dependencies, crucial for segmenting lesions of different shapes and sizes [7] and for excellent output results, supervised training of a large network and millions of parameters are required. But in the medical field, it was difficult to obtain even thousands of training images [8]. Fully convolutional network, also called u-net, was proposed to compensate for the shortcomings of difficulties. It features a contracting path for context capture and a symmetric expanding path for precise localization, maximizing the use of annotated samples through data augmentation [8].

In 2017, Google researchers introduced the transformer architecture, revolutionizing neural machine translation using attention mechanisms instead of convolutional layers [9]. Building on this, Hatamizadeh et al. [5] reformulated volumetric medical image segmentation as a sequence-to-sequence prediction problem, introducing UNEt TRansformers (UNETR), which combines a transformer encoder with a U-shaped network. This structure effectively captures multi-scale patterns and delivers precise semantic segmentation. To overcome the challenge arising from the difference between language and vision, such as large variations in the scale of visual entities and the high resolution of pixels in images, Liu et al. [10] proposed a hierarchical transformer using shifted windows. Inspired by the success of vision transformers, Hatamizadeh et al. [7] propose a novel segmentation model termed Swin UNEt TRansformers (Swin UNETR). Swin UNETR's hierarchical transformer efficiently processes high-resolution images, capturing the fine details necessary for accurate lesion classification in brain magnetic resonance imaging (MRI). Its U-shaped design with skip connections enables exact lesion localization, while the integration of attention mechanisms significantly enhances feature focus, crucial for identifying different lesion types.

The necessity of this study

In the acute phase of stroke care, determining the location of the infarct is essential for clinical decisions, such as patient triage, stroke mechanism investigation, and additional therapies [11]. While lesion–symptom mapping studies have advanced our understanding of brain-behavior relationships, modern imaging techniques have now surpassed the capabilities of traditional lesion analysis [12]. Voxel-based lesion-symptom mapping (VLSM) techniques involve comparing neurobehavioral scores across patients by analyzing the presence or absence of lesions on a voxel-by-voxel basis [12]. VLSM methods have proven useful in elucidating the impact of infarct location on motor [13], language [14], and cognitive recovery [15]. For example, location of the infarct was the most significant factor influencing positive cognitive results [15]. Given the significance of the infarct location, this study aimed to distinguish infarct location and type with the utmost precision using the advantages of the Swin UNETR architecture. Therefore, based on radiological interpretations, the datasets were divided into 110 categories, and a multilabel was assigned to allow for multiple categories to be applicable to a single case. Due to the limited resources available as an individual researcher, this study was planned within the scope feasible through Google Colab [16].

METHODS

This study was conducted in two phases using the Ischemic Stroke Lesion Segmentation Challenge (ISLES) 2022 open dataset and brain MRI data from 309 patients. First, we trained the Swin UNETR model on the ISLES 2022 dataset to create segmentation masks, focusing on differentiating infarctions from normal parenchyma. The model was trained using data from actual patients with official radiological interpretations to learn how to classify the regions already identified as infarcts.

Training Swin UNETR with the ISLES 2022 dataset

ISLES 2022 dataset

ISLES is a specialized competition to promote and advance the methods for automated segmentation of ischemic stroke lesions, with a slightly different purpose since 2015. The 2022 challenge concentrated on the segmentation of infarcts in multimodal MRI scans, encompassing both acute strokes (0 to 7 days post-onset) and sub-acute strokes (1 to 3 weeks post-onset) [17]. It aimed to identify not only large infarct lesions but also multiple embolic infarcts across 400 cases [17]. Participants included were 18 years or older and had undergone brain MR imaging for diagnosed or suspected stroke and the imaging

included at least fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences [17]. Image acquisition was performed on one of the following devices: Philips Achieva 3T MRI scanner (Philips Healthcare), Philips Ingenia 3T MRI scanner (Philips Healthcare), Siemens Verio 3T MRI scanner (Siemens Healthineers), Siemens MAGNETOM Avanto 1.5T MRI scanner (Siemens Healthineers), or Siemens MAGNETOM Aera 1.5T MRI scanner (Siemens Healthineers) [17]. The ISLES 2022 datasets were divided into training, validation, and inference datasets in an 8:1:1 ratio in this study. Data augmentation techniques used included random image rotation by 90 degrees, flipping randomly across the axial, sagittal, and coronal planes, and random adjustments to scale and intensity. Permission to use this data was granted by the ISLES 2022 organizer, Ezequiel de la Rosa.

Swin UNETR implementations

Swin UNETR is implemented using PyTorch-Ignite [18] and MONAI [19], trained on Google Colab [16] with A100 graphics processing units. The model was created by using a feature size of 48, which is compatible with the self-supervised pre-trained weights [20] and the Swin UNETR encoder was initialized from pre-trained weights [21]. Training involved the adaptive moment estimation with decoupled weight decay optimizer [22] with an initial learning rate of 1e-5 and a weight decay of 1e-1, using dice focal loss for about 24,000 iterations. We set the maximum epochs to 400 and configured the patience to 40, the number of events to wait if there is no improvement before stopping the training [23]. This approach ensures the training halts when further improvements are unlikely, helping to prevent overfitting and save computational resources. A detailed description of the Swin UNETR architecture is provided in Supplementary Table S1.

Loss function

The training loss function used was dice focal loss, which computes both dice loss (DL) and focal loss, and return the weighted sum of these two losses, calculated voxel-wise [24]. Focal loss is an extension of binary cross entropy (BCE) loss between the target and the input probabilities [24]. The dice coefficient (DICE) for the binary classification can be written as:

$$DICE_t = \frac{2\sum_{n=1}^{N}(p_{it}g_{it}+\varepsilon)}{\sum_{n=1}^{N}(p_{it})+\sum_{n=1}^{N}(g_{it}+\varepsilon)} \quad (1)$$

The variable g_{it}, which can be either 0 or 1, denotes the ground truth label of class t for pixel i, with N representing the total number of pixels in the image [25]. The variable p_{it}, represents the output probability, indicating that it falls within the range of 0 to 1 and the term ε is employed to prevent the numerical issue of division by zero [25]. The DL formula is as follows, where w represents the weight ω_t corresponding to each class t [25].

$$DL = \sum_t \omega_t (1 - DICE_t) \quad (2)$$

The focal dice loss (FDL) is defined by applying a factor of 1/β as the exponent to $DICE_t$ for each class, where the exponent parameter β is greater than or equal to 1 [25].

$$FDL = \sum_t \omega_t (1 - DICE_t^{1/\beta}) \quad (3)$$

Training loss was recorded every 100 iterations, and at the end of every epoch.

Evaluation metrics

Mean dice was used as the evaluation metric, calculating the dice score from full-size tensors and averaging over batches, class-channels, and iterations [26]. Train mean dice score and validation mean dice score were calculated using the validation and inference datasets.

Training a classification model with patients' brain MRI data

Patients data

We included subjects aged 18 years or older who received MR imaging for diagnosed stroke at Pohang SeMyeong Christianity Hospital. Images were acquired using Siemens MAGNETOM Vida 3T MRI scanner (Siemens Healthineers) and included DWI, apparent diffusion coefficient, and FLAIR modalities in all cases. The ISLES 2022 dataset focuses exclusively on segmentation for acute and subacute infarcts, thereby excluding chronic and old infarcts. Cases presenting only with intracranial hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, or other lesions, without infarct lesions, were also omitted. This study aimed to classify as meticulously as possible based on the interpretations of the Department of Radiology. For instance, although the regions indicated by the basal ganglia, caudate, and lenticulostriate arteries territory overlapped, they were distinguished in radiological interpretations, leading to their establishment as one of total 110 independent catego-

ries (Table 1).

In the categories, borderzone infarct and lacunar infarct followed the definitions set by the Department of Radiology. Borderzone infarct is characterized as ischemic lesions typically found at the intersection of two major arterial territories [27] and lacunar infarct are defined as small brain lesions (0.2 to 15 mm^3) [28].

The datasets from 309 patients were randomly divided into training, validation, and inference datasets in an 8:1:1 ratio, with data augmentation techniques similar to those used for the ISLES 2022 dataset. As the objective of this study is multilabel classification, all categories relevant to a single case were assigned, and subsequently, these were transformed into one-hot encoded vectors for further processing.

In this study, we confirm that the use of this clinical data was in full compliance with the ethical standards of the Pohang SeMyeong Christianity Hospital's Institutional Review Board

Table 1. Classification and frequency of infarcts

Location	Rt.	Lt.	Location	Rt.	Lt.	Location	Rt.	Lt.
ACA	3	3	MCA	32 (1) <1> [1]	29 (1) <1>	PCA	4	4
Acho.	2	1	SCA	4	3	PICA	3	5
Frontal	6 (5)	10 (3)	Temporal	4 (3) <1>	2 (3)	Parietal	9 (5)	3 (2)
Occipital	9 (5) <1>	4 (3) <1> [1]	Borderzone	6 <1>	6 <1>	Cerebellum	10 (10) <3>	2 (7) [1]
Precentral	3 (1)	3 (5)	Paracentral	(2) [1]	1 (1)	Postcentral		1 (2)
BG	7 (1)	5 <1>	LSA	9 (2)	8 (1)	Caudate	1	1 <1>
ICA	2		CR	5 (6)	8 (5)	PVWM		3
Parahippocam-pus	(1)	(1)	Hippocampus	1 (1)	1 (1)	LGB	1 <1>	1 <1>
Pons	10 <1>	7 (1)	Thalamus	3 (2) [2]	6 (3)	PLIC	3 (1)	1 (1) [1]
Medulla	4		Centrum semiovale	(6) [1]	3 (1) <1> [1]	Corpus callosum	1	(2)
Normal				20				
Acute embolic infarct				20 <1>				
Vermis				4 (1)				

The number of acute infarcts is indicated without brackets, the number of acute lacunar infarcts is represented by numbers within parentheses, the number of subacute infarcts is denoted by numbers within angle brackets, and the number of subacute lacunar infarcts is signified by numbers within square brackets.

Rt, right; Lt, left; ACA, anterior cerebral artery territory; MCA, middle cerebral artery territory; PCA, posterior cerebral artery territory; Acho., anterior choroidal artery territory; SCA, superior cerebellar artery; PICA, posterior inferior cerebellar artery territory; Frontal, frontal lobe; Temporal, temporal lobe; Parietal, parietal lobe; Occipital, occipital lobe; Border zone, characteristic locations at the junction between two main arterial territories; Precentral, precentral gyrus; Paracentral, paracentral gyrus; Postcentral, postcentral gyrus; BG, basal ganglia; LSA, lenticulostriatal artery territory; ICA, internal carotid artery territory; CR, corona radiata; PVWM, periventricular white matter; LGB, lateral geniculate body; PLIC, posterior limb of internal capsule.

(IRB no. PSMCHIRB-2024-16-1), ensuring adherence to necessary protocols for patient privacy and data security.

A classification model implementations

A classification model employs a Swin UNETR and the weights demonstrating the best checkpoint mean dice score of 0.5757 were loaded and utilized. The model inputs are tailored for image regions of interest and is designed to classify images into a predefined number of classes. Post-transformer processing includes an adaptive average pooling and layer normalization sequence, ensuring a consistent and stabilized feature representation before classification. The final classification is achieved through a fully connected linear layer, mapping the extracted and normalized features to the respective class probabilities, signifying the model's capacity for precise image-based classification. The maximal epochs were set to 400, and the patience was configured to 50.

Loss function

Our chosen loss function is BCE loss between the target and the input probabilities [24], calculated voxel-wise.

$$BCE = -M\sum_{m=1}^{M}[y_m \times log(h_\theta(x_m)) + (1-y_m) \times log(1-h_\theta(x_m))] \quad (4)$$

Where M: the number of training samples, y_m: ground truth label for training sample m, x_m: input for training sample m, h_θ: hypothesis(model) with weights θ [29]. Training loss was recorded every 5 iterations, and train and validation accuracies were calculated using the respective datasets at the end of each epoch.

Evaluation metrics

We calculated the true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values by comparing the predictions of the classification model with the ground truth labels. Accuracy for our multilabel data was derived as [30]:

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN} \quad (5)$$

RESULTS

Outcomes of training Swin UNETR using the ISLES 2022 dataset

During training of Swin UNETR with the ISLES 2022 dataset, the batch loss showed considerable fluctuation over 23,200 iterations but exhibited a decreasing trend as epochs progressed, reaching a value of 0.8885±0.1897 (Table 2, Fig. 1A). The training mean dice score was 0.4224±0.0710, indicating a general upward trend (Table 2, Fig. 1B). The validation mean dice score reached 0.4827±0.0607 (Table 2, Fig. 1C), increasing with the progression of epochs but then declining after 100 epochs. Based on these results, we selected the model weights with a validation mean dice score of 0.5747 as the best for further training and validation on actual patient brain MRI images. Training and validation were halted by an early stopping function set with a patience of 50 epochs.

Outcomes of training a classification model using the patients' dataset

For the classification model trained with patient data, batch loss significantly decreased from the start and then plateaued after 1,000 iterations, reaching 0.0565±0.0427 (Table 3, Fig. 2A). Training accuracy remained high, close to the maximum value for up to 25 epochs, then slightly decreased, showing a final value of 0.9842±0.0005 (Table 3, Fig. 2B). Validation accuracy similarly stayed high up to 21 epochs before decreasing, with a final value of 0.9837±0.0010 (Table 3, Fig. 2C). The training and validation phases were also stopped using an early stopping function with a patience of 50 epochs.

DISCUSSION

In summary, the Swin UNETR-based classification model, which was trained on brain MRI scans for infarct segmentation and categorized into 110 distinct classes, achieved an accuracy of 0.9837±0.0010. This significantly surpasses the accuracies reported in similar studies. For instance, Subudhi et al. [31] achieved

Table 2. Statistical summary of training and validation metrics for Swin UNETR using ISLES dataset

	Count	Minimum	Maximum	Mean	Median	SD
Train batch loss	232.0	0.1650	1.0830	0.8885	0.9819	0.1897
Train mean dice	116.0	0.1607	0.5660	0.4224	0.4276	0.0710
Validation mean dice	116.0	0.2335	0.5747	0.4827	0.4911	0.0607

Swin UNETR, Swin UNEt TRansformers; ISLES, Ischemic Stroke Lesion Segmentation Challenge; SD, standard deviation.

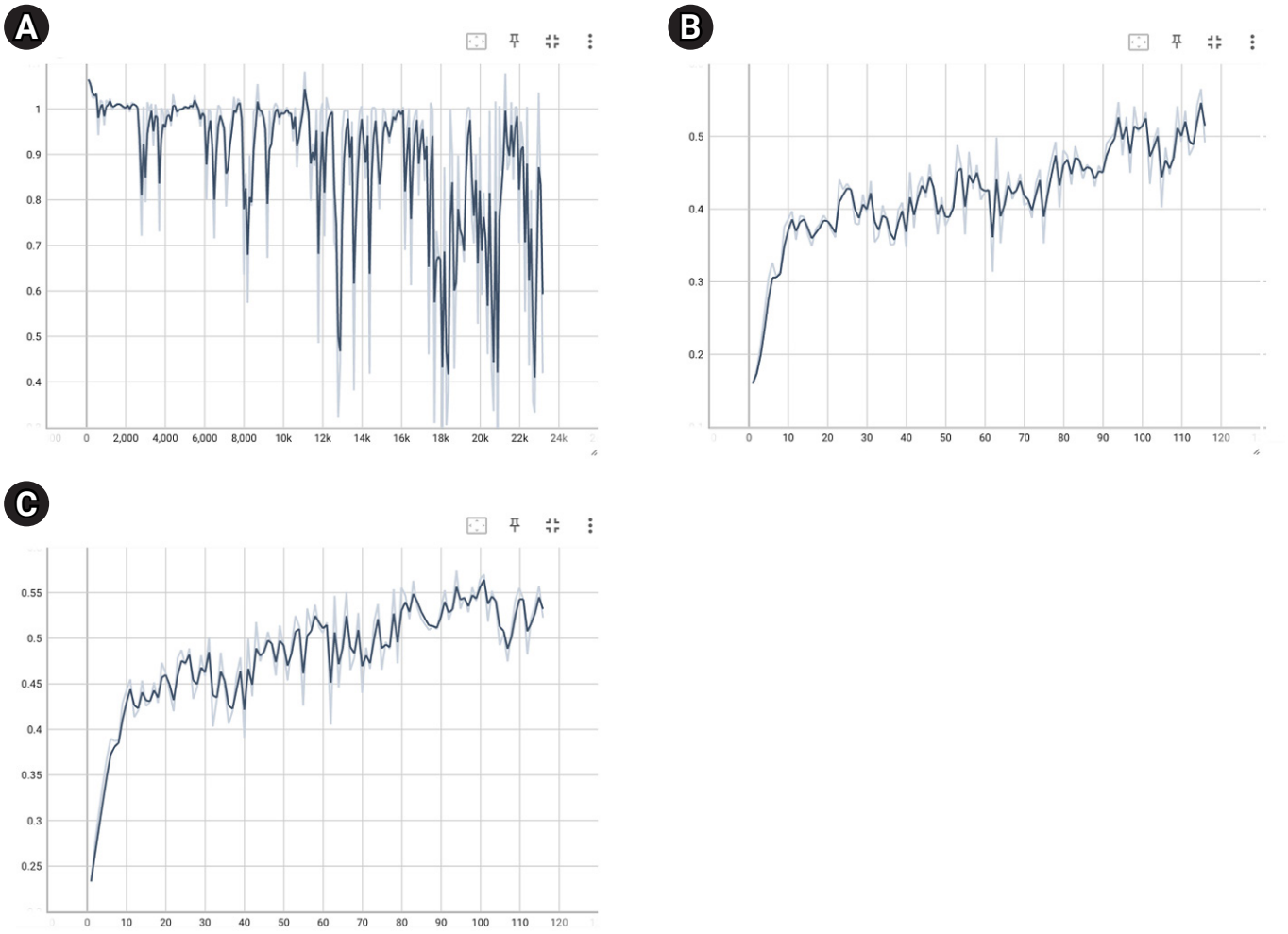

Fig. 1. Performance evaluation of Swin UNETR using ISLES 2022 data. (A) Training batch loss over 100 iterations. The x-axis indicates the number of iterations during the training process and the y-axis denotes the batch loss, reflecting the discrepancy between the model's predictions and the actual data for each iteration on the training dataset. The graph initially shows considerable fluctuations but trends downward as training advances, reaching a value of 0.8885±0.1897. (B) Training mean dice score over epochs. The x-axis signifies the number of epochs during the validation process and the y-axis represents the mean dice score, which is computed on the validation dataset. The mean dice score, indicating the degree of similarity between predicted and actual segmentations, generally trends upward, achieving a value of 0.4224±0.0710. (C) Validation mean dice score over epochs. The x-axis denotes the number of epochs in the validation process, while the y-axis indicates the mean dice score on the inference dataset. The mean dice score initially rises with the progression of epochs, peaking before declining after around 100 epochs. The highest recorded validation mean dice score was 0.5747, which was chosen for subsequent training and validation on patient brain MRI images. The overall mean dice score was 0.4827±0.0607. Swin UNETR, Swin UNEt TRansformers; ISLES, Ischemic Stroke Lesion Segmentation Challenge; MRI, magnetic resonance imaging.

an accuracy of 90.23% in classifying three types of stroke according to The Oxfordshire Community Stroke Project. Additionally, Cetinoglu et al. [32] reported a 93% accuracy in classifying three vascular territories (anterior cerebral artery, middle cerebral artery, watershed).

The superior performance of Swin UNETR over MobileNetV2 and EfficientNet-B0 CNN models, used in the two studies above, can be attributed to two main factors. Firstly, architectural differences are critical. Cetinoglu et al. [32] used modified versions of MobileNetV2 and EfficientNet-B0, these fully convolutional neural networks have limitations in modeling long-range information due to their convolution layers'

Table 3. Statistical summary of training and validation metrics for the classification model using patients dataset

	Count	Minimum	Maximum	Mean	Median	SD
Train batch loss	2,050.0	0.0083	0.5565	0.0565	0.0456	0.0427
Train accuracy	51.0	0.9815	0.9847	0.9842	0.9844	0.0005
Validation accuracy	51.0	0.9811	0.9844	0.9837	0.9840	0.0010

SD, standard deviation.

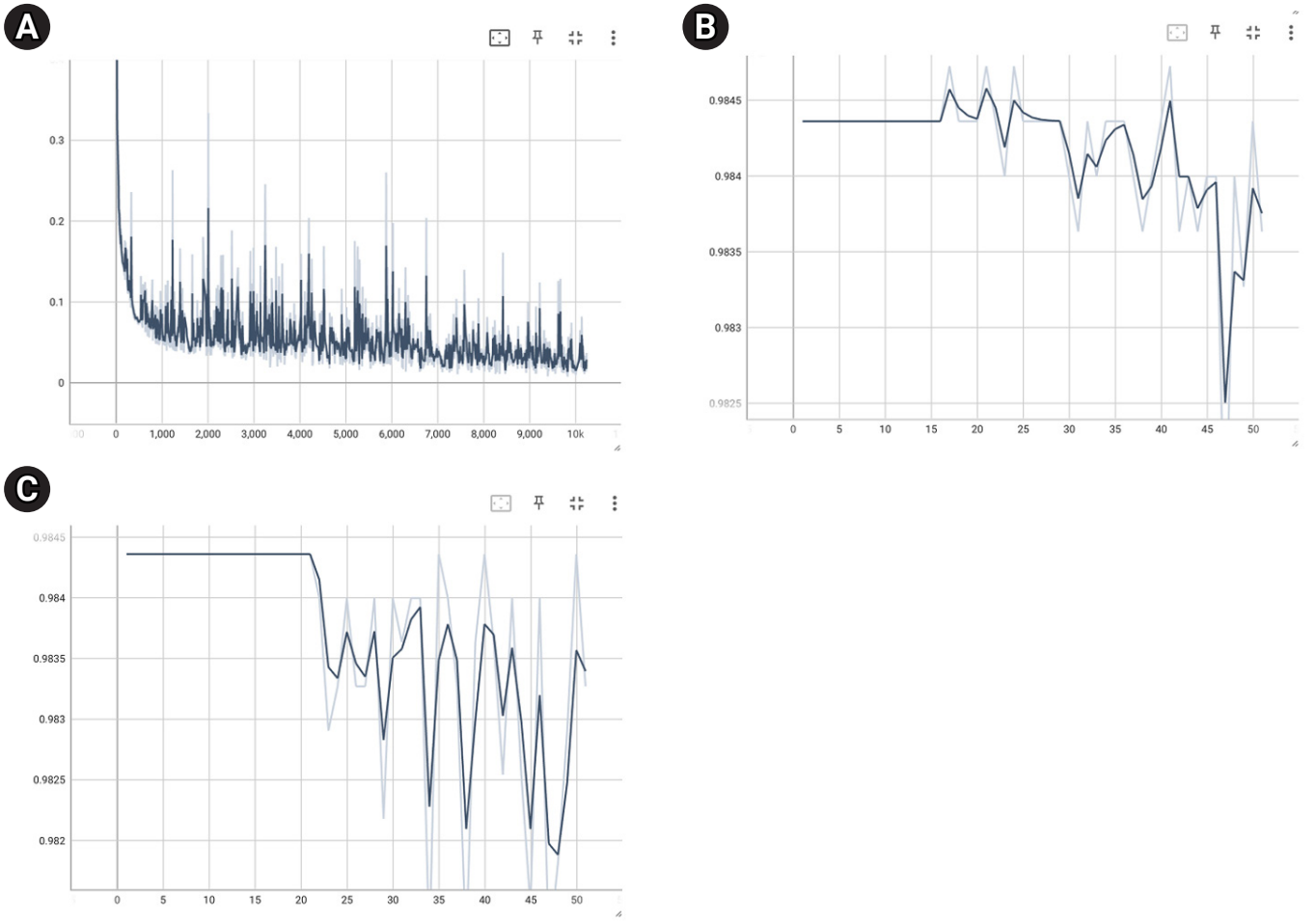

Fig. 2. Performance evaluation of the classification model using patients data. (A) Training batch loss over 100 iterations. The x-axis indicates the number of iterations during the training process, and the y-axis represents the batch loss, which measures the discrepancy between the model's predictions and the actual data for each iteration on the training dataset. The graph demonstrates a substantial initial reduction in batch loss, which then stabilizes after approximately 1,000 iterations, reaching a final value of 0.0565±0.0427. (B) Training accuracy over epochs. The x-axis represents the number of epochs during the validation process and the y-axis indicates the accuracy on the validation dataset. The accuracy remains high throughout the process, approaching its maximum value within the first 25 epochs and slightly decreasing thereafter, concluding with a final value of 0.9842±0.0005. (C) Validation accuracy over epochs. The x-axis represents the number of epochs during the validation process, while the y-axis denotes the accuracy on the inference dataset. The validation accuracy remains high up to 21 epochs before showing a slight decline, ending with a final value of 0.9837±0.0010.

limited kernel size. In contrast, Swin UNETR outperformed previous winning methodologies like 3D segmentation network with residual connections [33], no-new-Net [34], and Multimodal Brain Tumor Segmentation Using Transformer [35] in the research by Hatamizadeh et al. [7]. Secondly, Swin UNETR's pretraining on a specialized dataset of computed tomography (CT) scans likely contributed to its enhanced accuracy. The pretrained Swin UNETR encoder used weights from a cohort of 5,050 CT scans [20], whereas MobileNetV2 and EfficientNet-B0 were pretrained with the ImageNet dataset [36], a general visual database not specific to medical images. This difference in pretraining context and specificity is believed to have played a role in the improved accuracy.

However, our study has limitations. The decrease in validation accuracy after 20 epochs, as observed in Fig. 2, suggests overfitting. This issue is somewhat inevitable given the large number of classification categories (110) relative to the small number of patient MRI data (N=309). In such cases, while different categories were delineated based on radiological interpretations, merging classes that share overlapping areas could be attempted to reduce the total number of classes, thereby potentially overcoming overfitting. However, as previously stated in our research objectives, as a physiatrist dealing with brain imaging and patient symptoms, our primary goal was to distinguish infarct location and type with the utmost precision. And due to time and resource constraints, we were unable to perform hyperparameter tuning, just as we could not engage in the repetitive tasks of adjusting and experimenting with the number of categories. Future work, including acquiring more MRI data and employing regularization, dropout, and other techniques, is expected to improve generalizability.

Additionally, training exclusively on the ISLES 2022 dataset, which focuses on acute and subacute infarcts, did not include chronic or old infarcts. With the acquisition of more patient data in the future, it would be possible to conduct studies on chronic and old lesions.

Currently, there are several commercially available AI-based software solutions for stroke, demonstrating diagnostic accuracies for brain infarcts with MRI and other imaging techniques, with sensitivities and specificities of 44% to 83% and 57% to 93% for tissue ischemia, 80% to 96% and 90% to 98% for large vessel occlusion, and 96% and 95% for hemorrhage detection [37]. For instance, in detecting and quantifying ischemic core and penumbra, the e-ASPECTS software can outperform non-stroke experts and is at least as effective as stroke experts in applying the Alberta Stroke Programme Early CT Score (ASPECTS) for patients with acute ischemic stroke [38]. This paper is based on open datasets and brain MRI scans from 400 actual patients who visited the emergency room at Pohang SeMyeong Christianity Hospital. Although this is a relatively small dataset for deep learning applications, we achieved excellent results through augmentation techniques. Rehabilitation medicine, which prioritizes both brain MRI images and patients' symptoms, is ideally suited for such research, but clinical physicians' participation in studies is low. This paper will spark future interest and research among clinicians by presenting the data collection methods and sample sizes to those unfamiliar with deep learning and uncertain about how to begin research in this area. Embracing deep learning in rehabilitation medicine can significantly transform patient care. It enhances diagnostic accuracy, personalizes treatment plans, improves efficiency, and ultimately leads to better patient outcomes.

Conclusion

The classification model based on Swin UNETR architecture achieved high accuracy for 110 classes of acute and subacute brain infarcts through a two-stage learning process. This study highlights the potential for achieving detailed classification using open datasets as a supplement to limited patient data. This method is especially useful in scenarios where segmentation is constrained by resources. Such detailed classifications could significantly aid physicians in diagnosing infarcts in clinical settings.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Oh J. Methodology: Oh J, An H. Formal analysis: Oh J. Project administration: Oh J, An H. Visualization: Oh J. Writing – original draft: Oh J. Writing – review and editing: Oh J, An H. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS

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ORCID

Jaeho Oh, https://orcid.org/0000-0002-2203-897X
Hyunchul An, https://orcid.org/0009-0003-2666-6994

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Original Article

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Performance of Activities of Daily Living in Typically Developing Children in Korea: Normative Value of K-MBI

Mi-Jeong Yoon, MD, PhD[1,*], Sungwoo Paek, MD[1,*], Jongbin Lee, MD, MS[2], Youngdeok Hwang, MS[3], Joon-Sung Kim, MD, PhD[1], Yeun-Jie Yoo, MD, PhD[1], Bo Young Hong, MD, PhD[1]

[1]Department of Rehabilitation Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Rehabilitation Medicine, Ajou Rehabilitation Clinic, Ulsan, Korea
[3]Paul H. Chook Department of Information Systems and Statistics, Baruch College, City University of New York, New York, NY, USA

Objective: To determine the normative values of the Korean version of the Modified Barthel Index (K-MBI) score for typically developing children in Korea and assess its suitability for use in children.

Methods: Rehabilitation physicians and occupational therapists with children were invited through an online platform to participate in a survey assessing their children's performance of activity of daily living (ADL) using the K-MBI. The questionnaire encompassed queries on sociodemographic information of children and the assessment criteria outlined in the K-MBI. The standardized K-MBI scores by age were estimated using the nonlinear least squares method.

Results: The analysis incorporated responses from a total of 206 individuals. K-MBI total scores showed a rapid increase over the first 8 years of life, with 99% of children achieving a score of 90 or higher by age 8. Mobility scores exhibited a swift increase during early childhood, surpassing 90% of the maximum score at 3 years of age and nearing 100% at 7 years of age. In contrast, self-care scores demonstrated a more gradual advancement, achieving approximately 100% of the maximum score by the age of 10 years.

Conclusion: Age-specific normative values for K-MBI scores of typically developing children were established, which can be used as a reference in clinical care. While the K-MBI captured the overall trajectory of children's ADL development, it did not discern subtle differences across various developmental stages. There is a need for the development of more refined assessment tools tailored specifically to children.

Keywords: Activities of daily living, Child, Growth and development, Disability evaluation, Republic of Korea

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Correspondence:
Bo Young Hong
Department of Rehabilitation Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea.
Tel: +82-31-249-7650
Fax: +82-31-251-4481
E-mail: byhong@songeui.ac.kr

*These authors contributed equally to this work.

INTRODUCTION

Activities of daily living (ADLs) are fundamental skills required to fulfill basic needs in life. These are self-care tasks typically acquired at a young age and are also referred to as basic ADLs. Such activities comprise grooming/personal hygiene, dressing, toileting/continence, transferring/ambulating, and eating [1]. The performance of ADLs is an indicator of independence in life, and is widely used to assess the extent of assistance needed by the elderly, individuals with dementia, those affected with

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diseases, and persons with disabilities [2-4]. Dependent ADL is associated with decline in quality of life, elevated healthcare costs, and increased risk of mortality [1]. The evaluation of ADLs enables healthcare providers to identify challenges in an individual's ADL performance, set goals, and plan interventions. Therefore, the measurement of an individual's ADL is essential component of disability assessment.

Numerous assessment tools have been developed to evaluate ADLs. Among standardized ADL measures, Functional Independence Measure (FIM™) and Barthel Index (BI) are the most extensively utilized in a variety of rehabilitation settings [5]. FIM™ is commonly used in North America, and the BI and the Modified Barthel Index (MBI) are popular in Europe and Asia [6,7]. The MBI is commonly selected to evaluate the extent of disability or dependence in ADLs among stroke survivors; however, it is also frequently employed for patients with a diverse range of disabilities [7-10].

The MBI comprises 10 distinct items: personal hygiene, bathing, feeding, toileting, stair climbing, dressing, bowel control, bladder control, ambulation, and chair/bed transfers. These items are scored on a scale divided into five levels, with each level assigned a different score depending on the area's importance. For instance, personal hygiene and bathing items are scored from 0 (unable) to 5 (independent), while feeding, toileting, stair climbing, dressing, bowel control and bladder control items are scored from 0 (unable) to 10 (independent), and ambulation and chair/bed transfers items are scored from 0 (unable) to 15 (independent). Total score is calculated by summing the scores for each of 10 items described above, with a maximum achievable score of 100 (100=independent, 91–99=minimal assistance, 75–90=mild dependence, 50–74=moderate dependence, 25–49=severe dependence, and 0–24=total dependence) [11]. The Korean version of the MBI (K-MBI) is a translation of the 5th version of the MBI tailored to reflect Korean culture and lifestyle [12]. The K-MBI is a standardized assessment tool with proven validity and reliability for evaluating ADLs in patients with stroke [12].

ADLs begin to be mastered in early childhood and become increasingly sophisticated and complex as the child grows. Therefore, when assessing ADL in children, it is essential to consider the child's developmental stages. Functional Independence Measure for Children (WeeFIM®) and Pediatric Evaluation of Disability Inventory (PEDI) are assessment tools for developed for pediatric population. The PEDI assesses children from 6 months to 7.5 years old, including older children with functional abilities under 7 years. WeeFIM® evaluates children from 6 months to 8 years old, with extension up to 18 years for children with developmental disabilities [13]. However, the utilization of WeeFIM® is limited, as it requires payment for copyright access and mandatory training. The application of PEDI for children in Korea is relatively infrequent, resulting in insufficient available data [8].

Currently, the K-MBI is a mandatory evaluation item for determining brain lesion disability in Korea, as per the Disabled Welfare Law, and it is also employed when assessing disability in children and adolescents. To assess the daily living performance of children and adolescents, age-specific reference data is crucial, yet data on the K-MBI is currently lacking. Consequently, there are limitation in objectively evaluating children and adolescents with disabilities. The aim of this study is to establish a standard range of K-MBI scores with respect to age in typically developing children in Korea, explore trends in children's ADL development using K-MBI, and evaluate its utility.

METHODS

Study subjects and setting

In July 2021, a web-based questionnaire survey was administered to parents of typically developing children aged 18 years or younger. The participants in this survey were restricted to rehabilitation medicine doctors and occupational therapists who possessed adequate knowledge of K-MBI. To gather data from typically developing children, we excluded children with disabilities as defined by the Disabled Welfare Law, those with congenital diseases such as genetic disorders or other neurological deficits, and individuals who had undergone treatments that could potentially impact their ADLs within the last three months. This exclusion criterion was communicated to the survey respondents.

The questionnaire included the K-MBI usage guidelines provided by the Korean Society for NeuroRehabilitation. These guidelines served as a reference for the evaluator to follow while assessing the child's ADL. Additionally, this questionnaire asked the following information about the subject: (1) relationship between the child and the respondent; (2) exact age of the child; (3) gender of the child; (4) current residence; (5) institution attended by the child (school, kindergarten, home daycare center, etc.); (6) birth record (full-term or premature birth).

Rationale of sample size estimation

Subjects were categorized into five age groups: 0 to 3 years old, 4 to 6 years old, 7 to 9 years old, 10 to 12 years old, and 13 years old and above. For this study, we aimed to enroll 30 participants in each of the five age groups, totaling 150 individuals. The sample size for each age group was determined by considering the minimum number of samples required to assume normality according to the central limit theorem.

Statistical analysis

The normality of the data was verified through the Kolmogorov–Smirnov test. To obtain the standard K-MBI score according to the age, the performance score of ADLs measured with K-MBI was estimated using nonlinear least squares. Participants' mean growth is a monotone increasing from 0 to 100, so the growth is assumed to follow a cumulative distribution function of a gamma distribution, where the parameters associated with the distribution are estimated to find the best fit for the data. With the estimated parameters, 95% and 99% lower bounds were used for the predictive distribution. The K-MBI questionnaire were divided into two categories for further analysis: "Self-care" activities (a total of 60 points including personal hygiene, bathing, feeding, toileting, dressing, bowel control, and bladder control) and "Mobility" activities (a total of 40 points including stair climbing, ambulation, and wheelchair/bed transfer). Percentages were calculated by dividing each score by its maximum score. Statistical analysis was done using IBM SPSS for Windows version 18.0 (IBM Corp.) and R for Windows software (R Foundation for Statistical Computing).

Ethics statement

The present study protocol was reviewed and approved by Institutional Review Board of St. Vincent's Hospital (IRB approval No. VC21QISI0133); it was conducted in compliance with the relevant ethics guidelines. Consent was obtained by clearly stating that the survey is for research purposes and requesting participation only from those who agree to be involved in the study.

RESULTS

Basic characteristics

From July 7 to 23, 2021, a total of 210 people participated in the survey. Among them, 206 responses were included in the analysis, while four were excluded due to missing questions or age discrepancies. Out of the 206 participants, 93.2% of children (192 out of 206) were born full-term, 54.9% (113 out of 206) were female children, and 65.5% (135 out of 206) of responders were mothers of the children.

Respondents were distributed across various regions as follows: Seoul (n=70, 34.0%); Incheon, Gyeonggi-do (n=55, 26.7%); Busan, Ulsan, Gyeongsangnam-do (n=30, 14.6%); Daejon, Sejong, Chungcheong-do (n=21, 10.2%); Jeju-do (n=15, 7.3%); Gwangju, Jeolla-do (n=12, 5.8%); Daegu, Gyeongsangbuk-do (n=3, 1.5%); and Gangwon-do (n=0, 0.0%). The institutions attended by the children included elementary school (n=82, 39.8%), daycare center (n=46, 22.3%), middle school (n=33, 16.0%), kindergarten (n=22, 10.7%), homeschooled (n=16, 7.8%), and high school (n=7, 3.4%).

Distribution of the K-MBI scores

In Fig. 1, the distribution of K-MBI total scores by age was depicted using the nonlinear least squares method, resulting in a sigmoid curve distribution. K-MBI total scores of children exhibited rapid increase from birth to age 5, after which the rate of increase diminished, eventually reaching a plateau around the age of 8. The median, 5th percentile, and 1st percentile values of the K-MBI total score by age are shown in Table 1. Ninety-nine percent of 7-year-old children obtained a total K-MBI score of 90 or above. Additionally, most children in Group V, aged 13 years and older, achieved a score of 100.

Fig. 2 displays the age-related shifts in scores for each K-MBI item, while Supplementary Table S1 provides detailed scores. Notably, at 2 years of age, the ambulation item achieved more than 90% of the maximum score, whereas most self-care items, except for feeding, remained at or below 20% of the maximum score. Among the self-care items, the feeding item displayed substantial improvement around the age of 2, while bladder and bowel control exhibited notable progress around the age of 3.

Fig. 3 presents the attainment levels of sub-scores categorized into self-care items (including personal hygiene, bathing, feeding, toileting, dressing, bowel control, bladder control) and mobility items (comprising stair climbing, ambulation, chair/bed transfer) expressed as percentages for each age group. Mobility scores reached 90% of the maximum achievable score at 3 years of age and attained a score close to 100% of the maximum at 8 years of age. In contrast, the self-care scores achieved 90% of the maximum score at the age of 7 and reached a score approximately equal to 100% of the maximum by the age of 10.

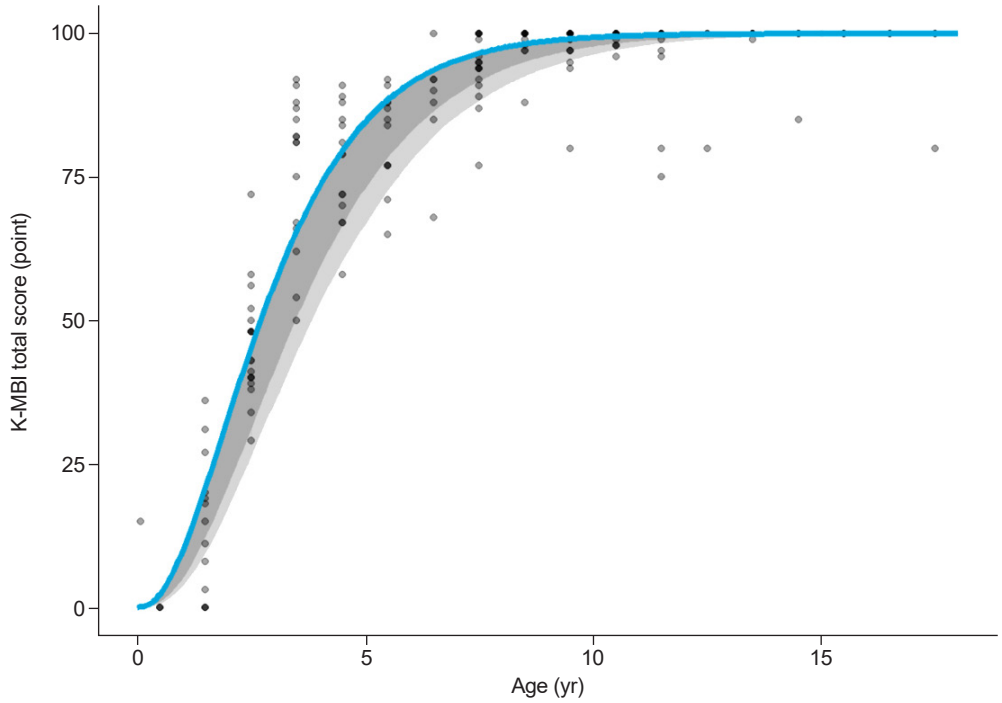

Fig. 1. The distribution of total scores of the Korean version of the Modified Barthel Index (K-MBI) according to age in typically developing children. The blue line depicts the standardized value of K-MBI total score. The dark grey area corresponds to the lower 5th percentile of K-MBI total score, and light grey area corresponds to the lower 1st percentile.

Table 1. Normative reference values of the K-MBI total score for each age (n=206)

Group (n, %)	Age (yr)	Total (n)	K-MBI total score		
			Median (point)	Lower 5th percentile (point)	Lower 1st percentile (point)
I (51, 24.8)	0	4	9.9	5.1	3.7
	1	13	33.3	21.3	17.3
	2	19	56.3	41.1	35.4
	3	15	73.4	59.1	52.8
II (33, 16.0)	4	14	84.7	73.1	66.7
	5	12	91.5	82.8	77.7
	6	7	95.4	89.4	85.5
III (48, 23.3)	7	19	97.6	93.6	90.6
	8	12	98.7	96.2	94.1
	9	17	99.3	97.8	96.3
IV (34, 16.5)	10	16	99.7	98.7	97.8
	11	15	99.8	99.2	98.7
	12	3	99.9	99.6	99.2
V (40, 19.4)	13	13	100.0	99.8	99.5
	14	10	100.0	99.9	99.7
	15	9	100.0	99.9	99.8
	16	4	100.0	100.0	99.9
	17	4	100.0	100.0	99.9

K-MBI, Korean version of the Modified Barthel Index.

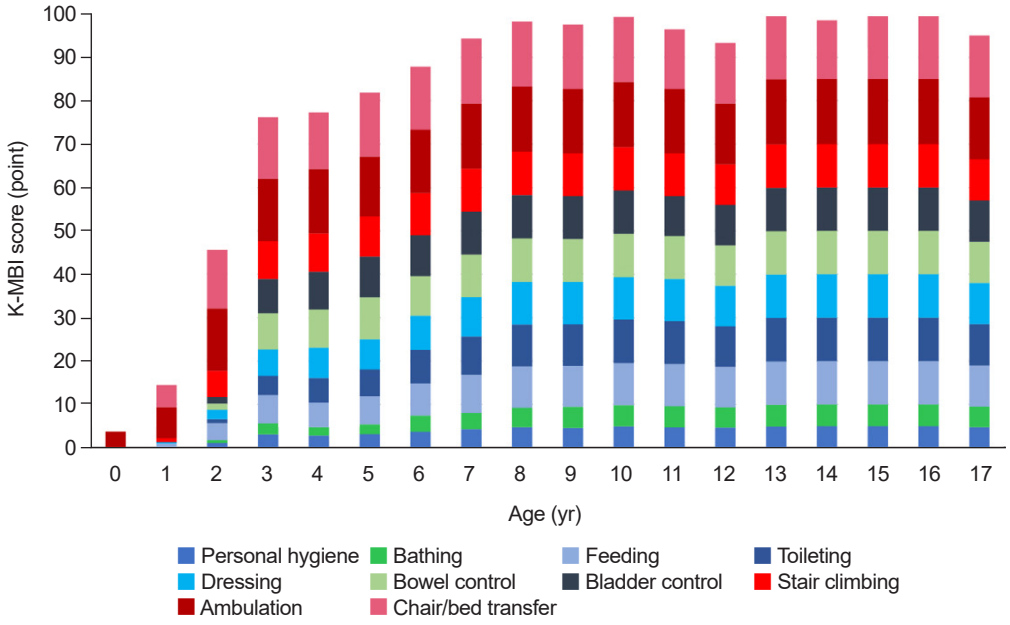

Fig. 2. Changes in scores by age for the 10 items of the Korean version of the Modified Barthel Index (K-MBI) evaluated in normally developing children (n=206). The blue and green series represents the self-care items (personal hygiene, bathing, feeding, toileting, dressing, bowel control, bladder control), and the red series represents the mobility items (stair climbing, ambulation, chair/bed transfer).

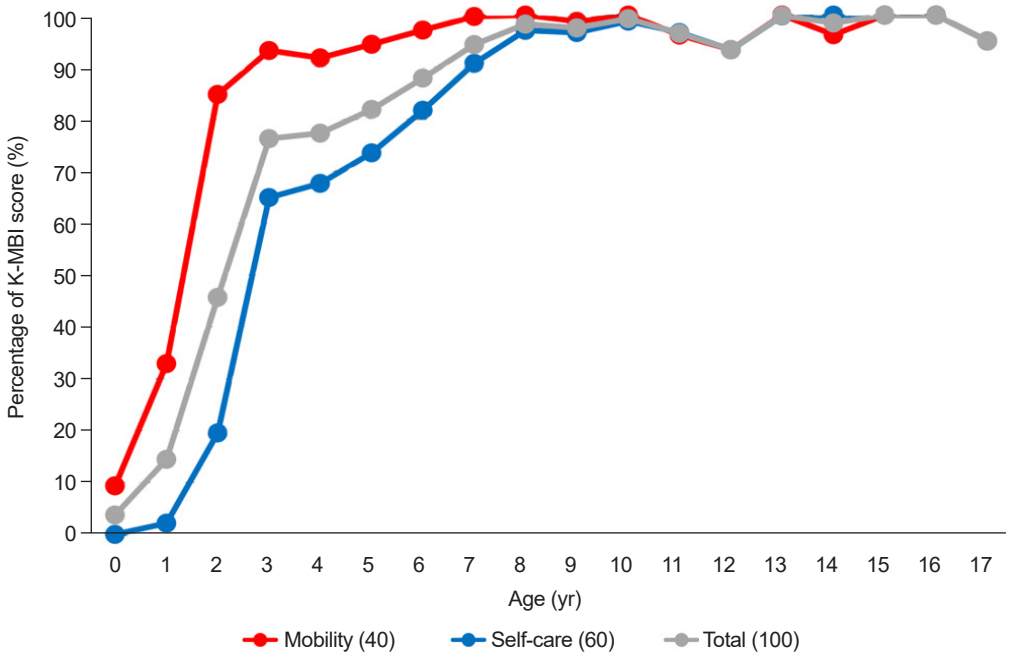

Fig. 3. Age-related changes in mobility scores and self-care scores on the Korean version of the Modified Barthel Index (K-MBI) (n=206). Percentages of sub-scores by age (n=206, %). The light grey line indicates the percentage of the total score, the red line represents self-care score percentage, and the blue line represents mobility score percentage. Percentages are calculated by dividing each score by its respective maximum value.

DISCUSSION

In this study, we provided the normative values in typically developing children for the K-MBI, a widely utilized assessment tool in Korea to assess ADL in children and adolescents. The K-MBI evaluation showed that the ADL performance of children and adolescents changes dynamically according to developmental age. The total K-MBI score exhibited rapid advancement up to the age of 5, after which the rate of increase decelerated, eventually plateauing around 8 years old, which reflects the nature of swift development in early childhood. Performance of mobility items were achieved rapidly before the age of 3, while progress in self-care items exhibited a more gradual trajectory thereafter.

To our knowledge, this study is the first to investigate the age-specific median, the lower 1% and 5% reference values of the K-MBI across a broad age spectrum among typically developing children and adolescents in Korea (Table 1). Despite the widespread use of K-MBI assessments in clinical settings involving Korean children and adolescents, comprehensive normative data based on developmental age has been lacking. The absence of this standard range complicates the precise evaluation of a child's deviation from the norms in ADL performance. Therefore, the findings from this study will be helpful in understanding the development of ADL according to the child's age and serve as essential reference material for clinical practitioners working with children who have developmental disabilities. A recent study has shown that the K-MBI presents good reliability and validity in evaluating children with congenital muscular dystrophy and Barth syndrome [14]. However, the reliability and validity of employing MBI in children with prevalent disabling conditions such as cerebral palsy have not yet been established and require further investigation.

The K-MBI assessment showed the typical trajectory of child development, marked by the rapid advancement of mobility in the early childhood and the progressive development of self-care skills as children grow. Mobility scores rapidly increased from a very young age, attaining 90% of the maximum score by the age of 3. In contrast, the self-care score exhibited a relatively gradual rise compared to the mobility score, reaching 90% of the total score at age 7. This distinction is attributed to the fact that self-care necessitates the development of dexterity and cognition, which typically mature later than the development of mobility skills [1].

Meanwhile, some components of the K-MBI appear inadequate in evaluating the distinctive ADL performance of children based on their developmental stage. When typically developing children were assessed with the K-MBI, their ambulation scores increased after 1 year of age. The K-MBI scores the ambulation item by focusing on independent walking and doesn't encompass the evaluation of movement methods besides walking, like crawling or rolling. Due to these limitations, the mobility score of K-MBI fails to capture the dynamic stages of gross motor development during the first year of life, making it challenging to accurately assess ADL performance related to motor skills in children under one-year old. Besides, respondents proposed refining the questions for assessing self-care items for more effective assessments of children. For example, it is not appropriate to ask young children about their ability to perform personal hygiene such as shaving or applying makeup. Accurate assessment of ADL in children, especially in younger age groups, requires the use of additional assessment tools. When evaluating a child's function to determine the degree of disability, it is important to understand both the level of development and ADL performance [15]. Comprehensive evaluation should be accompanied by neurodevelopmental assessment, especially for young children who inherently require assistance with ADL [15].

The present study has several limitations. Firstly, the recruitment was limited to children whose parents were rehabilitation medicine doctors or occupational therapists, potentially introducing selection bias. Secondly, the study involved a relatively small number of participants. According to the central limit theorem, when the sample size exceeds 30, the distribution of the sample mean tends to approximate a normal distribution. Although the sample size for each group surpassed 30 individuals, the number of subjects within each age category did not meet this threshold. Further research is needed with larger and more diverse populations to enhance the generalizability of our results. Additionally, as the study was conducted through an anonymous online survey, the possibility of typing errors exists. Unfortunately, due to the nature of the survey, we were unable to verify these potential errors. Consequently, data suspected to be the result of typing errors were excluded from the analysis. Another concern with this study is the large number of raters, which could potentially raise questions about the reliability of scoring. However, the MBI is known to have high inter-rater reliability [16]. The K-MBI also demonstrated robust inter-rater reliability, with Kendall's coefficient of concordance ranging from 0.93 to 0.98 [12]. Moreover, to enhance result reliability, we provided raters with the K-MBI usage guidelines issued

by the Korean Society for NeuroRehabilitation and instructed them to assess the child's ADL in accordance with these guidelines. However, despite these efforts, a few evaluators encountered challenges in objectively assessing their own children. Upon examining the scores for each item of the K-MBI (Supplementary Table S1), it was noted that the average score for 11- and 12-year-old children was marginally lower than that of 10-year-old children. It is presumed that a perfect score was determined based on how strictly the evaluator judged the child's level of daily living performance. This limitation is inherent in surveys relying on parental responses.

In conclusion, our study delineated the developmental patterns of ADL performance in typically developing Korean children through the K-MBI assessment and provided normative data. The identified cut-off values for K-MBI scores will serve as a basis for assessing ADL performance in children with developmental disabilities. Clinicians should understand the limitations associated with assessing children's ADL using the K-MBI and consider the use and development of alternative tools tailored for the children's developmental stage.

CONFLICTS OF INTEREST

Bo Young Hong is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript. Otherwise, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTION

Conceptualization: Hong BY, Lee J. Data curation: Paek S, Hong BY. Formal analysis: Hwang Y, Paek S, Yoon MJ. Investigation: Hong BY, Yoo YJ, Yoon MJ, Paek S. Methodology: Hong BY, Yoon MJ. Validation: Hong BY. Visualization: Paek S, Hwang Y. Writing – original draft: Paek S, Yoon MJ. Writing – review and editing: Yoon MJ, Hong BY, Kim JS. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.5535/arm.230040.

ORCID

Mi-Jeong Yoon, https://orcid.org/0000-0003-0526-6708
Sungwoo Paek, https://orcid.org/0000-0002-7499-2415
Jongbin Lee, https://orcid.org/0009-0001-4857-8421
Youngdeok Hwang, https://orcid.org/0000-0001-7563-5156
Joon-Sung Kim, https://orcid.org/0000-0001-7457-593X
Yeun-Jie Yoo, https://orcid.org/0000-0003-1323-4503
Bo Young Hong, https://orcid.org/0000-0001-9290-6173

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Smartphone Usage and Postural Stability in Individuals With Forward Head Posture: A Nintendo Wii Balance Board Analysis

Weerasak Tapanya, PhD, Noppharath Sangkarit, PhD

Department of Physical Therapy, School of Allied Health Sciences, University of Phayao, Phayao, Thailand

Objective: To assess postural stability, specifically center of body sway during single-leg standing balance, among individuals with and without forward head posture (FHP) during smartphone use.

Methods: The research recruited 53 healthy smartphone users, aged 18–25, and categorized them into FHP group comprising 26 subjects and the normal (control) group with 27 subjects. Participants were assigned the task of maintaining balance while engaged in smartphone typing during single-leg standing. The experiment involved four specific conditions according to neck posture and stable of surface. The study meticulously quantified body center of pressure (COP) sway amplitudes using the Nintendo Wii Balance Board.

Results: The research revealed that individuals with FHP exhibited significantly greater body sway compared to the control group when using smartphones. Notably, distinct variations were observed in path length sway, anteroposterior (AP), and mediolateral (ML) sway amplitude, particularly evident when maintaining flexed neck positions on a soft surface while engaged with smartphones.

Conclusion: These findings strongly suggest that individuals with FHP encounter deteriorated postural stability during smartphone use, particularly in challenging head positions.

Keywords: Postural balance, Smartphones, Posturography, Head posture, Center of pressure

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Correspondence:
Weerasak Tapanya
Department of Physical Therapy, School of Allied Health Sciences, University of Phayao, 19/2 Maeka Subdistrict, Muang District, Phayao 56000, Thailand.
Tel: +66-869236141
Fax: +66-54-466-697
E-mail: weerasak.ta@up.ac.th

INTRODUCTION

The literature consistently highlights a significant rise in smartphone users globally, coinciding with an increase in musculoskeletal issues related to prolonged smartphone use. Studies connect excessive smartphone use to musculoskeletal disorders like neck pain, upper extremity discomfort, and ergonomic problems due to poor posture and repetitive motions [1]. These issues impact physical health and quality of life. The widespread use of smartphones has revolutionized communication and information access, yet prolonged and frequent utilization of these devices has unveiled potential health implications. Long-term engagement with smartphones often leads to the adoption of a forward neck posture, commonly termed "text neck." This posture, characterized by a forward head position while looking down at the screen, significantly alters the cervical spine's natural curvature [2]. The persistent adoption of such a posture strains the muscles, tendons, and ligaments supporting the cervical spine [3]. Research indicates that the continuous application of this forward head position, typical during smartphone

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use, places immense stress on the cervical spine, potentially leading to musculoskeletal discomfort and an increased risk of developing chronic issues [4]. Over time, this maladaptive posture can result in structural changes, impacting the integrity of the cervical spine and potentially leading to long-term musculoskeletal issues.

Forward head posture (FHP) is characterized by the positioning of the head in front of a vertical line passing through the body's center of gravity (COG). Studies by Hansraj [5] underscore the significant impact of neck flexion on head weight. Their research findings reveal a compelling relationship between neck flexion and increased head weight. In their investigations, it was observed that as the neck flexes forward, the effective weight experienced by the cervical spine substantially escalates. Specifically, at a 60-degree head flexion angle, the effective weight borne by the cervical spine was estimated to reach approximately 28 kg [5]. This increased head weight, caused by greater neck flexion, imposes considerable stress on the cervical spine and surrounding structures, potentially contributing to the development of musculoskeletal issues associated with prolonged FHP [6].

Prolonged pressure on neck joints due to extended FHP can disrupt signals to the brain, impacting balance and neck proprioception [7]. This sustained compression and misalignment of cervical vertebrae may interfere with neural signal transmission [8]. Such disruption could compromise the brain's interpretation of head position and movement [9]. Balance and head-eye movement control rely on integrated input from vision, vestibular, and proprioception systems [9]. Disruptions from sustained neck joint pressure may compromise proprioception, affecting accurate spatial perception and potentially influencing coordination and balance [10]. Cervical proprioception plays a pivotal role in ensuring precise head orientation in space, maintaining trunk orientation, and contributing to overall body balance [11]. Research underscores the critical nature of cervical proprioception alongside vestibular and visual inputs for accurate orientation and effective postural control [12]. Previous studies emphasize the interdependence of these sensory systems in coordinating body movements and adjusting posture to external stimuli [13]. Moreover, a noteworthy association exists between neck pain and compromised balance as well as impaired coordination of head movements. Individuals experiencing neck discomfort often exhibit increased postural sway and encounter challenges in positioning their heads accurately [14]. This linkage between neck pain and diminished balance and head movement coordination highlights the intricate relationship between cervical proprioception, postural control, and overall musculoskeletal well-being [15].

FHP is widely recognized as a prevalent postural deviation associated with various musculoskeletal imbalances and balance disorders [16]. The maintenance of balance is a complex process involving the precise coordination of sensory inputs, including vestibular, visual, and somatosensory cues, alongside the musculoskeletal system. This intricate integration facilitates the stabilization of the body's center of mass within its base of support, minimizing postural sway, and is integral for executing daily activities [17]. Any postural changes leading to an altered COG within the base of support may contribute to the onset of balance disorders. Notably, proprioceptive impairment linked to FHP could potentially exacerbate these issues, as compromised cervical proprioception might disrupt the accurate perception of head position and movements, thereby impacting the body's ability to maintain a stable posture and affecting overall balance [7,18].

The Nintendo Wii Balance Board (NWBB) emerges as a cost-effective alternative to conventional force platforms for assessing balance across various conditions. Notably, the NWBB serves as a versatile tool capable of evaluating both static and quasi-dynamic balance. Previous research has established associations between FHP and alterations in postural balance, highlighting potential balance disorders arising from FHP [18]. However, an unexplored area lies in investigating the specific impact of FHP on balance utilizing the NWBB. This study aims to investigate the impact of FHP on postural stability during smartphone usage. It seeks to understand how FHP, characterized by the head's forward positioning relative to the body's COG, affects balance and stability or body center of pressure (COP) sway. Additionally, the research explores how smartphone use posture contributes to or worsens FHP, subsequently influencing postural control.

METHODS

Study design

The current cross-sectional investigation utilized convenience sampling methods to recruit participants, employing printed advertisements and social media channels for recruitment purposes. This study employed a randomized repeated design, examining smartphone use in two different neck postures (neutral and flexed) across two surface conditions (hard and soft), as de-

picted in Fig. 1. The research took place at the Physical Therapy Laboratory, School of Allied Health Sciences, University of Phayao, Thailand. Body COP sway was evaluated using the NWBB and recorded for each condition while participants performed text typing on a smartphone and underwent a single-leg standing test on both hard and soft surfaces.

Participants

A total of 66 healthy young adults were initially enrolled in this study. However, 13 subjects were excluded due to the following reasons: 6 were classified as overweight, 4 were obese, and 3 did not pass the screening balance test. As a result, the final cohort comprised 53 subjects with equal representation of sexes and ages ranging from 18 to 25 years. Following measurement of

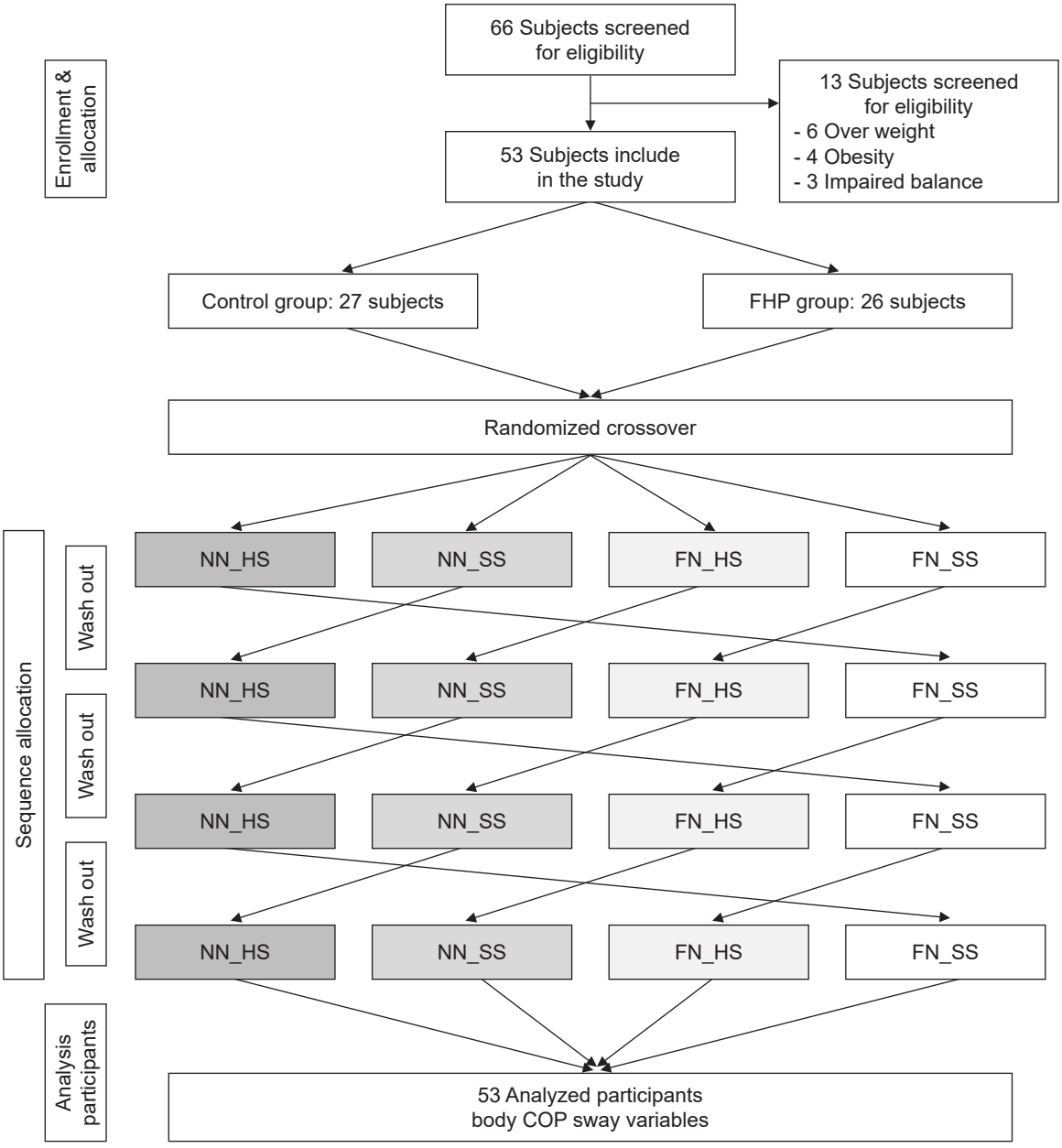

Fig. 1. The procedural flowchart for participant testing. FHP, forward head posture; NN_HS, neutral neck on hard surface; NN_SS, neutral neck on soft surface; FN_HS, flexed neck on hard surface; FN_SS, flexed neck on soft surface; COP, center of pressure.

their craniovertebral (CV) angle, subjects were categorized into two groups: a control group (n=27) consisting of those with an angle ≥48° and an FHP group (n=26) comprising those with an angle <48° [19]. All participants included in the study were exclusively right-handed and had a minimum of one year of prior experience using smartphones, dedicating an average of at least four hours daily to their device usage. Crucially, none of these participants disclosed any recent history of trauma or musculoskeletal discomfort in the neck or upper extremities within the past week. The calculation for the sample size was executed using the G*Power software, utilizing mean and standard deviation (SD) values derived from a previous study on postural sway [20]. A power calculation was conducted, with a critical α-value set at 0.05 and aiming for a robust power level of 90%. Furthermore, all participants underwent verification to confirm the absence of any neurological or musculoskeletal conditions, and they disclosed no engagement in any balance-specific training over the preceding six months. Additionally, assessing limb dominance revealed that, as per their preferred leg for kicking a ball [21], all participants displayed right leg dominance, aligning consistently with their dominant hand (i.e., their writing hand).

CV angle

The CV angle is described as the angle formed between a horizontal line passing through C7 and a line extending from the tragus of the ear to C7. To measure this angle, photometry is utilized, employing a camera positioned at a fixed distance of 1.5 meters. The camera's height is adjusted to match the subject's shoulder height [22]. For accurate measurement, two markers are positioned one at C7 and the other at the ear tragus. Subjects are instructed to maintain a relaxed posture and gaze straight ahead [23]. The participant was directed to stand facing straight and was positioned laterally in front of the camera. A lateral view photograph was captured of each participant in their standing position. Subsequently, the photographs were transferred to a computer and analyzed utilizing Kinovea software. In the analysis, a virtual line was drawn between the midpoint of the tragus and the spinous process of the C7 vertebra. Additionally, a horizontal line was drawn through the spinous process of the C7 vertebra (Fig. 2). Participants exhibiting a CV angle measuring less than 48 degrees were classified as having a FHP. The reliability of CV angle measurements demonstrates strong consistency, with a test-retest reliability ranging between 0.85–0.86 and an inter-examiner intraclass correlation coefficient (ICC) of 0.88–0.89 [24].

Experimental protocol

Prior to participating in the study, all participants provided written consent prior to their involvement in the study. Preceding the commencement of the experiment, a random allocation process assigned each participant to one of four distinct conditions. These conditions encompassed smartphone usage in conjunction with neutral neck posture on both hard and soft surfaces, denoted as the NN_HS (neutral neck on hard surface) and NN_SS (neutral neck on soft surface) conditions, respectively (Fig. 3). Additionally, participants were assigned to flexed neck posture on both hard and soft surfaces, FN_HS (flexed neck on hard surface) and FN_SS (flexed neck on soft surface) conditions. This allocation process utilized simple randomization techniques to mitigate potential systematic biases stemming from the sequence of the experimental conditions. Each participant, over separate days, experienced all four conditions.

The postures while using smartphones, neck and shoulder angles, smartphone height, and distance were customized for each participant based on their habitual smartphone usage pat-

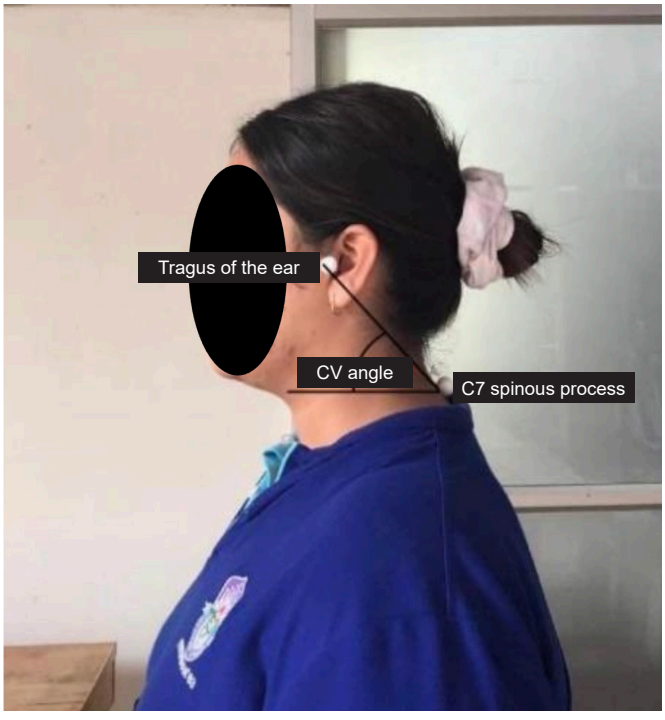

Fig. 2. The angle of the craniovertebral (CV) junction was evaluated directly using a side-view photograph.

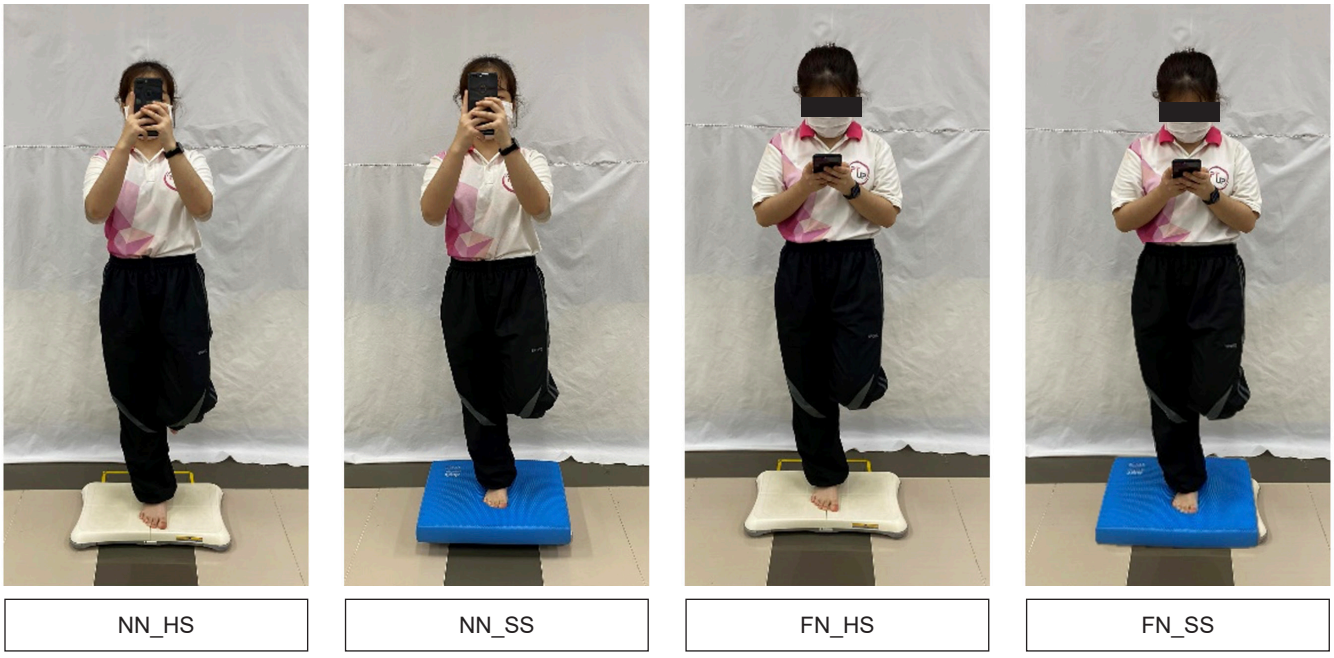

Fig. 3. The smartphone texting task performed during single-leg standing under various conditions. NN_HS, neutral neck on hard surface; NN_SS, neutral neck on soft surface; FN_HS, flexed neck on hard surface; FN_SS, flexed neck on soft surface.

terns. This personalization process was aligned with their typical everyday interaction with smartphones, ensuring a tailored fit for each individual. Participants were given three minutes to familiarize themselves with the measurement process, employing a method adapted from Xie et al. (2016) [25]. During each test condition, participants were guided to conduct a single-leg standing test on their dominant leg while continuously typing the English alphabet (A–Z) on their smartphone using both thumbs, while securely holding the device with both hands. Each session had a duration of 1 minute, and a 2-minute break was provided between the two trial sessions. The single-leg standing test began with participants initially standing with both feet on the ground. Subsequently, upon instruction from the researcher, participants were asked to shift their weight to their dominant leg while ensuring both hands retained control of the smartphone, and the non-dominant knee was flexed at a 90-degree angle [21].

NWBB for assessment of postural sway during quiet standing

The NWBB is manufactured using plastic composite material and is outfitted with four load sensors positioned at each corner to measure vertical forces. Data extraction was performed using readily available software, establishing a connection between the NWBB and a laptop via Bluetooth. A Windows-based laptop facilitated data streaming from the NWBB using customized programs and Bluetooth protocol. Sampling of data from the NWBB occurred at a frequency of 30 Hz, a selection based on its similarity to frequencies (10–50 Hz) employed in prior studies [26]. Subsequently, the signal underwent filtering with a 10 Hz cut-off. Before each trial, calibration of the NWBB was executed by applying a known weight (20.4 kg) onto the board [27]. The COP variables were evaluated concerning path length sway, anteroposterior (AP) sway amplitude, and mediolateral (ML) sway amplitude, measured in centimeters. Path length sway measures the total COP travel distance, indicating overall stability. AP sway amplitude quantifies forward-backward displacement, while ML sway amplitude measures side-to-side displacement. High values in these measures suggest instability in their respective directions, providing a comprehensive view of balance [28].

Statistical analysis

The statistical analysis involved the use of IBM SPSS software version 26.0 (IBM SPSS Statistics), with a pre-set significance level (α) of a=0.05. Descriptive statistics, such as means and

SDs, were used to showcase the demographic data of the participants. A Shapiro–Wilk test was performed to examine the normal distribution of the variables. After testing for normal distribution and confirming that all variables were normally distributed, we employed an independent t-test to compare body COP sway variables between different groups across each test condition.

Ethical approval

In accordance with the Declaration of Helsinki, all volunteers provided written, informed consent before participating in the study. Additionally, all experimental procedures were conducted following the approval of the Institutional Review Board of the University of Phayao, Thailand (Approval Code No. UP-HEC 1.2/079/66).

RESULTS

Participant demographics and anthropometric data are presented in detail in Table 1. No statistically significant differences ($p>0.05$) were observed between the control and FHP groups in any demographic or anthropometric variable except for CV angle. The control group exhibited a significantly higher CV angle (mean±SD: 54.46°±3.76°) compared to the FHP group (45.51°±3.57°, $p<0.001$).

The findings from the NWBB test indicated that the path length sway of the FHP group was notably higher compared to the control group across various posture, with the most significant difference observed in the standing position with a FN_SS, the path length sway was greater in the FHP group than in the control group (184.05±45.87 cm vs. 141.42±33.06 cm). However, in the standing position with a FN_HS, there was no significant difference observed between the FHP group and the control group (145.42±35.40 cm vs. 128.21±36.76 cm) as shown in Fig. 4 and Table 2.

The FHP group exhibited notably higher AP sway amplitude compared to the control group. The most significant difference in AP sway amplitude between the FHP group and the control group was observed in the standing position with a FN_SS (5.73±1.90 cm vs. 4.62±0.99 cm). However, there was no notable difference in AP sway amplitude between the FHP group and the control group in the standing positions with a NN_HS (4.35±1.67 cm vs. 3.85±0.68 cm) and with a FN_HS (4.83±1.03 cm vs. 4.51±0.69 cm) as shown in Fig. 4 and Table 2.

The FHP group displayed notably higher ML sway amplitude compared to the control group across various test positions, except for the standing position with a FN_HS. The most substantial difference in ML sway amplitude between the FHP group and the control group was observed in the standing position with a FN_SS (4.23±0.74 cm vs. 3.58±0.44 cm) as shown in Fig. 4 and Table 2. Moreover, an example of sway trajectories for participants in each group was presented in Fig. 5.

DISCUSSION

The research revealed that individuals with FHP exhibited significantly greater body sway compared to the control group when using smartphones. Notably, distinct variations were observed in path length sway, AP, and ML sway amplitude, particularly evident when maintaining flexed neck positions on a soft surface while engaged with smartphones. These findings highlight the impact of FHP on postural stability, suggesting that the combination of poor posture and smartphone use can exacerbate balance issues, potentially leading to increased risks

Table 1. The demographic information and anthropometric characteristics variables of the subjects (n=53)

Variable	Control group (n=27)	FHP group (n=26)	p-value
Sex (male/female)	9/18	9/17	0.697
Age (yr)	20.22±1.12	20.54±1.03	0.290
Weight (kg)	55.43±6.90	56.12±11.49	0.792
Height (m)	164.59±6.97	162.77±9.87	0.439
Body mass index (kg/m^2)	20.37±1.64	20.95±2.06	0.266
Craniovertebral angle (degree)	54.46±3.76	45.51±3.57	<0.001**
Total experience time of smartphone use (yr)	6.86±1.58	7.15±1.86	0.550
Daily duration of smartphone use (h)	5.04±1.95	5.41±1.53	0.451

Values are presented as number only or mean±standard deviation.
FHP, forward head posture.
**A significant difference between conditions at p-value<0.01.

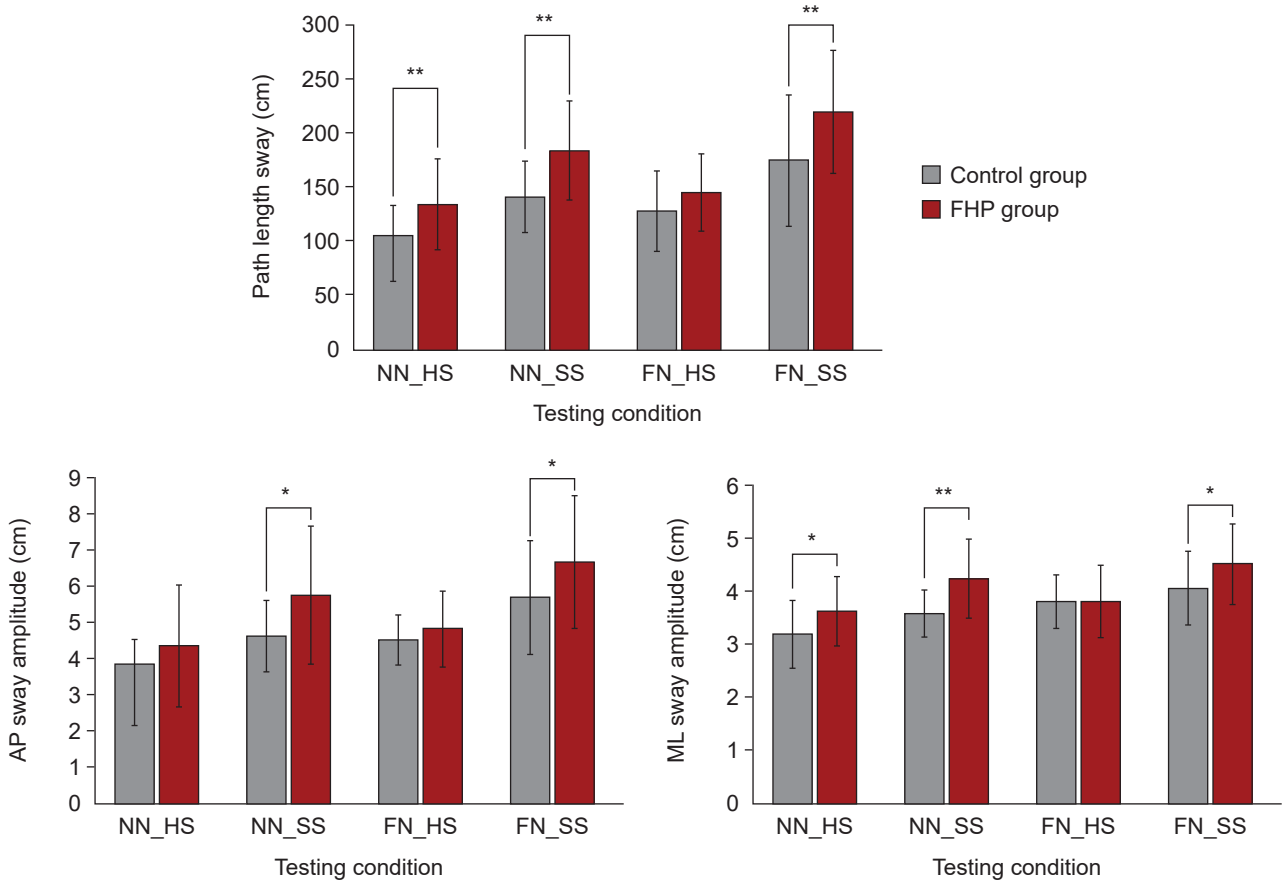

Fig. 4. The comparative analysis of postural stability between the forward head posture (FHP) group and the normal group when utilizing a smartphone and maintaining single-leg stance in different positions. NN_HS, neutral neck on hard surface; NN_SS, neutral neck on soft surface; FN_HS, flexed neck on hard surface; FN_SS, flexed neck on soft surface; AP, anteroposterior; ML, mediolateral. *A significant difference between conditions at p-value<0.05. **A significant difference between conditions at p-value<0.01.

Table 2. Comparison of body COP sway variables in each direction between FHP and normal group, whether on soft or hard surfaces (n=53)

Variable	Testing condition	Normal group (n=27)	FHP group (n=26)	Mean difference	p-value
Path length sway (cm)	NN_HS	105.38±28.46	134.52±41.77	-29.14	0.004**
	NN_SS	141.42±33.06	184.05±45.87	-42.63	<0.001**
	FN_HS	128.21±36.76	145.42±35.40	-17.21	0.089
	FN_SS	174.93±60.55	219.85±56.86	-44.92	0.008**
AP sway amplitude (cm)	NN_HS	3.85±0.68	4.35±1.67	-0.50	0.154
	NN_SS	4.62±0.99	5.73±1.90	-1.12	0.010*
	FN_HS	4.51±0.69	4.83±1.03	-0.32	0.196
	FN_SS	5.68±1.57	6.66±1.83	-0.97	0.043*
ML sway amplitude (cm)	NN_HS	3.19±0.64	3.62±0.65	-0.43	0.018*
	NN_SS	3.58±0.44	4.23±0.74	-0.66	<0.001**
	FN_HS	3.79±0.50	3.81±0.67	-0.02	0.917
	FN_SS	4.06±0.70	4.51±0.75	-0.45	0.027*

COP, center of pressure; FHP, forward head posture; NN_HS, neutral neck on hard surface; NN_SS, neutral neck on soft surface; FN_HS, flexed neck on hard surface; FN_SS, flexed neck on soft surface; AP, anteroposterior; ML, mediolateral.
*A significant difference between conditions at p-value<0.05.
**A significant difference between conditions at p-value<0.01.

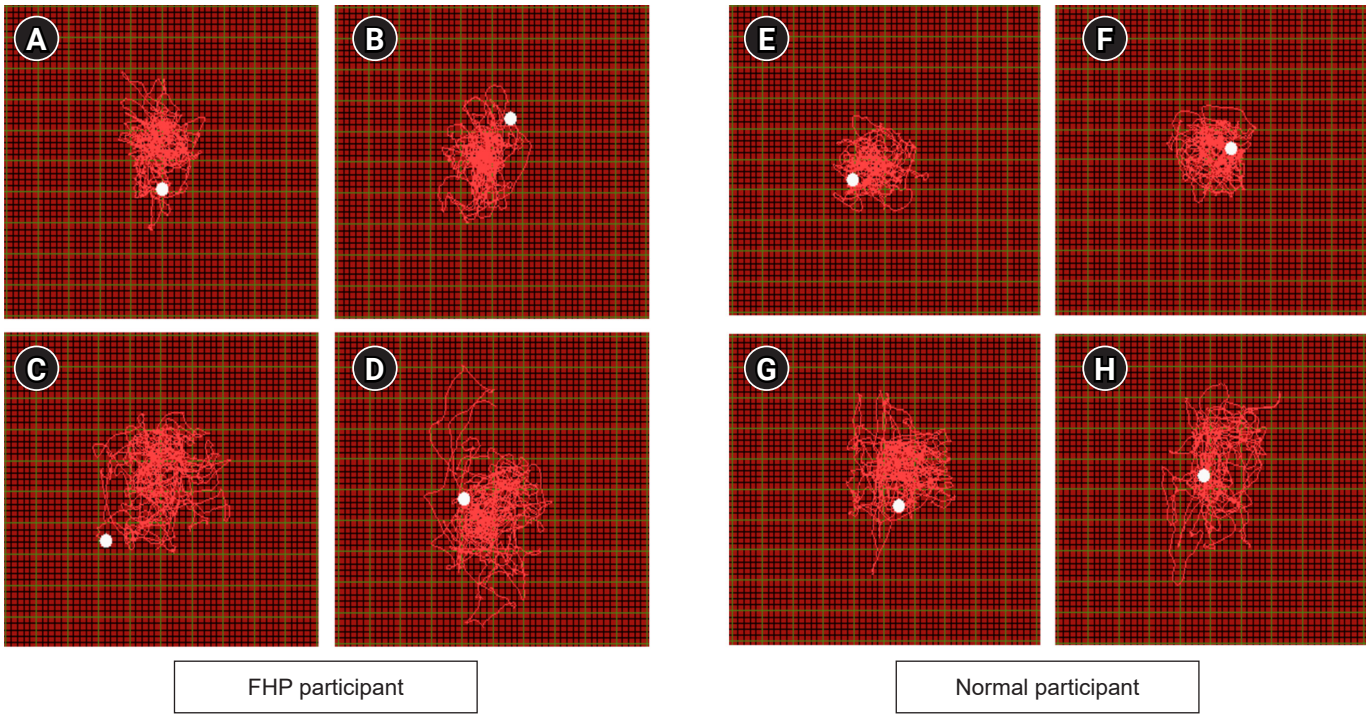

Fig. 5. An example of sway trajectories for participants in each group. (A, E) The neutral neck on hard surface (NN_HS) condition; (B, F) the flexed neck on hard surface (FN_HS) condition; (C, G) the neutral neck on soft surface (NN_SS) condition; and (D, H) the flexed neck on soft surface (FN_SS) condition. FHP, forward head posture.

of falls and musculoskeletal discomfort.

Maintaining balance and postural stability is vital for the overall health and well-being of smartphone users. While smartphone use itself might not directly affect balance or posture, extended periods spent on these devices can result in musculoskeletal issues, spinal misalignment, increased risk of falls, compromised breathing and circulation, muscular fatigue, and even impact psychological well-being [29]. Proper posture during smartphone use can prevent problems like neck strain, back pain, and shoulder discomfort. Overall, prioritizing balance and postural stability during smartphone use is integral to maintaining overall health and averting potential health complications associated with prolonged screen time [30]. FHP, often associated with prolonged smartphone usage, can significantly impact balance, and increase fall risks in healthy smartphone users [30]. When the head protrudes forward from its natural alignment, it alters the positioning of the spine and affects the body's COG [16]. This misalignment can compromise proprioception, the body's ability to sense its position in space, leading to instability and difficulties in maintaining balance [11]. As a result, individuals with FHP may experience challenges in equilibrium, especially when standing or moving, thereby increasing the risk of falls or accidents. The disrupted alignment of the spine due to prolonged FHP can negatively affect the body's coordination and spatial awareness, making it harder for individuals to react appropriately to changes in their environment and increasing the likelihood of losing balance and falling [18,31]. These falls can lead to injuries such as sprains, strains, fractures, or other trauma, particularly when compounded by distracted smartphone use that diverts attention away from the surroundings.

In this study, FHP participants exhibited significantly greater sway compared to the control group across various postures measured by the NWBB. Path length sway and AP sway amplitude showed the most pronounced differences, particularly in the standing position with FN_SS. Notably, no significant sway differences were observed between groups in the FN_HS standing position. ML sway amplitude followed a similar pattern, with FHP exhibiting greater sway in all positions except FN_HS. These findings suggest that FHP participants have greater postural instability during smartphone using, especially in challenging FN_SS postures. Several potential factors contribute to

the heightened postural instability observed in individuals with FHP during smartphone use. Firstly, an Altered COG emerges as a significant reason. FHP displaces the COG forward, imposing greater strain on the muscles of the neck and upper back for maintaining equilibrium [32]. Consequently, this increased load makes it more challenging to swiftly respond to postural disturbances induced by smartphone interactions [16]. Diminished proprioception stands as another contributing factor to the postural challenges associated with FHP [33]. The compression of nerves in the neck, a consequence of FHP, interferes with proprioception, the body's inherent ability to perceive its position in space [34]. This interference leads to a decreased sense of self-awareness regarding body position and movement, thus complicating the adjustment of posture for maintaining balance while engaging with a smartphone [30]. Increased muscle tension is a notable outcome associated with FHP, resulting in the tightening of muscles located in the neck and chest regions [35]. This heightened tension imposes restrictions on the usual range of motion and limits the spine's flexibility [36]. Consequently, individuals with FHP encounter difficulties in executing subtle postural adjustments necessary for maintaining balance, especially when engaged in smartphone use that involves holding the device in front of the body. The constrained movement caused by this muscle tightness further complicates the body's ability to adapt and stabilize during such activities.

Engaging in dual-tasking, such as standing on one leg while using a smartphone, impacts postural stability through several key mechanisms. Firstly, attentional resource competition arises from the simultaneous demand for attention in maintaining balance and allocating cognitive resources to smartphone tasks, potentially leading to insufficient resources for balance control and increased instability [37]. Secondly, cognitive engagement can disrupt the automatic postural adjustments triggered during single-leg standing, resulting in delayed or inadequate responses and heightened sway [38]. Thirdly, sensory-motor interference from smartphone use can overload the visual system, causing conflicting signals about body position and movement, hindering effective balance control [37]. Additionally, tasks demanding higher cognitive processing on smartphones increase the mental load, further depleting resources for balance control. Emotional stress induced by dual-tasking can divert attention from balance, exacerbating instability, especially in individuals with existing balance concerns [39]. Moreover, the biomechanical stress of single-leg stance coupled with smartphone usage challenges the musculoskeletal system, intensifying postural instability [40]. These factors collectively contribute to compromised balance control during dual-tasking activities.

One notable finding from the research is the absence of distinctions between groups when employing a smartphone in the FN_HS position. Conversely, in the NN_HS position, differences emerged among groups concerning path length and variables related to ML sway. However, upon comparing these conditions, it became evident that using a smartphone in the FN_HS position resulted in greater sway in all directions compared to the NN_HS position. This suggests that adopting a flexed neck posture while using a smartphone led to deteriorated stability in maintaining posture. The reason behind the lack of difference between the groups in this scenario might be attributed to the possibility that both individuals with a normal posture and those with a FHP experience a similar degree of balance disturbance when in the FN_HS posture. Conversely, the use of smartphone in NN_HS posture might accentuate the contrast between the two groups. Additionally, the shift in the COG of the head, particularly in individuals with FHP, could contribute to these observed differences in postural stability in NN_HS posture.

This study's limitation lies in its design as a short-term cross-sectional experiment, restricting its capacity to solely elucidate the immediate effects of smartphone utilization on postural stability in individuals with FHP. Nevertheless, while acknowledging this constraint, the findings obtained from this study are likely to offer a representative glimpse into the impact of smartphone use on the balance of individuals with FHP. Thus, despite its short-term nature, the study's outcomes can still contribute meaningfully to describing the effects of smartphone usage on the balance of individuals dealing with FHP. Future studies in this field could explore longitudinal research tracking prolonged smartphone effects on postural stability among individuals with FHP. Additional constraint of this study is the absence of consideration for the subjects' neck pain. The research solely focused on including smartphone users with FHP based on the analysis of the CV angle. Not accounting for individuals experiencing neck pain may have influenced the outcomes, potentially leading to distinct results. Future studies should consider including individuals specifically experiencing neck pain alongside FHP to assess potential variations in the effects of smartphone use on postural stability. Another limitation of this study is the absence of an evaluation involving single leg standing without using a smartphone. This restricts our ability to assess the pure effect of FHP on postural stability. Future

research should incorporate assessments of single leg standing both with and without smartphone usage to better isolate and understand the specific impact of FHP on balance and stability.

In conclusions, our study assessed balance maintenance using the NWBB across different conditions involving flexed neck postures (FN_HS and FN_SS) and neutral neck postures (NN_HS and NN_SS) on both hard and soft surfaces. The results consistently revealed significantly increased body COP sway lengths in individuals with FHP using smartphones compared to the control group, except in the scenario of flexed neck posture on a hard surface. This suggests that individuals with FHP, while using smartphones, experience notable decreases in balance, particularly in situations involving flexed neck postures on soft surfaces and when multitasking. These findings underscore the potential challenges individuals with FHP may face in maintaining balance during smartphone use in specific postures and environmental conditions. Ultimately, these research implications underscore the importance of further exploration, awareness, and intervention strategies to promote better posture and mitigate balance challenges among smartphone users, especially those with FHP, thereby enhancing overall musculoskeletal health and well-being in the digital age.

DATA AVAILABILITY STATEMENT

Raw data for this study is unavailable for public access due to proprietary constraints. However, summarized data supporting the findings can be provided upon request from the corresponding author.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTION

Conceptualization: Tapanya W, Sangkarit N. Methodology: Tapanya W. Formal analysis: Tapanya W. Funding acquisition: Tapanya W. Data curation: Tapanya W. Software: Tapanya W. Visualization: Tapanya W, Sangkarit N. Supervision: Tapanya W. Writing – original draft: Tapanya W, Sangkarit N. Writing – review and editing: Tapanya W, Sangkarit N. Approval of final manuscript: all authors.

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ORCID

Weerasak Tapanya, https://orcid.org/0000-0002-7080-5213
Noppharath Sangkarit, https://orcid.org/0000-0003-4622-5638

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Instructions for authors

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Annals of Rehabilitation Medicine

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When a manuscript is not resubmitted within 2 months of notification, it will be considered that the authors have withdrawn the manuscript from submission. Manuscripts accepted for publication are generally published in order of submission, depending on the category of the manuscript and the date of acceptance for publication.

7. PREPARATION OF THE MANUSCRIPT

Use Microsoft Office Word (versions after 2003) and ensure correct spelling and grammar. Setup the MS Word document for 1-inch margins on letter or A4-sized paper. The manuscript must be written in 12-point font and the sentences must be double-spaced, including tables and figure legends. Each page should be numbered in the middle of the lower margin, and all sentences must be numbered sequentially throughout the entirety of the manuscript, starting with the title page. All papers must be accompanied by a title page. The title page should contain the title of the manuscript, a short running title, the authors' names, academic degrees, respective affiliations, and ORCID. The corresponding author must be identified, and his or her contact information (postal address, e-mail, telephone and fax numbers) should be listed. The title should clearly describe the objective of the study and contain less than 20 words. The first letter of each word of the title should be in capital letters except for prepositions, articles, and conjunctions. Provide a short running title containing less than 10 words. In cases in which the authors belong to multiple affiliations, the affiliations during the study being reported should be matched to the authors' names using a superscript of Arabic numerals. Conflicts of interest, funding information, author contribution and acknowledgements (when applicable) should also be located in the title page.

1) ORIGINAL ARTICLES

Original papers should be structured in the following order: Abstract, Introduction, Methods, Results, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. Maximum word count is limited to 5,000 words.

(1) Abstract

A structured abstract with the headings of Objective, Methods, Results, and Conclusion must succinctly describe the paper in 250 words or less. Use complete sentences and do not number the results. At the end of the abstract, list up to 5 relevant keywords which are in accordance to the Medical Subject Headings (MeSH) in the Index Medicus (http://www.nlm.nih.gov/mesh).

(2) Introduction

Clearly present the objective of the study and its relationship to earlier work in the field. A brief background to inform the readers of the relevance of the study may be necessary. However, avoid extensive review of the literature.

(3) Methods

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 ± SD, and mean and standard error as mean ± 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.

(10) References

- Cite only references which are quoted in the text. Limit the number of references 40.

- When quoting a reference in the text, refrain from stating the author's name, and identify references with Arabic numerals in brackets such as [1], [2-4], and [5,7,9].
- The references should be listed in order of citation in the text.
- List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."
- Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).
- For more on references, refer to the NLM Style Guide for Authors, Editors, and Publishers (http://www.nlm.nih.gov/citingmedicine).

Journals

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

Book & Chapter of book

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

Proceedings of academic conference

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

Thesis (Dissertation)

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

(11) Tables

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

(12) Figure legends

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

(13) Figures

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

2) REVIEW ARTICLES

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

3) BRIEF REPORTS

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

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

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

5) IMAGES IN THIS ISSUE

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

6) LETTERS TO THE EDITOR

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

7) REPORTING GUIDELINES FOR SPECIFIC STUDY DESIGNS

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

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and metaanalyses	http://www.prisma-statement.org
STROBE	Observational studies	http://www.strobe-statement.org
MOOSE	Meta-analyses of observationa studies in epidemiology	http://www.consort-Statement.org/resources/downloads/other-instruments/moose-statement-2000pdf

8. SUBMISSION APPLICATION & COPYRIGHT TRANSFER

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

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9. MANUSCRIPTS AFTER ACCEPTANCE

ARM is published in English bi-monthly on the last days of February, April, June, August, October, and December.

1) FINAL VERSION UPLOAD

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

2) GALLEY PROOF

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

3) PUBLICATION

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

Checklist for Authors

Annals of Rehabilitation Medicine

General

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

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

☐ The text is consecutively line numbered.

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

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

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

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

References

☐ All references have been checked for accuracy and completeness.

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

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

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

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

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

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

Figure Legends

☐ Figure legends are provided for each figure.

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

☐ The title of the tables should be written in phrases, and capitalized the first letter of the first word.

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

☐ Tables are cited in numeric sequence in the text.

Figures

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