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Aims and Scope

Annals of Rehabilitation Medicine (ARM) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, nearly 8,000 physiatrists receive this journal every two months as a member benefit. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Pacific Society of Physical and Rehabilitation Medicine (APSIRM). International members comprise approximately half the editorial board and conduct peer-review of submitted manuscripts.

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

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Corrigendum

228 Correction: Reliability and Validity of the Korean Version of the Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool
Kyunghyun Lee, Sung Eun Hyun, Hyung-Ik Shin, Hye Min Ji
The survival rate of children admitted in the neonatal intensive care unit (NICU) after birth is on the increase; hence, proper evaluation and care of their neurodevelopment has become an important issue. Neurodevelopmental assessments of individual domains regarding motor, language, cognition, and sensory perception are crucial in planning prompt interventions for neonates requiring immediate support and rehabilitation treatment. These assessments are essential for identifying areas of weakness and designing targeted interventions to improve future functional outcomes and the quality of lives for both the infants and their families. However, initial stratification of risk to select those who are in danger of neurodevelopmental disorders is also important in terms of cost-effectiveness. Efficient and robust functional evaluations to recognize early signs of developmental disorders will help NICU graduates receive interventions and enhance functional capabilities if needed. Several age-dependent, domain-specific neurodevelopmental assessment tools are available; therefore, this review summarizes the characteristics of these tools and aims to develop multidimensional, standardized, and regular follow-up plans for NICU graduates in Korea.

**Keywords:** Low birth weight infant, Neonatal intensive care unit, Neurodevelopmental disorder, Premature birth, Rehabilitation
INTRODUCTION

Recent advances in neonatal care have led to an increase in the survival rates of preterm infants or those with low birth weight in Korea [1]. The average birth weight is declining, and the incidence of preterm births is on the increase [1,2]. Because preterm or low birth weight infants are at high risk of developmental delays or disorders, early and regular assessments of neurodevelopmental outcomes of graduates of neonatal intensive care units (NICUs) should continue immediately after discharge [3]. However, there is significant heterogeneity in the neurodevelopmental assessment follow-up policies in different countries [4]. A variety of development assessment tools are available for each domain and age range; however, a consensus gold standard is still lacking in terms of defining the best neurodevelopmental assessment and follow-up program for the early diagnosis of developmental delay [5,6].

Early identification of infants at high risk of developmental delays or disorders is critical for timely referral for appropriate intervention and family counseling. Proper surveillance of neurodevelopmental outcomes of infants is necessary due to the following: (1) early detection or diagnosis of developmental delay or neurodevelopmental disorders; (2) timely intervention and provision of individualized care within critical periods for better outcomes; (3) to educate family/caregivers regarding the developmental status, prognosis, and any possible problems or dangers of infants to prevent further deterioration; and (4) to improve functional outcomes of these infants and the well-being and quality of life of the entire family. Earlier involvement of parents in the care of babies with neurodevelopmental impairments before hospital discharge from the NICU is known to be effective in improving the parent-infant relationship, providing a nurturing environment, and targeting the intervention for individualized infant and family needs [7]. There should be sufficient parental education on useful and safe home exercises or play, information on proper feeding, positioning, sleep, and any available social services. In the future, these developmental interventions beyond the NICU should be updated with evidence-based intervention techniques for individual diagnoses.

Regular hospital visits for neurodevelopmental assessments after NICU discharge is widely acknowledged; however, there should be a systematic follow-up program for both appropriate diagnosis of neurodevelopmental delay and assessment of the efficacy of developmental interventions [5]. Developmental surveillance programs for NICU graduates should include all domains of neurological, motor, language, cognition, perception, and social skills. Moreover, this program should be encouraged to consider each child's developmental status, caregiver’s socio-economic status, individualized therapeutic program, healthcare resources, and social services or welfare [8,9]. This review summarizes the current evidence of available neurodevelopmental assessment tools for each domain and suggests appropriate Korean surveillance guidelines for NICU graduates.

I. EARLY NEURODEVELOPMENTAL ASSESSMENT PLAN

Developmental surveillance should consider appropriate timing and intervals in terms of cost-effectiveness and availability of healthcare resources. If NICU graduates have more severe risk factors, they would be at an even higher risk of various developmental problems [10-12]. Several risk factors that must be evaluated during NICU stay are summarized in Table 1 for clinicians not to delay neurodevelopmental evaluation for referral to the Department of Pediatric Rehabilitation Medicine. According to the numbers and grades of risk factors (Table 1), a corrected age (CA) to visit for neurodevelopmental surveillance and follow-up periods are suggested in Fig. 1 [3,5,10,13,14].

Early developmental screening is recommended within less than 1 month after discharge if there is at least one high risk factor; any organic brain lesion, such as grade 3 or 4 intraventricular hemorrhage, cystic periventricular leukomalacia, infarction, hypoxic ischemic encephalopathy, neonatal meningitis or encephalitis, and congenital brain malformation, ventriculomegaly, etc.; any feeding disorders associated with malnutrition; neonatal sepsis; bronchopulmonary dysplasia with mechanical ventilation until gestational age of 36 weeks; hyperbilirubinemia; any congenital or neuromuscular disorder, confirmed with gene study; extremely preterm (<28 weeks); extremely low birth weight (<1,000 g); high social risk such as any domestic violence or child abuse, severe poverty or homelessness, no antenatal care provided, caregivers’ intellectual disability or psychological problems; any tone abnormality of hyper/hypotonia or fluctuating tones are observed; or a history of infantile spasm or status epilepticus (Table 1). If any neurodevelopmental delay is suspected at the initial immediate follow-up, next follow-up visits or further evaluations should be determined at the physician’s discretion according to the individual infant’s medical and neurological conditions. Otherwise, later visits can be scheduled as routine follow-ups for low-risk NICU graduates. Further-
Table 1. Risk factor checklist for a surveillance of neurodevelopmental assessment after neonatal intensive care unit discharge

<table>
<thead>
<tr>
<th>High risk factors</th>
<th>Moderate risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain lesion</td>
<td>Very preterm (28–32 wk) OR very low birth weight: less than 1,500 g</td>
</tr>
<tr>
<td></td>
<td>Extremely low birth weight (less than 1,000 g)</td>
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<tr>
<td></td>
<td>High social risk (e.g., domestic violence, previous child abuse, severe poverty or homelessness, no antenatal care, intellectual disability or psychologic problem of caregiver, multicultural family)</td>
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<tr>
<td></td>
<td>Known sensory abnormality (hearing, vision [including severe retinopathy of prematurity], etc.)</td>
</tr>
<tr>
<td></td>
<td>Small for gestational age: birth weight &lt;10th percentile for gestational age</td>
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<tr>
<td></td>
<td>Major surgery including necrotizing enterocolitis operation (brain, cardiac, thoracic, or abdominal)</td>
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<tr>
<td></td>
<td>Moderate to late preterm (32–37 wk) OR low birth weight: less than 2,500 g</td>
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<tr>
<td></td>
<td>Any feeding disorders associated with malnutrition</td>
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<tr>
<td></td>
<td>Neonatal sepsis</td>
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<tr>
<td></td>
<td>Bronchopulmonary dysplasia with mechanical ventilation until gestational age of 36 wk</td>
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<tr>
<td></td>
<td>Hyperbilirubinemia (bilirubin &gt;400 μmol/L or clinical evidence of bilirubin encephalopathy)</td>
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<tr>
<td></td>
<td>Diagnosis of genetic or neuromuscular disease (spinal muscular atrophy, myopathy, etc.)</td>
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<tr>
<td></td>
<td>Extremely preterm (less than 28 wk)</td>
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<tr>
<td></td>
<td>Extremely low birth weight (less than 1,000 g)</td>
</tr>
<tr>
<td></td>
<td>History of infantile spasm or status epilepticus</td>
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<tr>
<td></td>
<td>Tone abnormality (definite hyper- or hypotonia, fluctuating tone)</td>
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<tr>
<td></td>
<td>Any feeding disorders associated with malnutrition</td>
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<tr>
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<td></td>
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</table>

More, an immediate intervention plan and/or education can be suggested for those with high-risk factors while still in hospital, rather than waiting for a confirmative diagnosis of developmental impairments [3].

Afterwards, moderate risk factors should be screened: very preterm (28–32 weeks) or very low birth weight (1,000–1,500 g) neonates; multiple pregnancies more than twins or discordant twins who show significantly different birth weight between twins; diagnosis of sensory abnormality, such as hearing or visual impairment, and severe retinopathy of prematurity; small for gestational age, that is, birth weight less than 10th percentile for gestational age; major perinatal surgery in the brain, heart, thorax, or abdomen including necrotizing enterocolitis operation; moderate to late preterm (32–37 weeks) or low birth weight (1,500–2,500 g) with any clinical perinatal event like epilepsy or feeding problems (Table 1). If two or more moderate risk factors are present, NICU graduates are required to be followed-up for neurodevelopmental screening within less than 1 month after discharge, similar to the existence of one high-risk factor. On the other hand, if there is only 0–1 moderate risk factor, it is recommended that NICU graduates should have regular checkups at a CA of 3–4 months for the first visit. Thereafter, further follow-up visits for neurodevelopmental assessment are recommended at CA of 8–9 months, 12–18 months, 24 months, and 36 months (Fig. 1).

However, the follow-up schedule should be refined by clinicians based on the functional and/or medical status of each infant. For example, if any special diagnosis is made, such as genetic or neurodegenerative diseases, the follow-up schedule should be individualized through experts’ and multidisciplinary care plans. Although the Bayley Scales of Infant Development (BSID) is an extensive formal developmental assessment tool for diagnosing developmental delays in early childhood for 1 to 42 months old babies (Table 2), it cannot predict long-term outcomes of development, especially when assessed at a young age such as before CA of 24 months old [13,15]. For those still undiagnosed with extremely preterm birth (<28 weeks) or extremely low birth weight (<1,000 g), BSID is strongly recommended at a CA of 36 months. Likewise, individual decision-making regarding which and when each neurodevelopmental assessment tool to choose would enrich better clinical practice and more accurate assessments.

II. OVERVIEW OF NEURODEVELOPMENTAL ASSESSMENT TOOLS

Currently available neurodevelopmental assessment tools are extremely varied at each age band. A regular neurodevelopmental follow-up program should include all developmental domains for more accurate surveillance and diagnosis, including motor, sensory perception, cognition, and language. Irrespective of how comprehensive neurodevelopmental assessment tools are employed, they are often insufficient, and clinicians should decide on additional specialized diagnostic tools for specific domains regarding individual functional status. Based on a comprehensive history taking and physical/neurological examination,
Neurodevelopmental surveillance and follow-up periods according to risk factors after discharge from neonatal intensive care unit (NICU). CA, corrected age; BSID, Bayley Scales of Infant Development.

including growth, primitive reflexes, postural reactions, developmental history, social/family history, and musculoskeletal evaluation, experienced clinicians should be able to decide any necessary further evaluations, including blood tests, genetic studies, or imaging modalities [5].

Categorical neurodevelopmental assessment tools are summarized and compared in detail in Table 2. Each assessment tool is characterized by its target age range, test type, whether it is norm-referenced or criterion-referenced, suggesting a clear cut-off score for diagnosis, evaluation of components within domains, diagnostic criteria, average time to administer, and immediate availability of the Korean-translated version and/or education for evaluators. Among them, the Denver Development Screening Tool (DDST), BSID, Korean-Developmental Screening Test (K-DST), Peabody Developmental Motor Scales (PDMS), Korean-Wechsler Preschool and Primary Scale of Intelligence-IV, and Developmental Test of Visual-Motor Integration-6 (VMI-6) are currently covered by National Insurance in Korea.

Furthermore, currently accumulated evidence on predictive accuracy regarding the reliability, internal consistency, and validity of each development assessment tool is searched and gathered in the Supplementary Tables S1-S4 to help healthcare professionals make a more convenient decision. Reliability is the extent to which patients can be distinguished from normal despite measurement errors and is evaluated through inter-/intra-rater intraclass correlation coefficient (ICC) or Cohen's weighted kappa values. It is “+” if ICC or kappa ≥0.70, “–” for <0.70, and “0” if no available information is found for reliability. Internal consistency is the extent to which items within a domain are inter-correlated to measure the same construct; it is “+” if factor analysis was provided with adequate sample size and Cronbach's alpha values are ≥0.70, “–” if Cronbach's alpha <0.70, and “0” if no available information was found for consistency. Content validity is the comprehensiveness of items in the assessment tools for the domain of interest: “+” if a clear description about the measurement aim, target population, and item selection while target population and evaluators or experts were involved in this item selection, “–” if target population or experts did not involve item selections, “0” if no information was found, and “?” if the...
<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Age range</th>
<th>Test type</th>
<th>Components tested</th>
<th>Diagnostic Criteria</th>
<th>Time to administer (min)</th>
<th>Availability of Korean version &amp; education</th>
<th>Equipment/cost</th>
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<tbody>
<tr>
<td><strong>Developmental delay screening</strong></td>
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<tr>
<td>DDST-II</td>
<td>0–6 yr</td>
<td>Criterion</td>
<td>Personal-social, fine motor-adaptive, language, gross motor</td>
<td>Item interpretation:&lt;br&gt;- Caution: items that can be completed by 75%–90% of children but are failed&lt;br&gt;- Delay: items that can be completed by 90% of children but are failed&lt;br&gt;- Overall interpretation:&lt;br&gt;- Abnormal: in each area of development, more than 2 delays&lt;br&gt;- Caution: 1 delay and/or 2 or more caution&lt;br&gt;- Normal: no more than one caution&lt;br&gt;Delay: items that can be completed by 90% of children but are failed&lt;br&gt;Caution: 1 delay and/or 2 or more caution&lt;br&gt;Normal: no more than one caution</td>
<td>10–30</td>
<td>Korean ver.: available&lt;br&gt;Education: none</td>
<td>Manual: ₩10,000&lt;br&gt;Total equipment: ₩130,000</td>
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<tr>
<td>K-DST</td>
<td>4–71 mo</td>
<td>Norm (3,010 children, Korea, 2010)</td>
<td>&lt;18 mo: gross motor, fine motor, cognition, language, social skills&lt;br&gt;≥18 mo: same as above &amp; self-help</td>
<td>Cutoff points at each domain, age&lt;br&gt;- Recommendation for further evaluation: &lt;2 SD&lt;br&gt;- Need for follow-up: -1 SD to -2 SD&lt;br&gt;- Peer level: -1 SD to +1 SD&lt;br&gt;- High level: &gt;1 SD&lt;br&gt;- Further assessment needed: at least one score below cutoff&lt;br&gt;- Provide learning activities &amp; monitor: at least one score adjacent to cutoff&lt;br&gt;- Development is on track: all scores from each domain are above cutoff</td>
<td>5–10</td>
<td>Korean ver.: available&lt;br&gt;Education: National Health Insurance Corporation&lt;br&gt;Online education</td>
<td>Free (provided by Korea Centers for Disease Control and Prevention)</td>
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<tr>
<td>K-ASQ</td>
<td>4–60 mo</td>
<td>Criterion</td>
<td>Communication, fine motor, gross motor, problem solving, personal-social</td>
<td>Further assessment needed: at least one score below cutoff&lt;br&gt;- Provide learning activities &amp; monitor: at least one score adjacent to cutoff&lt;br&gt;- Development is on track: all scores from each domain are above cutoff</td>
<td>10</td>
<td>Korean ver.: available&lt;br&gt;Education: none</td>
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<tr>
<td><strong>Developmental delay diagnosis (discriminative)</strong></td>
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<td>BSID-III&lt;sup&gt;a)&lt;/sup&gt;</td>
<td>1–42 mo</td>
<td>Norm (1,700 children from USA, 2000)</td>
<td>Gross motor, fine motor, cognitive, communication, social/emotional, adaptive</td>
<td>Developmental delay:&lt;br&gt;- &lt;25-percentile or below 2 SD&lt;br&gt;- ≥25 percentile but ≤2 SD</td>
<td>30–90</td>
<td>Korean ver.: available&lt;br&gt;Education: DVD, webinars, and workshops</td>
<td>1 set: ₩1,380,000&lt;br&gt;Free (provided by Korea Centers for Disease Control and Prevention)</td>
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<td><strong>Motor function evaluation</strong></td>
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<td>GMs</td>
<td>Preterm–5 mo</td>
<td>Criterion</td>
<td>Visual inspection of spontaneous movement</td>
<td>Preterm–6 wk: writhing movement&lt;br&gt;- Normal&lt;br&gt;- Abnormal (poor repertoire, cramped synchronized or chaotic)&lt;br&gt;9–20 wk: fidgety period&lt;br&gt;- Present&lt;br&gt;- Abnormal&lt;br&gt;- Absent</td>
<td>5–20</td>
<td>Korean ver.: none&lt;br&gt;Education: 4–5 day of authorized training course from GMs trust, providing certificates for each course (Basic, Advanced)</td>
<td>Free</td>
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<table>
<thead>
<tr>
<th>Assessment tool</th>
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<th>Time to administer (min)</th>
<th>Availability of Korean version &amp; education</th>
<th>Equipment/cost</th>
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<tbody>
<tr>
<td>TIMP</td>
<td>34 wk (PMA)–4 mo (17 wk post-term)</td>
<td>Norm (939 infants, at risk of poor neurological outcome, USA, 2006)</td>
<td>Gross motor: 42 items of postural and selective control of movement - 13 Observed items for spontaneous movement: yes-no; 1–0 scores - 29 Elicited items in supported sitting, supine, prone, side lying, supported standing: 0–3, 0–4, 0–5, 0–6 scores</td>
<td>Raw score</td>
<td>20–40</td>
<td>Korean ver.: none</td>
<td>Manual: $38 Workshops, or e-Learning Course: theimp.com</td>
</tr>
<tr>
<td>MAI</td>
<td>0–12 mo (m/c 4 mo)</td>
<td>Criterion</td>
<td>Gross motor, fine motor, muscle tone, primitive reflex, automatic reactions, volitional movements Total 65 items - Muscle tone: 1–6 points - Others: 1–4 points - High risk +1 points for each item</td>
<td>Cutoff of total scores (not validated) Developmental delay or abnormal : suspect 8–13 : high risk &gt;13 : later neurological abnormality &gt;10 : most probably normal &lt;4</td>
<td>30–90</td>
<td>Korean ver.: none</td>
<td>Manual: free Training recommended 2-day seminar; currently not available Standardized equipment is necessary (including 2 chairs, bell, rattle, red ball, etc.)</td>
</tr>
<tr>
<td>AIMS</td>
<td>0–18 mo</td>
<td>Norm (2,200 infants, Canada, 1990–1992)</td>
<td>Gross motor (no. of items) Prone (21), supine (9), sitting (12), standing (16) : total 58 items Items observed as voluntary movements are identified among above 4 posture-specific items</td>
<td>Among all observed voluntary movements, the highest and lowest development stages are scored as window score Previous items created (below window score) are all checked as +1 Age-adjusted subscale score (sum) Developmental delay or abnormal: At CA 4 mo: &lt;10th percentile At CA 8 mo: ≤5th percentile</td>
<td>20–25</td>
<td>Korean ver.: none</td>
<td>Guideline book: $80 Scoring sheets (on-line free) <a href="https://bpna.org.uk/userfiles/HINE%20proforma_07_07_17.pdf">https://bpna.org.uk/userfiles/HINE%20proforma_07_07_17.pdf</a></td>
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### Table 2. Continued

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<th>Assessment tool</th>
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<th>Test type</th>
<th>Components tested</th>
<th>Diagnostic Criteria</th>
<th>Time to administer (min)</th>
<th>Availability of Korean version &amp; education</th>
<th>Equipment/cost</th>
</tr>
</thead>
</table>
| PDMS-II        | 0–6 yr (using CA until 2 yr) | Norm (2,003 infants, USA & Canada, 1997–1998) | A total of 6 subsets  
   A. Gross motor  
   - Reflex: 2 wk–11 mo  
   - Stationary: body control  
   - Locomotion: transfer (crawling, walking, running, hopping, jumping)  
   - Object manipulation: 12 mo+: catch, throw  
   B. Fine motor  
   - Grasping: hand function: hold, pincer grasp, buttoning/unbuttoning, etc.  
   - Visual-motor integration: complex eye-hand coordination | Raw scores for each subtest  
   Sum scores converted to standard score, % rank, age-equivalent  
   Standard score sum  
   TMQ (total motor quotient)  
   GMQ (gross motor quotient)  
   FMQ (fine motor quotient)  
   <-1 SD: below average, caution  
   <-2 SD: suspicious of developmental delay | 45–60 (20–30 if only for motor-related subtest) | Korean ver.: available (for research-use only)  
   Manual: $100 | Test kit provides most of all equipment  
   Online scoring & report system: available |
| NSMDA          | 1 mo–6 yr | Criterion | 6 Subscales (gross motor, fine motor: neurological, primitive reflexes, postural reactions, motor response to sensory input); abnormal, suspicious, normal | Functional score  
   6–8: normal motor function  
   9–11: minimal motor problem  
   12–14: mild motor problem  
   15–19 moderate motor problem  
   20–25 severe motor problem  
   >25 profound disability | 20–45 | Korean ver.: none  
   Comprehensive manual: £35  
   Specific toys required but easily accessible |
| Language function evaluation (Korean) |  |  | 56 Questions for receptive and expressive language, respectively | Raw scores, equivalent age, percentile for semantics, phonology, syntax, and pragmatics  
   <-1 SD: caution  
   <-2 SD: advised for further evaluation about language delay |  |  |  |  
| SELSI          | 4–35 mo   | Norm     |  |  |  |  |  |
| PRES           | 2–6 yr (pre-school) | Norm | 45 Questions for receptive and expressive language, respectively | Raw scores, equivalent age, percentile for semantics, phonology/syntax, and pragmatics |  |  |  |
| P-FA           | Preschool, elementary & middle school | Norm | Fluency: word picture, repetition, sentence picture, reading, story picture, speaking picture (according to age level)  
   Communication skills (not in preschool evaluation): any burden/difficulty in speaking or stuttering | Raw scores, score distribution and percentile |  |  |  |  

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<thead>
<tr>
<th>Assessment tool</th>
<th>Age range</th>
<th>Test type</th>
<th>Components tested</th>
<th>Diagnostic Criteria</th>
<th>Time to administer (min)</th>
<th>Availability of Korean version &amp; education</th>
<th>Equipment/cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-M-B CDI</td>
<td>8–17 mo (infant)</td>
<td>Norm</td>
<td>Parent-report form to evaluate communication skills</td>
<td>Level I (infant): words and gestures; short form – 89-word vocabulary checklist</td>
<td>18</td>
<td>W 90,000 (including all equipment and manual)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18–30 mo (toddler)</td>
<td></td>
<td></td>
<td>Level IIA/B (toddler): words and sentences; 100-word productive vocabulary checklist, questions about combining words</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PPVT-R</td>
<td>2 yr–8 yr 11 mo</td>
<td>Norm</td>
<td>Language comprehension, receptive vocabulary skills</td>
<td>The first question is determined by age.</td>
<td>18</td>
<td>W 1,400,000 (including all equipment and manual)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>: Total 178 vocabulary</td>
<td>If 8 correct answers consecutively, this point is set as the baseline. (all questions before the point are scored as correct)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If 6 out of 8 consecutive questions are incorrect, the last incorrect questions is the upper limit;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Raw score with only correct answers to be calculated as percentile, equivalent age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REVT</td>
<td>2 yr 6 mo–16 yr</td>
<td>Norm</td>
<td>Receptive/expressive vocabulary skills (initially developed for Korean vocabulary)</td>
<td>Scoring is same with PPVT-R &lt; −1 SD: below average, caution</td>
<td>18</td>
<td>W 380,000 (including all equipment and manual)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>: 185 Questions (using pictures) for receptive and expressive domain, respectively</td>
<td>&lt; −2 SD: advised for further evaluation for vocabulary development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCAT</td>
<td>2–12 yr or preschool</td>
<td>Criterion (% accuracy)</td>
<td>Ability to modulate consonant pronunciation (using pictures) : 30 Words including 43 phonemes</td>
<td>For speech therapy for articulation, consider &lt; −1 SD, demand &lt; −2 SD</td>
<td>18</td>
<td></td>
<td></td>
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<tr>
<td>Cognitive function evaluation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>K-WPSSI-IV</td>
<td>2 yr 6 mo–3 yr 11 mo &amp; 4 yr–7 yr 7 mo</td>
<td>Norm</td>
<td>FSIQ Primary index scale (comprehensive cognitive functioning): composite scores of verbal comprehension index, visual spatial index, working memory index and fluid reasoning index, processing speed index for older age band Ancillary index scale: verbal acquisition index, nonverbal index, general ability index and cognitive proficiency index for older age band</td>
<td>Raw scores from the subset Age-corrected standard scores of scaled and composite scores (percentile) for FSIQ and each subset scores</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory-perception function evaluation</td>
<td></td>
<td></td>
<td></td>
<td>Raw scores: success until 3 consecutive &amp;Is Equivalent age, standard score, percentile for screening visual motor coordination function</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMI-6</td>
<td>2–90 yr</td>
<td>Norm (1,882 Korean, 2–90 yr)</td>
<td>Visual-motor integration, visual perception, motor coordination (spontaneous scribbling task, imitated scribbling task, imitation task)</td>
<td></td>
<td>10</td>
<td>Korean ver.: available With manual : W 110,000 Without manual : W 90,000</td>
<td></td>
</tr>
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<table>
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<tr>
<th>Assessment tool</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Visual Assessment</td>
<td>GA 35 wk–1 yr</td>
<td>Norm (110 healthy full-term neonate at 72 h, Italy)</td>
<td>9 Items of spontaneous ocular motility, ocular movements with target, fixation, tracking (horizontal, vertical, arc), reaction to a colored contrast target, ability to discriminate stripes, attention at distance</td>
<td>Each item scored 0 if &lt;90 percentile, scored 1 if abnormal Global score ≥2: abnormal</td>
<td>5–10</td>
<td>Korean ver.: none</td>
<td>Education: none</td>
</tr>
<tr>
<td>PreViAs</td>
<td>CA 0–24 mo</td>
<td>Norm (298 children from Spain)</td>
<td>Questionnaires of 30 items, 4 domains: visual attention; visual communication; visual-motor coordination; visual processing</td>
<td>Mean scores of each domain Cut off points for each visual domain and each age group by 2 mo</td>
<td>20–30</td>
<td>Korean ver.: none</td>
<td>Education: none</td>
</tr>
<tr>
<td>SP1</td>
<td>Infant SP1 0–6 mo Toddler SP1 7–36 mo SP1 3–10 yr Adolescent/Adult SP1 ≥11 yr</td>
<td>Norm (1,037 children without disability, 32 children with autism and 61 with ADHD from USA)</td>
<td>Sensory processing (auditory, visual, vestibular, touch, multisensory, oral sensory). Modulation (sensory processing related to endurance/tone, body position/movement, movement affection activity level, sensory input affecting emotional responses, visual input affecting emotional responses and activity). Behavioral and emotional responses (emotional/social responses, behavioral outcomes of sensory processing, items indicating thresholds for responses)</td>
<td>Sensory seeking, emotionally reactive, low endurance/tone, oral sensory sensitivity, inattention/distraictibility, poor registration, sensory sensitivity, sedentary, fine motor/perceptual Typical performance &lt; -1 SD: possible difference &lt; -2 SD: definite difference</td>
<td>5–30</td>
<td>Korean ver.: available Comprehensive manual: included in questionnaire</td>
<td>Questionnaire: $193</td>
</tr>
<tr>
<td>SP2</td>
<td>Infant SP2 0–6 mo Toddler SP2 7–35 mo Child SP2 3–14 yr 11 mo Short SP2 3–14 yr 11 mo School companion SP2 3–14 yr 11 mo</td>
<td>Norm (1,791 from USA)</td>
<td>Sensory sections: auditory, visual, touch, movement, body position, oral Behavioral sections: conduct, social emotional, attentional Caregiver questionnaire for 5 Likert score (1–5)</td>
<td>Seeking score: degree to which a child obtains sensory input Avoiding score: degree to which a child is bothered by sensory input Sensitivity: degree to which a child detects sensory input (notification of sensory input) Registration: degree to which a child misses sensory input Raw scores, percentile range, standardized scores -1 SD to +1 SD: normal &lt; -1 SD: less than others &lt; -2 SD: much less than others &gt; +1 SD: more than others &gt; +2 SD: much more than others Typical range (T-score: 40–59) Some problems range (T-score: 60–69) Definite dysfunction range (T-score: 70–80)</td>
<td>5–20</td>
<td>Korean ver.: none Comprehensive manual: included in questionnaire</td>
<td>Questionnaire: $292</td>
</tr>
<tr>
<td>SPM-P</td>
<td>2–5 yr</td>
<td>Norm (651 typically developing children from USA)</td>
<td>Social participation, vision, hearing, touch, total sensory system/taste and smell, body awareness, balance and motion, planning and ideas</td>
<td>Typical range (T-score: 40–59) Some problems range (T-score: 60–69) Definite dysfunction range (T-score: 70–80)</td>
<td>15–20</td>
<td>Korean ver.: none</td>
<td>Education: none</td>
</tr>
</tbody>
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description of these aspects is lacking. Criterion validity is the extent to which the test scores are related to a gold standard, and is demonstrated through the correlation coefficient: “+” if coefficient ≥0.70, “-” if <0.70, and “0” if no information is suggested. Construct validity is the extent to which scores on a specific domain measure the intended theoretical construct or concept. It is assessed as “+” if specific hypotheses were formulated and ≥75% of the results are in accordance, “-” if <75% of hypotheses were confirmed, “0” if no information was available, and “?” only if doubtful hypotheses or method exists [16].

Developmental delay screening

Screening tools are often used prior to an accurate diagnosis of developmental delay. A literature search for proper developmental delay screening tools, revealed that K-DST [17], and Korean-Ages and Stages Questionnaires (K-ASQ) [18,19] are available in Korean versions. The first screening is usually performed with DDST-II, inclusive of the gross motor, fine motor-adaptive, language, and personal-social domains [20]. “Delay” is indicated if a child fails an item that more than 90% of children of the same chronological age were able to do, and “caution” is indicated if a child fails an item that 75%–90% of children of the same chronological age were able to do. Developmental delay was suspected if there were two or more cautions and/or one or more delays. This criterion-based test showed a high inter-observer and test-retest reliability and sensitivity of 0.83 and specificity of 0.51, respectively [21,22]. If a developmental disorder is suspected from DDST-II, a more thorough, discriminative evaluation of BSID is usually recommended to follow as a diagnostic assessment, which is norm-based test to evaluate gross motor, fine motor, cognition, communication, social/emotional, and adaptive domains, which can suggest a high risk of developmental delay if below 2 standard deviation (<25 percentile) [23,24]. BSID is popularly used to diagnose developmental delay in terms of which domain shows a problem and how much delay is presented in terms of percentiles [18,25]. In particular, BSID at the age of 2 years is known to predict motor impairment at the age of 4 years old [10,26].

Motor function

Standardized neuromotor assessment tools are intended to discriminate or identify any abnormalities in antigravity and/or spontaneous movements elicited by infant motor patterns, reflexes, or muscle tone [27]. In contrast, most neurobehavioral assessment tools assume that the emergence of motor skills follows
the same sequence as rolling, sitting, crawling, and walking and evaluate social/attentional and autonomic responses of infants according to gestational age. Although the Hammersmith Infant Neurologic Examination (HINE) evaluates both neurological and neurobehavioral domains, only a neurological domain of cranial nerve function, posture, voluntary movement, tone, and reflexes/reactions are scored to describe the risk of cerebral palsy (CP). Also, the Movement Assessment of Infants (MAI), PDMS for infant (from 2 weeks to 11 months CA), and Neurosensory Motor Developmental Assessment (NSMDA) evaluate both domains; scoring primitive reflexes, postural reactions, and muscle tone for neuromotor assessment as well as checking gross and fine motor development through observing elicited or volitional movements for neurobehavioral assessment.

The general movements (GMs), HINE, and Test of Infant Motor Performance (TIMP) are the most popular neurodevelopmental assessment tools that are recommended for the early diagnosis of CP before 5 months’ CA, together with brain imaging evaluations [14]. As well as considering risk factors (Table 1), early detection of CP or other developmental disorders can be achieved with using a combination of several standardized motor assessment tools and proper neuroimaging [14]. In infants with later infancy after 5 months’ CA, additional to HINE, the physical development domain of Developmental Assessment of Young Children, Alberta Infant Motor Scale (AIMS), and NSMDA are also recommended in combination as known to be predictive in the diagnosis of motor impairments, especially when brain magnetic resonance imaging is neither affordable nor available due to safety conditions [14,28].

During the earliest age, GM is useful and “fidgety” movement during CA between 3 and 4 months of age has been shown to have the best predictive validity of motor impairments [29,30]. Both GM and TIMP showed the strongest psychometric properties and predictive validity to better anticipate future motor outcomes and evaluate the effect of interventions [27]. On the other hand, HINE focuses more on neurologic impairment than on current motor function to propose a cutoff score in each age range to discriminate the risks of permanent motor impairment [31,32]. PDMS and AIMS have strong discriminative validity because they have a norm-referenced value from sufficiently large populations [33,34]. MAI is strong at an earlier age (younger than 4 months), such as GM and TIMP, while AIMS and NSMDA are generally for older ages (8–12-month-old) [35].

Various assessment tools exist specifically for each age band and subtest domain for NICU graduates to detect subtle changes in motor development for stratification of the severity of motor impairments and evaluation of the effect of treatment. Therefore, a uniform use of comprehensive motor assessment tools for sequential follow-up with a large population would be helpful in clarifying how NICU graduates follow and catch up on motor development milestones. Unfortunately, only PDMS is available in the formerly Korean-translated version; however, most other tools are already in common use with the English version. Although motor development is assumed to be similar in different countries, the new population displays different norms for each assessment tool [36]. Professionals involved in motor surveillance should also remember cultural effects on motor milestones and context-specific test results.

**Language and cognitive function**

If the language scale from the BSID results is suggestive of language function impairments, standardized language assessment batteries usually follow. New language assessment tools using the Korean language should be developed to evaluate communication skills. For comprehensive language evaluation, the Preschool Receptive-Expressive Language Scale (PRES) and the Sequenced Language Scale for Infants (SELSI) are the most popular and widely used tools with 56 questions on SELSI and 45 questions in PRES for receptive and expressive language, respectively [37]. The Paradise-Fluency Assessment (P-FA) assesses fluency using a picture representing words, sentences or speaking, and repetition task [38]; and Korean-MacArthur-Bates Communicative Development Inventories (K-M-B CDI) utilizes parent-report questionnaires about a vocabulary checklist to evaluate communication skills [39]. The Peabody Picture Vocabulary Test-Revised (PPVT-R) and the Receptive Expressive Vocabulary Test (REV) are tools for assessing vocabulary capacity. Although different target age ranges are suggested for each assessment tool, a combination of several tools is usually recommended owing to the different test domains and scoring methods (Table 2) [37].

These language assessment tools use structured question orders, since more difficult questions for older children appear later than easier questions. Therefore, a norm-based interpretation can be used based on score distributions according to each age band, usually at 2–3-month intervals, with mean values and standard deviations. Then, the result can report the raw scores of each domain, which can be calculated as equivalent age and percentile. Picture consonant articulation test (PCAT) is only a criterion-based test that calculates percentage of correctly pro-
nounced consonants (% accuracy). It uses an object containing the phoneme to be tested or a corresponding picture, and asks children to speak the word to evaluate the accuracy of articulation and to determine any disability or articulation based on the age at which certain consonants are acquired [40].

In Table 2, the time to administer and the availability of Korean versions/education are empty for language assessment tools. The time taken for language assessments varies considerably according to individual cooperation or cognitive level, medical status, and environment. It is difficult to accurately estimate the time required; however, 30–60 minutes are usually allocated as the evaluation time. Education for language assessment is unavailable to common users because speech and language pathologists with professional training, degrees, and national certification oversee every language assessment and treatment in Korea. Therefore, essential personnel preparation must first be established for follow-up language assessments.

As an initial screening tool for cognition, the cognitive scale from the BSID is useful for the age range of up to 42 months. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) is the most popular assessment tool for evaluating cognition. The Wechsler Intelligence Scale for Children (WISC) is for higher age, although some overlapping age bands exist around 6 to 7 years [41]. When interpreting the different results of each evaluation tool around this age, clinicians should remember that the two tests can produce a different cognitive profile, and WISC could result in lower scores on the subtest of vocabulary, matrix reasoning, and bug/symbol search compared to WPPSI [41].

Sensory-perception function
Sensory perception is important in early development, especially during critical periods of neuroplasticity and refinement [42]. Because most early interventions focus on an enriching environment for this neuroplasticity, the existence of sensory deprivation is a huge barrier for NICU graduates to catch up on developmental milestones after discharge. Most NICU graduates suffer from visual perception, visual-motor integration, and coordination impairments that affect later learning disabilities and school activities [43]. Therefore, appropriate sensory perception function assessments must be combined with regular developmental follow-up programs.

For visual sense assessment tools, the neonatal visual assessment is for the earliest age from 35 weeks to 1 year of age, which is appropriate for use during NICU stay [44]. Preverbal Visual Assessment (PreViAs), a simple questionnaire of 30 items, is for 0–24 months old babies [44,45], while the VMI-6, a nonverbal test using figure and shapes, culture-free, standardized easy tool, is for 2–90 years old including adults, which can provide a result of equivalent age for visual motor coordination function [46]. The Sensory Processing Measure-Preschool (SPM-P) is for preschool age of 2–5 years old and assesses how the child is processing sensory stimuli and how the sensory needs are reacting to different environments. The social participation measure is unique in the SPM-P and can evaluate over/under-responsiveness to sensory stimuli [47]. Sensory Profile 2 is a recently updated version of Sensory Profile 1 for infant (0–6 months), toddler (7–35 months), and child (3–14 years old). This tool requests for caregiver observations or judgment about sensory processing patterns and impact on functional performance, giving the score for each quadrant of searching, avoiding, sensitivity, and registration [48,49]. The Test of Sensory Functions in Infants (TSFI) tests five domains: tactile deep pressure, visual tactile integration, vestibular functions, ocular motor control, and reactivity to vestibular stimulation [50,51]. A stronger understanding of how children's sensory processing patterns can impact daily function, participation, and daily activities is needed to plan further interventions.

CONCLUSION
This guideline summarizes neurodevelopmental surveillance methods for patients who have been cared for and discharged from the NICU until the age of approximately 3 years. This is based on risk factor stratification and currently available assessment tools for each development domain. This surveillance program aims to enable early diagnosis and timely intervention for people with developmental disorders to support their functions and quality of life. Although there is still a lack of evidence-based early treatment guidelines for NICU graduates, this standardized post-discharge neuromotor development surveillance program would lead to a more concrete database for identifying those who need early rehabilitation interventions in the future.

CONFLICTS OF INTEREST
Jeong-Yi Kwon, Bo Young Hong, and Jin A Yoon are the 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: Kwon BS, Kwon JY. Methodology: all authors. Formal analysis: all authors. Funding acquisition: Kwon BS. Project administration: Kwon JY, Hyun SE. Visualization: all authors. Writing – original draft: Hyun SE, Kwon JY, Kwon BS, Hong BY, Yoon JA, Choi JY, Hong J. Writing – review and editing: all authors. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.5535/arm.23038.

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REFERENCES

INTRODUCTION

Cardiac surgery is a procedure associated with increased survival and quality of life, but there are deleterious effects such as worsening pulmonary function and functional capacity [1]. These last two events are related to the decrease in ventilatory muscle strength common in this patient submitted to cardiac surgery, which may increase the length of hospital stay and postoperative complications [1-3].

In this scenario, inspiratory muscle training (IMT) appears as a fundamental strategy to minimize the negative damage caused by the surgical procedure, being a non-invasive technique, with good applicability in the hospital environment and in the intensive care unit (ICU). Some studies suggest that the IMT improves the respiratory muscle strength, tidal volume and peak expiratory flow [4-9]. Our group has already demonstrated that performing IMT and decreasing muscle loss is associated with improved functional capacity and potential benefit over other treatments.
length of hospital stay in patients undergoing coronary artery bypass grafting (CABG) [10,11].

Thus, it becomes necessary to identify the best scientific evidence on the effect of IMT performed in the postoperative period and its influence on the clinical and functional aspects of these patients. The last review on the topic is in 2017 [4]. In recent years, new articles have been published making the update valid. The aim of our work is to review the effects of IMT and its impact on respiratory muscle strength, pulmonary function, functional capacity, and length of hospital stay in patients undergoing cardiac surgery.

METHODS

Protocol and registration
This meta-analysis was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [12] guidelines. It is registered in PROSPERO (international prospective register of systematic reviews) under number CRD42021218265.

Eligibility criteria
To perform this systematic review, the Population, Intervention, Control, Outcomes and Study type (PICOS) [13] strategy was used, where the Population studied were patients undergoing myocardial revascularization, the Intervention was IMT, compared with patients who did not undergo the training or traditional method. Traditional method was defined as that performed without adjustment based on anaerobic threshold. The Outcomes were related to inspiratory and expiratory muscle strength, pulmonary functional (tidal volume and peak expiratory flow), functional capacity and length of hospital stay. Functional capacity was assessed by a submaximal test called the 6-minute walk test (6MWT). The point in time was until the moment of hospital discharge. Randomized controlled trials were used, without language and year restriction.

Information sources
We performed a computer-based search, querying Ovid MEDLINE, LILACS, CINAHL (Cumulative Index to Nursing and Allied Health), PubMed, PEDro (Physiotherapy Evidence Database), and the CENTRAL (Cochrane Central Register of Controlled Trials). We also searched the list of references from previous systematic reviews and from the clinical trials eligible for this review. The search for the articles started in August 2020 and finished in November 2020.

Search
The research was based on the PICOS [13] strategy previously described and Boolean operators AND and OR. We used as descriptors for the population cardiac surgery, cardiac surgeries, coronary artery bypass graft, CABG, and myocardial revascularization. For the intervention we used exercise, IMT, respiratory exercise, and breathing exercises. For outcomes were muscle strength, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), MIP, MEP, inspiratory pressure, expiratory pressure, volume tidal, peak flow, functional capacity, and length of stay. As descriptors for the study design, we use randomized controlled trials clinical trials, and controlled trials.

Study selection
Randomized controlled trials enrolling cardiac surgery patients were included in this systematic review. To be eligible, the clinical trial should have assigned CABG surgery patients to a group of IMT alone. Studies with adults (18 years and older), regardless of sex, were also included. IMT was defined as training methods that applied loads only during inspiration and that aimed to increase strength and/or endurance of the inspiratory muscles.

Exclusion criteria were studies that involved another type of exercise combined with muscle training, aerobic exercises and IMT initiated in the preoperative period.

Data collection process
To extract the selected articles, we checked titles (first stage), abstracts (second stage), and complete reading (third stage). Then, an exploratory reading of the selected studies was carried out one, later, selective and analytical reading. The data extracted from the articles were summarized in authors, magazine, year, title, and conclusions, to obtain important information for the research.

The evaluation of the methodological quality of the studies was carried out by two independent reviewers. When there was disagreement between them, the article was read in full for reassessment. If the disagreement persisted, a third reviewer assessed and made the final decision.

Data items
Two authors independently (ALLC and LOS) extracted data from the published reports using standard data extraction considering: (1) aspects of the study population, such as the average...
age, sex, number of patients, diagnosis; (2) aspects of the intervention performed (sample size, type of IMT performed, presence of supervision, intensity, frequency, length, and duration of each session); (3) follow-up; (4) loss to follow-up; (5) outcome measures; and (6) presented results.

The quality of each study
Methodological quality was assessed according to the criteria of the PEDro scale, which scores 11 items, namely: 1, eligibility criteria; 2, random allocation; 3, hidden allocation; 4, baseline comparison; 5, blind individuals; 6, blind therapists; 7, blind evaluators; 8, adequate follow-up; 9, intention to treat the analysis; 10, comparisons between groups; and 11, point estimates and variability. Items are scored as present (1) or absent (0), generating a maximum sum of 10 points, with the first item not counting [14]. Whenever possible the PEDro scores were extracted from the PEDro database itself. When the articles were not found in the PEDro database, two trained independent reviewers assessed the article with the PEDro scale. The studies were considered of high quality if they had scores equal to or greater than 6. Studies with scores lower than 6 were considered as having low quality.

Synthesis of results
The presence of heterogeneity was evaluated using the chi-squared test and the $I^2$ statistic. This statistic illustrates the percentage of variability in effect estimates from heterogeneity rather than sampling error.

Statistical assessment
The mean difference (MD) between groups and the respective 95% confidence interval (CI) were calculated and used to quantify the effect of continuous outcomes. For the meta-analysis in which the studies used the same scales, the results were presented as MD and 95% CI. Otherwise, the effects were calculated using standardized mean difference (SMD) and 95% CI. The effect size of the interventions was defined as small (MD<10% of the scale or SMD<0.4); moderate (MD=10%–20% of the scale or SMD=0.41–0.70), or large (MD>20% of the scale or SMD>0.70) [15].

RESULTS

Selection and characteristics of studies
We found 3,512 articles, of which seven studies [3,10,11,16-19] were considered eligible for systematic review (Fig. 1). Table 1 presents the characteristics of the studies.

Results of methodological quality
In the evaluation of methodological quality with the PEDro scale, the scores of seven articles were already available in the PEDro database [3,14,16-19] and that of an article [11] was evaluated by two independent reviewers, as it has not yet been available. The scores ranged from 3 to 7 points on a scale of 0 to 10 points (Table 2). All studies lost points in the items related to the blinding of the patient and therapist, and only three studies [3,11,16] blinded the evaluator.

IMT protocols for different outcomes
Seven studies [3,10,11,16-19] applied IMT after myocardial revascularization followed up to hospital discharge (n=181). Manapunsopee et al. [16] compared the performance of incentive spirometry associated with breathing exercise with breathing exercise only (n=43); patients were encouraged to perform incentive spirometry 10 times an hour awake and were instructed to perform maximum slow inspirations while holding the sphere for 3–5 seconds, or as long as possible. The study by Zanini et al. [3] was composed of four groups, but for our analysis, the IMT group was compared with the control group (n=10); the training was carried out with the Threshold Respironics IMT, but without reporting the exercise prescription.

Cordeiro et al. [10] compared IMT with conventional physiotherapy treatment (n=25); IMT with a pressure linear load device (Threshold Respironics IMT; Respironics, Inc., Murrysville, PA, USA), with 40% of the MIP performing 3 sets with 10 repetitions. Barros et al. [17] compared the IMT plus conventional physiotherapy with the control group that performed only conventional physiotherapy (n=15); the IMT protocol was performed with three sets of 10 repetitions, once a day, during all postoperative hospitalization days with a load of 40% of the MIP value.

The study by Matheus et al. [18] compared conventional physical therapy associated with IMT with conventional physical therapy (n=24); IMT was performed daily in the first three days after the surgical procedure, with three series with 10 repetitions, twice a day with a load of 40% of MIP. Cordeiro et al. [11] compared IMT based on the anaerobic threshold with conventional training that was recognized as control (n=21); patients were submitted to exercise prescription according to the glycemic threshold on the first day after the surgical procedure. In the study by Praveen et al. [19] compared the IMT with the control...
group that performed the usual hospital protocol (n=30); IMT was started on the fourth postoperative day with three series of 10 repetitions, patients were reevaluated on the eighth day and continued training until the 18th postoperative day.

**IMT on ventilatory muscle strength**

Seven studies [3,10,11,16-19] analyzed the impact of IMT on maximal inspiratory pressure in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model was used ($I^2=62\%$, df=6, $p=0.02$), in which there was a statistically significant difference between the groups in the comparison between the IMT and the control (difference between the means=12.24 cmH$_2$O; 95% CI, 6.74–17.74; Fig. 2A). Another four studies [3,11,17,18] analyzed the impact of IMT on MEP in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model ($I^2=80\%$, df=3, $p=0.002$) was used, in which there was a statistically significant difference between the groups in the comparison between the IMT and the control (difference between the means=15.87 cmH$_2$O; 95% CI, 1.16–30.58; Fig. 2B).

**IMT for pulmonary function**

Three studies [11,17,18] analyzed the impact of IMT on peak expiratory flow in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model was used ($I^2=9\%$, df=2, $p=0.33$), in which there was a statistically significant difference between the groups in the comparison between the IMT and the control (difference between the means=40.98 L/min; 95% CI, 4.64–77.32, Fig. 2C).

Two other studies [17,18] analyzed the impact of IMT on tidal volume in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model was used ($I^2=81\%$, df=1, $p=0.02$), in which there was a statistically significant difference between the groups in the comparison between the IMT and the control (difference between the means=184.75 mL; 95% CI, 19.72–349.77; Fig. 2D).

**IMT to functional capacity**

Three studies [3,10,11] analyzed the impact of IMT on functional capacity in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model was used ($I^2=84\%$, df=2, $p=0.002$), in which there was no statisti-
Table 1. General characteristics of each study and description of the intervention and control group protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Interventions</th>
<th>Measurements</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordeiro et al., 2016 [10]</td>
<td>Brazil</td>
<td>50</td>
<td>Randomized controlled trial</td>
<td>Patients undergoing cardiac surgery</td>
<td>Usual physiotherapy+IMT, 3 sets of 10 repetitions, load of 40% of the initial MIP, 2 sets a day, 7 sets a wk from the 1 POD until the moment of hospital discharge</td>
<td>MIP and 6MWT</td>
<td>Statistically significant improvement in MIP and 6MWT. The IG had a higher value in MIP at discharge compared to the CG in the same period 69.5±14.9 (CG) vs. 83.1±19.1 (GT), p=0.0073. The distance traveled on the 6MWT to the IG was significantly greater at discharge than the CG (422.4±102.8 [CG] vs. 502.4±112.8 [GI], p=0.0031)</td>
</tr>
<tr>
<td>Cordeiro et al., 2020 [11]</td>
<td>Brazil</td>
<td>42</td>
<td>Randomized controlled trial</td>
<td>Patients undergoing cardiac surgery</td>
<td>The GT performed IMT with a linear pressure loading device, based in anaerobic threshold, 3 sets of 15 repetitions, 7 sets a wk from the 1 POD until the time of hospital discharge based in glycemic threshold</td>
<td>MIP, MEP, TV, PEF, and 6MWT</td>
<td>Smaller reductions in MIP were found in the GT (p&lt;0.01) 95% CI, 15 (9–19). In the 6MWT, the GT showed less loss in the distance covered 57±30 m (p=0.04) 95% CI, -1.2 (-2 to -0.1) and on the day of hospital discharge the GT walked 37 m more than the than CG (p&lt;0.001). A MEP 95% CI, 7 (-3 to 13) p=0.33; PEF 95% CI, -35 (-41 to 9) p=0.33; and TV 95% CI, 2 (-4 to 4) p=0.44 there was no statistical difference between groups</td>
</tr>
<tr>
<td>Manapunsoperee et al., 2020 [16]</td>
<td>Thailand</td>
<td>90</td>
<td>Randomized controlled trial</td>
<td>Patients 18 yr or older who underwent elective CABG</td>
<td>Usual physiotherapy+flow incentive spirometry, 10 times an hour, performing maximum slow inspirations while holding the ball at the same level for 3–5 s, or as long as possible, 7 sets a wk from 1 POD until the time of hospital discharge</td>
<td>MIP</td>
<td>There was a significantly smaller reduction in MIP compared to the GT with the CG (33.06±23.2% vs. 47.26±20.1; p=0.006, 95% CI, 3.9–23.3).</td>
</tr>
<tr>
<td>Zanini et al., 2019 [3]</td>
<td>Brazil</td>
<td>40</td>
<td>Single-blind, single-center randomized controlled trial</td>
<td>Patients aged 18 to 70 yr who underwent elective CABG</td>
<td>IMT</td>
<td>MIP, MEP, and 6MWT</td>
<td>All groups had similar behavior in MIP (p=0.29) and MEP (p=0.02). The result of the 6MWT shows that the greatest impairment in functional capacity was observed in G3 275 (23) and G4 291 (22) compared to G1 365 (23) and G2 401 (20), ps&gt;0.001</td>
</tr>
</tbody>
</table>

(Continued to the next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Interventions</th>
<th>Measurements</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barros et al., 2010</td>
<td>Brazil</td>
<td>38</td>
<td>Randomized controlled trial</td>
<td>Adult patients undergoing CABG with CPB</td>
<td>Usual physiotherapy+IMT, 3 sets of 10 repetitions, load of 40% of the initial MIP value, from the 1 POD until the moment of hospital discharge</td>
<td>MIP, MEP, PEF, and TV</td>
<td>Statistically significant improvement in the GT of MIP (p=0.01), TV (p=0.00), MEP (p=0.02), and PEF (p=0.02) on the last day of hospitalization</td>
</tr>
<tr>
<td>Matheus et al., 2012</td>
<td>Brazil</td>
<td>47</td>
<td>Randomized controlled trial</td>
<td>Patients undergoing CABG undergoing median sternotomy, with an internal mammary artery graft, complemented with saphenous vein bridges</td>
<td>Usual physiotherapy+IMT with Threshold® IMT Respironics®, 3 sets of 10 repetitions, 2 sets a day twice a day, load of 40% of the MEP measured at 1 POD, 1 POD until hospital discharge</td>
<td>MIP, MEP, TV, and PEF</td>
<td>There was no significant statistical difference between the groups in the values of MIP (p=0.1680), MEP (p=0.168), and PEF (p=0.4750). TV (p=0.0490) and TV (p=0.0222) found a significant difference between CG and GT on the 3rd postoperative day</td>
</tr>
<tr>
<td>Praveen et al., 2009</td>
<td>India</td>
<td>30</td>
<td>Randomized controlled trial</td>
<td>Patients of both sexes, aged 45 to 65 yr, undergoing CABG without a history of cardiac surgery, valve associated with cardiac disorder or diabetes mellitus</td>
<td>Usual physiotherapy+IMT was started on the 4th day in the experimental group; 3 sets a day, 3 sets of 10 repetitions were performed in one session with a one-minute rest period between sets</td>
<td>MIP</td>
<td>MIP in the GT improved significantly more than the subjects in the CG with an average of 86.07±7.99 cm of H2O and 69.53±8.62 cm of H2O, respectively (p&lt;0.001)</td>
</tr>
</tbody>
</table>

IMT, inspiratory muscle training; MIP, maximum inspiratory pressures; POD, post operatory day; 6MWT, 6-minute walk test; IG, intervention group; CG, control group; GT, group training; MEP, maximum expiratory pressure; TV, tidal volume; PEF, peak expiratory flow; CI, confidence interval; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.
cally significant difference between the groups in the comparison between the IMT and the control (difference between the means=29.93 m; 95% CI, -27.59 to 87.45; Fig. 2E).

**IMT on length of hospital stay**

Five studies [3,10,11,17,18] analyzed the impact of IMT on the length of hospital stay in the postoperative period of cardiac surgery. For the meta-analysis of this comparison, a random model was used ($I^2=0\%$, df=4, $p=0.46$), in which there was a statistically significant difference between the groups in the comparison between the IMT and control (difference between the means=-1.25 days; 95% CI, -1.77 to -0.72; Fig. 2F).

**DISCUSSION**

Based on the results of our meta-analysis, we found that IMT performed in the postoperative period has a positive impact on inspiratory and expiratory muscle strength, peak expiratory flow, tidal volume and length of hospital stay, but does not alter the functional capacity of this patient profile.

Seven studies [3,10,11,16-19] demonstrated that the IMT performed in the postoperative period had a positive impact on inspiratory muscle strength. Cordeiro et al. [11] highlight that the objective of the IMT is to decrease the loss of strength at discharge, since factors such as sternotomy, pain and immobilization are associated with a decline in postoperative strength. In this study, the beginning of IMT was on the first or second day after surgery and on discharge from the ICU, extending to the third day or hospital discharge.

The reduction in the loss of inspiratory muscle strength may be associated with the improvement of clinical outcomes such as postoperative complications and functional as well as functional capacity [5]. The increase in MIP makes it possible to take deep breaths, increasing lung capacity and reversing hypoventilation and atelectasis, which reduces the incidence of pulmonary complications [4].

Although they are not directly affected by IMT, expiratory muscles also benefit from this treatment option. Our meta-analysis showed a better result in this outcome in the patients who received the training. With the increase in the MEP, the cough becomes effective, allowing the displacement and elimination of bronchial secretions [15]. This hygiene reduces the risk of respiratory infections and may be associated with a decrease in hospital stay [7].

Based on the three studies included in this meta-analysis, which assessed functional capacity in patients undergoing IMT, there was no difference between the interventions. One possible explanation for this lies in the fact that performance on the 6MWT does not depend only on muscle and lung capacity. Cardiac function must also be taken into account, along with factors inherent to the surgical process such as pain.

Another relevant factor associated with the optimization of inspiratory and expiratory muscle strength is the improvement in functional performance. The strengthened diaphragm enhances minute ventilation and increases the delivery of oxygen to the muscle [20,21]. Still on the functional capacity in this meta-analysis, it is worth remembering the high heterogeneity, using a random process in an attempt to equalize, and the low sample size.

The variables of pulmonary function, peak expiratory flow and tidal volume showed positive results among patients who underwent IMT. This improvement is related to the increase in

### Table 2. Methodological quality of eligible studies (n=7), PEDro scale

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordeiro et al., 2016 [10]</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>3/10</td>
</tr>
<tr>
<td>Cordeiro et al., 2020 [11]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7/10</td>
</tr>
<tr>
<td>Manapunsoopee et al., 2020 [16]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7/10</td>
</tr>
<tr>
<td>Zanini et al., 2019 [3]</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>7/10</td>
</tr>
<tr>
<td>Barros et al., 2010 [17]</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>4/10</td>
</tr>
<tr>
<td>Matheus et al., 2012 [18]</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>4/10</td>
</tr>
<tr>
<td>Pravenn et al., 2009 [19]</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>4/10</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

1, eligibility criteria; 2, random allocation; 3, concealed allocation; 4, baseline comparability; 5, blind subjects; 6, blind therapists; 7, blind assessors; 8, adequate follow-up; 9, intention-to-treat analysis; 10, between-group comparisons; 11, point estimates and variability. Y, yes; N, No. aDoes not contribute to the total score.
**Fig. 2.** Forest plot of the results of the meta-analysis. (continued to the next page)
### Study or subgroup | IMT Mean (day) | SD (day) | Total | Control Mean (day) | SD (day) | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI
---|---|---|---|---|---|---|---|---|---|---
Barros et al., 2010 [17] | 7 | 2 | 23 | 8 | 2 | 15 | 15 | 16.2% | -1.00 (-2.30, 0.30)
Cordeiro et al., 2016 [10] | 6.2 | 1.3 | 25 | 8.4 | 2.8 | 26 | 18.7% | -2.20 (-3.41, -0.99)
Cordeiro et al., 2020 [11] | 7 | 1.3 | 21 | 8.2 | 1.3 | 21 | 44.3% | -1.20 (-1.99, -0.41)
Matheus et al., 2012 [18] | 6.2 | 2 | 23 | 6.7 | 2.95 | 24 | 13.3% | -0.50 (-1.94, 0.94)
Zanini et al., 2019 [3] | 7 | 0.6 | 10 | 8 | 3 | 10 | 7.6% | -1.00 (-2.90, 0.90)
Total (95% CI) | 102 | 95 | 100.0% | -1.25 (-1.77, -0.72)

Heterogeneity: $\tau^2=0.00$; $\chi^2=3.64$, df=6 (p=0.46); $I^2=0$

*Test for overall effect: $Z=4.67$ (p<0.00001)*

**Fig. 2.** Forest plot of the results of the meta-analysis. (A) Comparison of the inspiratory muscle training (IMT) with the control over the maximum inspiratory pressure outcome. The values presented are the average effects (difference between the means) and a 95% confidence interval (CI). The average effect was calculated using a random-effect model. (B) Comparison of the IMT with the control over the maximum expiratory pressure outcome. The values presented are the average effects (difference between the means) and a 95% CI. The average effect was calculated using a random-effect model. (C) Comparison of the IMT with the control over peak expiratory flow outcome. The values presented are the average effects (difference between the means) and a 95% CI. The average effect was calculated using a random-effect model. (D) Comparison of the IMT with the control over the tidal volume outcome. The values presented are the average effects (difference between the means) and a 95% CI. The average effect was calculated using a random-effect model. (E) Comparison of the IMT with the control over the functional capacity outcome. The values presented are the average effects (difference between the means) and a 95% CI. The average effect was calculated using a random-effect model. (F) Comparison of the IMT with the control over the outcome length of hospital stay. The values presented are the average effects (difference between the means) and a 95% CI. The average effect was calculated using a random-effect model. SD, standard deviation.

**CONCLUSION**

Based on the findings of this systematic review, IMT proved to be effective in improving inspiratory, expiratory muscle strength, tidal volume, peak expiratory flow and length of hospital stay. The only non-significant variable was the functional capacity assessed through the 6MWT.

The evidence brought by this review favors the use of IMT after cardiac surgery in clinical practice. The clinician needs to understand the reasons for muscle weakness and intervene early to restore strength, favoring changes in clinical and functional outcomes.

**CONFLICTS OF INTEREST**

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

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None.

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review and editing: Cordeiro ALL, Souza LO, Gomes-Neto M,

J. Writing – original draft: Cordeiro ALL, Souza LO. Writing –

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exercises and early mobilization improves oxygenation in high-risk

Impact of Extra-Corporeal Membrane Oxygenation and Blood Purification Therapy on Early Mobilization in the Intensive Care Unit: Retrospective Cohort Study

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Objective: To investigate the effect on early mobilization in patients undergoing extra-corporeal membrane oxygenation (ECMO) and acute blood purification therapy in the intensive care unit (ICU).

Methods: We conducted this multicenter retrospective cohort study by collecting data from six ICUs in Japan. Consecutive patients who were admitted to the ICU, aged ≥18 years, and received mechanical ventilation for >48 hours were eligible. The analyzed were divided into two groups: ECMO/blood purification or control group. Clinical outcomes; time to first mobilization, number of total ICU rehabilitations, mean and highest ICU mobility scale (IMS); and daily barrier changes were also investigated.

Results: A total of 204 patients were included in the analysis, 43 in the ECMO/blood purification group and 161 in the control group. In comparison of clinical outcome, the ECMO/blood purification group had a significantly longer time to first mobilization: ECMO/blood purification group 6 vs. control group 4 (p=0.003), higher number of total ICU rehabilitations: 6 vs. 5 (p=0.042), lower mean: 0 vs. 1 (p=0.043) and highest IMS: 2 vs. 3 (p=0.039) during ICU stay. Circulatory factor were most frequently described as barriers to early mobilization on days 1 (51%), 2 (47%), and 3 (26%). On days 4 to 7, the most frequently described barrier was consciousness factors (21%, 16%, 19%, and 21%, respectively).

Conclusion: The results of this study comparing the ECMO/blood purification group and the untreated group in the ICU showed that the ECMO/blood purification group had significantly longer days to mobilization and significantly lower mean and highest IMS.

Keywords: Early mobilization, Extra-corporeal membrane oxygenation, Acute blood purification, Intensive care unit, Barrier
INTRODUCTION

In recent years, advances in life-saving technology for critically ill patients in the intensive care unit (ICU) have significantly improved survival rates. However, even if they survive, 25%–70% of them in the ICU have severe disease, and invasive treatment and inactivity cause serious physical impairments such as ICU-acquired weakness (ICU-AW) and decreased activities of daily living (ADL), leading to increased medical costs and worsened life prognosis [1].

In Japan, in the 2022 medical fee revision, for patients who require acute blood purification or extra-corpooreal membrane oxygenation (ECMO), the upper limit of days for calculation of special ICU management fee extended from 14 to 25 days. It is stated as a calculation condition that a sufficient system be developed for efforts aimed at early recovery of patients, but the maximum number of days for ICU rehabilitation medical treatment system has not been changed from 14 days [2].

As a preventive measure against physical dysfunction after leaving the ICU, early mobilization starting within one week of admission to the ICU is attracting international attention. Previous studies have reported the effects of early mobilization to prevent delirium, shorten the duration of mechanical ventilation and length of ICU stay, and improve physical function [3-6]. In Japan, early mobilization rehabilitation additional calculation has been allowed since 2019, and the number of implementation cases is increasing, mainly for nurses and physical therapists [7]. However, while many benefits are expected for early mobilization of critically ill patients, it has been reported that there are many barriers to actual implementation [8]. The main obstacles are limited activities due to the use of equipment such as ECMO and acute blood purification, disturbance of consciousness due to sedation, and lack of manpower for team staff. Therefore, even if the patient’s general condition improves, there are cases in which the patient’s mobilization does not progress due to general muscle weakness or delirium.

The purpose of this study was to investigate the effect on early mobilization in patients undergoing ECMO and acute blood purification therapy in the ICU. This study focused on patients who underwent ECMO and acute blood purification in the ICU and examined how much it affected the attainable level of mobilization compared with those who did not.

METHODS

Study design, setting, and patients

The medical records of patients admitted to the ICU of one of six Japanese tertiary hospitals between April 2019 and March 2020 were retrospectively reviewed. This multicenter retrospective cohort study was conducted at the Nagoya Medical Center and by that of five other participating hospitals. This study was approved by the Ethics Committee of Nagoya Medical Center (approval number: 2021-012). It was conducted in accordance with Helsinki Declaration and the need for informed consent, according to national legislation, was waived by the IRB listed above because this was a retrospective cohort study. All patients admitted to the ICU of one of six Japanese tertiary hospitals between from April 2019 to March 2020 were screened. Patients were excluded if they were weaning mechanical ventilation for within 48 hours, were less than 18 years old, were unable to walk independently before hospitalization, were neurologically impaired, had difficulty communicating, were considered terminal; all other patients were included. The analyzed were divided into two groups: the ECMO/blood purification group that underwent ECMO or blood purification therapy upon admission to the ICU, or control group that did not. The definition of blood purification therapy in this study was the use of all renal support therapy administered during ICU admission, including continuous and intermittent hemofiltration dialysis, excluding chronic maintenance dialysis and peritoneal dialysis [9].

Data collection

Data on the participant’s age, sex, body mass index, Charlson comorbidity index, ICU admission diagnosis, operation, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment score, and Barthel index before hospitalization, were recorded as basic characteristics.

Outcomes

The clinical outcomes of this study were time to first rehabilitation and first mobilization and first walking exercise from the ICU admission, number of total ICU rehabilitations, number of daily ward rehabilitations, ICU length of stay, duration of mechanical ventilation, ICU-AW at ICU discharge, mean and highest ICU mobility scale (IMS) during ICU stay, delirium during ICU stay, Barthel index at hospital discharge, hospital length of stay, and in-hospital mortality. The IMS is a sensitive 11-point
ordinal scale, with scores ranging from 0 (no mobilization) to 10 (independent ambulation) [10]. ICU-AW was evaluated using Medical Research Council score by the responsible physical therapist, and a value of less than 48 was defined as having developed an ICU-AW [11]. For the assessment of delirium, either the delirium screening tool of the Intensive Care Delirium Screening Checklist was used [12].

Subanalysis
To examine factors for delayed mobilization in ECMO/blood purification therapy or control group, we investigated predefined barriers described in previous studies for 7 days from ICU admission. These included consciousness, subjective symptoms, and respiratory, circulatory, device, subject, and medical staff factors [8]. If several barriers were identified in one session, only the primary reason was recorded, and not the individual components of categories. During each rehabilitation session, a physical therapist in the ICU determined the primary barrier preventing mobilization by the end of the session according to the algorithm shown in Fig. 1. The rehabilitation intensity higher than the level of sitting at the bedside was defined as “mobilization” [8].

Data analysis
Results are expressed as the median and quartiles for quantitative data and as number and percent for categorical data. Chi-square test or Fisher’s exact test was used to assess the associations between intervention groups and categorical variables. The Mann–Whitney U-test was used for intergroup comparison of continuous variables. In addition, a one-way analysis of variance was used to compare the mean IMS from ICU admission to day 7 in the ECMO/blood purification group and the control group. We also used a chi-square test to compare the rate of each barrier from ICU admission to day 7 in the ECMO/blood purification group and the control group. All analyses were performed using JMP software (version 13.0; SAS Institute Inc., Cary, NC, USA). Statistical tests were two-sided, and statistical significance was defined as p<0.05.

RESULTS
During the study period from April 2019 to March 2020, 639 patients were screened, and 206 patients were enrolled in this study (Fig. 2). In this study, 43 patients were divided into the ECMO/blood purification group (ECMO, 15; continuous hemodiafiltration, 34; intermittent hemodialysis, 20; direct hemoperfusion with polymyxin B immobilized fiber, 20) and 161 control groups.

The baseline characteristics and clinical outcome during hospitalization of the study population are shown in Tables 1 and 2. In comparison of baseline data, the ECMO/blood purification
A comparison of ICU admission diagnoses revealed that the ECMO/blood purification group had higher rates of gastric or colonic surgery and sepsis than the control group. In comparison of clinical outcome, the ECMO/blood purification group had a significantly longer time to first mobilization: ECMO/blood purification group 6 (4–8) vs. control group 4 (3–8) (p=0.003) and first walking exercise: 25 (15–58) vs. 12 (9–18) (p=0.007), higher number of total ICU rehabilitations: 6 (4–9) vs. 5 (3–7) (p=0.042), longer ICU length of stay: 8 (6–11) vs. 2 (0–4) (p=0.016) and duration of mechanical ventilation: 6 (4–9) vs. 4 (3–6) (p=0.010), higher incidence of ICU-AW: 13 (40%) vs. 20 (17%) (p=0.007), lower mean: 0 (0–1) vs. 1 (0–3) (p=0.043) and highest IMS: 2 (0–4) vs. 3 (1–5) (p=0.039) during ICU stay, lower Barthel index at hospital discharge: 50 (25–90) vs. 93 (56–100) (p<0.001), longer hospital length of stay: 40 (28–73) vs. 30 (21–47) (p=0.002; Table 2).

Comparison of mean IMS from ICU admission to day 7 was significantly lower in the ECMO/blood purification group compared with the control group (p<0.001; Fig. 3).

Circulatory factor were most frequently described as barriers to early mobilization (EM) on days 1 (51%), 2 (47%), and 3 (26%). On days 4 to 7, the most frequently described barrier was consciousness factors (21%, 16%, 19%, and 21%, respectively; Table 3). Also device factor, subject factor, and medical staff factor also tended to increase from day 3 to day 7. Medical factors were the most frequently described as barriers to EM in the control group from days 1 to 7. In addition, compared to the ECMO/blood purification group, the control group tended to have lower device and conscious factors, and a higher achievement of mobilization. Comparing the rate of each barrier from ICU admission to day 7, there was a significant difference between two groups in consciousness factor (p=0.003) and device factor (p=0.037), achieved rate of EM (p=0.041).

**DISCUSSION**

In previous study on critically ill patients in the ICU, factors such as circulation factors, awareness factors such as sedation, activity restrictions by devices, and staff shortages have been reported as barriers to getting out of bed [8]. However, there are few papers that consider the intervention time of rehabilitation and barriers to mobilization, such as how long it takes for ECMO/blood purification therapy patients to mobility out of bed. In this study, we investigated the number of days required for ambulation and the duration of rehabilitation in ECMO/blood purification therapy patients.

In previous studies on early rehabilitation, there have been some reports that examined single factors such as the start time and exercise intensity [13,14]. Additionally, in a previous study that focused on the number of days until mobilization in ICU patients, the percentage of independent walking at discharge was significantly higher in the group that achieved mobilization within 7 days in the ICU compared to the group that did not. In
Japan, early mobilization/rehabilitation additions have been calculated since 2019, but the target number of days until mobilization is being explored at each hospital. In this study, the number of days until mobilization was significantly longer in the ECMO/blood purification group, and the number of ICU rehabilitation sessions was also significantly higher in the ECMO/blood purification group. In blood purification therapy, it is important for the staff to coordinate the environment in order to provide safe medical care, such as crisis management, physical restraints to ensure rest, posture management, mental care, and rehabilitation in cooperation with various occupations [15]. Previous studies in critically ill patients have reported an association between dose of rehabilitation and ADL dependence, assessed based on rehabilitation intensity, time and frequency [13,16]. The rehabil-

| Table 1. Comparison of items related to baseline data |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Variable                        | Total (n=204)   | ECMO/blood purification (n=43) | Control (n=161) | p-value         |
| Age (yr)                        | 70 (62–77)      | 70 (65–77)       | 70 (59–77)      | 0.331           |
| Sex, male                       | 139 (68.1)      | 26 (60.5)        | 113 (70.2)      | 0.269           |
| Body mass index (kg/m²)         | 23 (20–27)      | 22 (20–27)       | 23 (20–27)      | 0.778           |
| Charlson comorbidity index       | 1 (0–3)         | 2 (0–4)          | 1 (0–2)         | 0.032           |
| ICU admission diagnosis         |                 |                 |                 |                 |
| Acute respiratory failure       | 34 (16.7)       | 1 (2.3)          | 33 (20.5)       | <0.001*         |
| Cardiovascular disease          | 87 (42.6)       | 11 (25.6)        | 76 (47.2)       |                 |
| Gastric or colonic surgery      | 44 (21.6)       | 17 (39.5)        | 27 (16.8)       |                 |
| Sepsis, non-pulmonary           | 29 (14.2)       | 12 (27.9)        | 17 (10.6)       |                 |
| Other diagnoses                 | 12 (5.9)        | 2 (4.7)          | 10 (6.2)        |                 |
| Operation                       | 44 (21.6)       | 5 (11.6)         | 39 (24.2)       | 0.091           |
| APACHE II score                 | 23 (17–28)      | 26 (20–31)       | 23 (17–27)      | 0.007           |
| SOFA at ICU admission           | 8 (6–10)        | 8 (7–12)         | 8 (6–10)        | 0.084           |
| Barthel index before hospitalization | 100 (100–100) | 100 (90–100)     | 100 (100–100)   | 0.114           |

Values are presented as median (25th–75th percentile) or number (%).
ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extra-corporeal membrane oxygenation.
*p<0.001.

| Table 2. Comparison of clinical outcomes |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                       | ECMO/blood purification (n=43) | Control (n=161) | p-value         |
| Time to first rehabilitation from the ICU admission (day) | 2 (1–3)         | 1 (1–3)         | 0.292           |
| Time to first mobilization from the ICU admission (day)  | 6 (4–8)         | 4 (3–8)         | 0.003           |
| Time to first walking exercise from the ICU admission (day) | 25 (15–58)     | 12 (9–18)       | 0.007           |
| Number of total ICU rehabilitations (day) | 6 (4–9)         | 5 (3–7)         | 0.042           |
| Number of daily ward rehabilitations (min/day) | 27 (20–43)  | 30 (20–43)      | 0.956           |
| ICU length of stay (day)               | 8 (6–11)        | 2 (0–4)         | 0.016           |
| Duration of mechanical ventilation     | 6 (4–9)         | 4 (3–6)         | 0.010           |
| ICU-AW at ICU discharge                | 13 (30.0)       | 20 (12.4)       | 0.007           |
| Mean IMS during ICU stay               | 0 (0–1)         | 1 (0–3)         | 0.043           |
| Highest IMS during ICU stay            | 2 (0–4)         | 3 (1–5)         | 0.039           |
| Delirium during ICU stay               | 21 (38.2)       | 57 (35.4)       | 0.269           |
| Barthel index at hospital discharge    | 50 (25–90)      | 93 (56–100)     | <0.001*         |
| Hospital length of stay (day)          | 40 (28–73)      | 30 (21–47)      | 0.002           |
| In-hospital mortality                  | 5 (11.6)        | 13 (8.1)        | 0.542           |

Values are presented as median (25th–75th percentile) or number (%).
ICU, intensive care unit; ICU-AW, ICU-acquired weakness; IMS, ICU mobility scale; ECMO, extra-corporeal membrane oxygenation.
*p<0.001.
Fig. 3. Algorithm to determine the primary barrier preventing mobilization. The barrier to mobilization was determined by the intensivist in charge of the patient following this algorithm. In every rehabilitation session, only one selected barrier was recorded in the medical record. SpO₂, oxygen saturation of the peripheral artery; FiO₂, fraction of inspiratory oxygen; PEEP, positive end-expiratory pressure; RASS, Richmond agitation sedation scale; BPS, behavioral pain scale; NRS, numerical rating scale.

Regarding the increase in ICU days associated with ECMO/blood purification therapy, in a report based on data processing center, the mean ICU length of stay was the longest in the group of patients undergoing blood purification+mechanical ventilation [16]. Similarly, in this study, the length of ICU stay in the blood purification group was significantly longer than that in the control group [18]. In Japan, based on the medical fee revision in 2018, early mobilization and rehabilitation premiums were in-
Table 3. Primary barriers preventing the achievement of early mobilization in the extra-corporeal membrane oxygenation/blood purification group

<table>
<thead>
<tr>
<th>Medical contraindication</th>
<th>Circulatory factor</th>
<th>Respiratory factor</th>
<th>Consciousness factor</th>
<th>Device factor</th>
<th>Subject factor</th>
<th>Medical staff factor</th>
<th>Achievement of EM</th>
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<td>Day 4 (n=43)</td>
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<td>6 (20.7)</td>
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</tbody>
</table>
| Values are presented as number (%). EM, early mobilization.

Table 4. Primary barriers preventing the achievement of early mobilization in the control group

<table>
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<tr>
<th>Medical contraindication</th>
<th>Circulatory factor</th>
<th>Respiratory factor</th>
<th>Consciousness factor</th>
<th>Device factor</th>
<th>Subject factor</th>
<th>Medical staff factor</th>
<th>Achievement of EM</th>
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<td>Day 3 (n=161)</td>
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<td>Day 5 (n=123)</td>
<td>Day 6 (n=106)</td>
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<td>0.037</td>
<td>0.466</td>
<td>0.124</td>
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</table>
| Values are presented as number (%). The chi-square test was used to compare the rates of each barrier from intensive care unit admission to day 7 in the extra-corporeal membrane oxygenation/blood purification group and the control group. EM, early mobilization.

In the ICUs. In addition, from 2021, “calculation of the specified ICU management fee in excess of the maximum number of 14 days” is permitted for cases requiring long-term ICU management. However, under the current medical fee system, the maximum number of days for calculation is extended to 25 days for patients undergoing ECMO/blood purification therapy, but the maximum number of days for early mobility rehabilitation is 14 days. Risk factors for the development of physical dysfunction in critically ill patients are multifactorial, including age, delirium, occurrence of ICU-AW, and immobility [3,6,7]. Of these, supine rest is an easily ameliorated risk factor. Given these proposed mechanisms, rehabilitation time for patients staying longer than 14 days was considered inadequate and a risk factor for physical dysfunction.

Regarding barriers to achieving mobilization in the ECMO/blood purification therapy group, circulatory factor were the most common on days 1 to 3, but consciousness factor were the most common on days 4 to 7. In addition, device factors, subjective symptom, and medical staff factors increased from the 4th day. In a previous study examining barriers to mobilization in the ICU, device factors were significantly associated with achieving mobilization [19]. Furthermore, achievement of mobilization was associated with independent ADLs at discharge [19]. Barriers to achieving mobilization may be an important parameter for achieving ADL independence at discharge. In this study as well, the ECMO/blood purification group had a significantly lower achieving of mobilization than the control group, and significantly higher for device factors. Furthermore, when primary barriers were determined based on the algorithm shown in Fig. 1, there was a significant difference in the consciousness factor among the top factors between the two groups. The consciousness factor in the ECMO/blood purification therapy group appeared as the major barrier from days 4 to 7. The consciousness factor, similar to previous studies showing that deep sedation is a barrier to mobilization [20], it could have impeded EM of ECMO/ blood purification therapy groups. Pain
agitation and delirium guidelines recommend routine use of sedation protocols intended for light sedation [21]. However, no studies have examined whether an appropriate sedation protocol promotes EM, and its effects remain unclear. The impact of initiating routine use of sedation protocols in the ICU on EM needs further study. However, previous studies have reported that these factors are barriers that can be dealt with by interprofessional collaboration on the part of medical personnel and an increase in intervention time [8]. It was suggested that it is necessary to promote multidisciplinary collaboration after ensuring sufficient mobilization intervention time and frequency.

This study contains several limitations and the interpretation of the results should be interpreted with caution. This study is a retrospective study by multicenter study, and the survey period and the number of samples are limited. In this study, the number of patients was small, and there were many patients who used both ECMO and other blood purification therapies, so it was not possible to divide them into groups and analyze them. The severity of the patient may differ depending on the details of each device for ECMO and blood purification therapy, and it is necessary to increase the number of cases and examine it in the future. Furthermore, in this study, the number of days until mobilization was evaluated, but the evaluation of activities outside the rehabilitation period, such as activities by the patients themselves, was not sufficiently verified. Due to the nature of this retrospective cohort study, it is not possible to prove a causal relationship between ECMO and blood purification therapy and the number of days until mobilization. Randomized studies based on higher evidence, however, are considered very difficult to implement due to ethical considerations for non-interventional groups. Therefore, we cannot conduct a randomized study at this time, and we judge that a cohort study is the best possible study design. In the future, it is necessary to increase the number of cases and use a physical activity meter to verify the results.

In conclusion, the results of this study comparing the ECMO/blood purification group and the untreated group in the ICU showed that the ECMO/blood purification group had significantly longer days to mobilization and significantly lower mean and highest IMS.

In ECMO/blood purification therapy patients, multiple occupations require gracious rehabilitation to remove barriers to mobilization, and the current upper limit of 14 days may not be sufficient.

CONFLICTS OF INTEREST

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

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None.

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AUTHOR CONTRIBUTION

Conceptualization: Watanabe S. Methodology: Watanabe S, Iida Y. Formal analysis: Watanabe S. Project administration: Iida Y, Morita Y. Visualization: Watanabe S. Writing – original draft: Watanabe S, Iida Y, Hirasawa J. Writing – review and editing: Naito Y, Mizutani M, Uemura A, Nishimura S, Suzuki K. Approval of final manuscript: all authors.

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INTRODUCTION

Intoeing gait is a major cause of pediatric outpatient referral to pediatric clinics and is caused by increased femoral anteversion, internal tibial torsion, and metatarsus adductus [1]. Especially after the age of 3 years, increased femoral anteversion is known to be the most frequent cause of an intoeing gait [2]. Femoral anteversion angle (FAA) is defined as the angle formed by the transcondylar axes of the distal femur and proximal femoral neck. Typically, the FAA is approximately 30° at birth; however,
in the majority of cases, it decreases to a range (15°–25°) during early adolescence. Generally, it shows spontaneous improvement before the age of 8 years without specific interventional techniques [3,4]. In addition to aesthetic issues, gait can lead to functional problems such as unsteady gait and frequent falls [5]. Furthermore, compensatory external tibial rotation can be induced in the long term, causing pain in the knee and hip joints. Previous studies have demonstrated an association between increased FAA levels and femoroacetabular impingement, labral tears, and patellofemoral malalignment [6-8].

Most cases of intoeing gait can be managed conservatively with simple postural education as well as the use of orthotics and shoe modifications [9]. However, evidence for the effectiveness of conservative management is still lacking. In some rare cases, surgical intervention such as femoral derotational osteotomy may be required. Although there are no unified guidelines for surgical indications, Nelitz [10] suggested in their review that surgical treatment should be considered for symptomatic patellofemoral malalignment and FAA exceeding 30°. Hartigan et al. [11] established surgical indications for extreme anteversion of 35° or more, prominent intoeing gait, hip internal rotation exceeding 65° on physical examination, and the presence of anterior hip pain. Therefore, it is essential for clinicians to closely monitor children with intoeing gait and determine whether active intervention is necessary if increased FAA levels do not spontaneously improve. Accurate measurement of the FAA is crucial for making informed decisions.

Traditionally, computed tomography (CT), magnetic resonance imaging, and other imaging techniques are commonly used to measure the FAA. However, errors can occur depending on the position of imaging owing to the complex three-dimensional (3D) structure of the femur, and the measured values may vary by up to 20°, even for the same person, depending on the imaging technique and landmarks used [12,13]. Recently, studies using 3D-CT to measure FAA have been published to compensate for these errors, and it has been demonstrated that 3D-CT is a useful tool for measuring FAA with high accuracy and reliability [12,14,15]. In addition, Shalaby et al. [16] reported that the 3D technique is superior to the two-dimensional technique in measuring FAA in patients with unilateral developmental dysplasia of the hip.

Until now, most studies reporting FAA changes in children with intoeing gait have been based on Western data [17,18]. In countries where floor culture is prevalent, such as Japan and Korea, children with increased FAA are more likely to assume the W-sitting position, which can act as a significant impediment to the natural resolution of FAA. A previous study investigated the changes in FAA in Korean children with an intoeing gait using 3D-CT [19]. The study examined the effects of age, sex, and initial FAA on FAA changes over time and showed the largest decrease in the 4–6-year-old group during a follow-up period of >1 year. Additionally, it was found that females, younger children, and those with larger initial FAA had greater FAA changes.

To the best of our knowledge, few studies have observed changes in the FAA in children with intoeing gait for a follow-up period of at least three years using 3D-CT. Furthermore, no previous study has examined long-term FAA changes in Asian populations. Therefore, the primary objective of this study was to investigate longitudinal changes in femoral FAA in Korean children with intoeing gait using 3D-CT for a minimum follow-up period of three years. Second, we analyzed the correlation between age, initial FAA level, and sex and their influence on FAA reduction. Finally, we sought to determine the number of children with an intoeing gait who achieved a normal or near-normal FAA by the time they turned 8 years old compared to their initial severity.

**METHODS**

**Participants**

We retrospectively analyzed 3D-CT data of children with intoeing gait in Gyeongsang National University Hospital from 2006 to 2022. The initial screening process included patients who presented with an intoeing gait and had undergone 3D-CT measurements at least three times. The inclusion criteria were exhibiting more than 5° of internal rotation on visual inspection and preference to observe the natural progression of FAA reduction over time through periodic follow-up 3D-CT scans rather than undergoing active treatment, such as using corrective devices. The exclusion criteria were as follows: (1) an interval of <3 years between the initial and final follow-up 3D-CT scans; (2) implementation of corrective devices or other interventions during the follow-up period; and (3) the presence of abnormal gait due to orthopedic problems or developmental disorders.

This retrospective study was approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (IRB No. 2023-02-011). The requirement for informed consent was waived due to the retrospective design of the present study.
However, their personal information was anonymized and de-identified before analysis.

Initially, a total of 171 patients were screened. Among them, 68 patients had intervals of less than three years between their initial and follow-up 3D-CT scans, and 17 individuals were excluded due to chief complaints other than intoeing gait, the presence of neurodevelopmental disorders, or other orthopedic issues. Another 23 patients were excluded due to the implementation of active treatment such as corrective devices. Finally, a total of 126 limbs from 63 children were included in the analysis (Fig. 1). All initial and available follow-up images were included, with a minimum time interval of 3 years between the first and last 3D-CT scans.

In order to evaluate the improvement of intoeing gait, we included initial and follow-up foot progression angle (FPA) data measured using the Gaitview AFA-50 system (aFOOTs, Seoul, Korea) for patients who underwent dynamic foot pressure measurement through chart review.

The children did not receive corrective devices or surgical treatment, but they received simple posture-correction education, such as the tailor position and Achilles tendon and hamstring stretching, during their initial visit. The participants visited the follow-up clinic at intervals of 3–6 months to confirm whether their intoeing gait had improved visually and were encouraged to perform simple posture correction exercises during each visit. Additionally, to evaluate changes in the FAA angle, 3D-CT was performed at intervals of approximately one year or more.

In this study, the severity of femoral anteversion was assessed as a categorical predictor variable and classified as mild (<25°), moderate (25°–40°), or severe (>40°). The cutoff values were selected based on the results of a previous investigation of 100 Korean children with intoeing gait, where the average initial femoral anteversion (with standard deviation) was 31.1°±7.8°, as determined by 3D-CT scans [19]. The “moderate” category for femoral anteversion severity was determined by selecting values around one standard deviation below and above the previously established mean of 31.1°±7.8° on 3D-CT images. As a result, the lower and upper values of the “moderate” category were set at 25° and 40°, respectively.

We calculated the severity of excessive FAA using the FAA value measured at the initial visit and when the child was 8 years old. We compared the severity of excessive FAA between these time points. Furthermore, we observed changes in FAA severity up to 8 years of age and analyzed them according to sex. The reason for reevaluating the severity at the age of 8 years was that Fabry et al. [17] reported no significant regression of increased femoral anteversion after this age.

**Radiologic evaluations using 3D-CT**

A 64-channel CT scanner (Brilliance 64; Philips Medical Systems, Amsterdam, Nederland) was used for the CT scans. Children were instructed to lie supine on a sliding table with lower limbs fully extended. The legs were secured with a strap to prevent movement. CT images were obtained for both legs. Image acquisition parameters were: field of view=314 mm; detector collimation=64.0×0.6 mm; table movement speed=44.4 mm/rotation; gantry rotation speed=1 second; kVp=120; and mAs/slice=36. The image was remodeled with a thickness of 2 mm and spacing of 1 mm.

The volume-rendering method was employed to reconstruct the 3D images using the Extended Brilliance Workspace ver. 2.0 software from Philips Medical Systems. Corresponding images were acquired after 3D-CT reconstruction (Fig. 2). Based on the obtained images, FAA was measured by a doctor from the Department of Rehabilitation Medicine. We employed the method for FAA measurements as described by Byun et al. [14] in their study.

The femur neck angle was calculated by measuring the angle between the neck axis of the femur and the horizontal axis. The neck axis of the femur, which served as the reference axis for proximal measurement, was defined as the line that intersected two central points of the neck and head of the femur in Fig. 1. Flowchart of patient inclusion. 3D-CT, three-dimensional computed tomography.
a craniocaudal direction. To calculate the condylar angle, the angle of the medial and lateral condylar axis against the horizontal axis was measured. Similarly, the medial and lateral condylar axis was used as the reference axis for distal. It was set as the line encountering the most posterior aspects of medial and lateral condyles of the distal femur from the caudocranial of the 3D image (Fig. 2C). The FAA was calculated by subtracting the condylar angle from the femur neck angle if they were oriented in the same direction against the horizontal axis or by adding the two angles if they were in the opposite direction.

Data analysis
Chart reviews were conducted to collect the patients’ clinical information, including age at the initial visit, sex, body weight, preterm birth status, presence of spasticity, and Achilles tendon tightness, as well as the FAA in both limbs at the time of the 3D-CT scan. The follow-up periods between the initial and final FAA were also recorded. FAAs of both lower extremities were calculated from all 3D-CT scans, allowing us to obtain values for the initial FAA, final follow-up FAA, and FAA changes. The difference between the initial and follow-up FPA was also analyzed as well. Additionally, we analyzed the average FAA according to age at the time of 3D-CT using all the 3D-CT data obtained in this study. Lastly, the study classified the severity of patients’ initial FAA values and those measured at approximately 8 years of age and compared the changes in severity between the two time points.

Statistical methods
Normal distribution was checked for all data; otherwise, non-parametric tests were performed. We performed a ANOVA and Tukey honest significant difference test to identify differ-
ences in demographic and clinical characteristics. To confirm differences in clinical findings between the two groups, we conducted independent t-tests for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables. Statistical significance was set at p<0.05, and R3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analysis. We conducted correlation analysis to investigate the relationship between age and changes in FAA as well as between initial FAA and changes in FAA, using Pearson's correlation coefficient.

Table 1. The characteristics of the patients studied

<table>
<thead>
<tr>
<th>Femoral anteversion angle</th>
<th>Total (n=63)</th>
<th>Male (n=30)</th>
<th>Female (n=33)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>5.11±1.05</td>
<td>5.27±1.14</td>
<td>4.97±0.95</td>
<td>0.265</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>43.59±7.74</td>
<td>43.3±6.25</td>
<td>43.85±8.98</td>
<td>0.781</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>110.65±7.95</td>
<td>112.85±9.49</td>
<td>108.64±5.67</td>
<td>0.040*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.02±3.68</td>
<td>21.23±4.71</td>
<td>18.92±1.88</td>
<td>0.017*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>16.27±1.50</td>
<td>16.51±1.67</td>
<td>16.05±1.33</td>
<td>0.232</td>
</tr>
<tr>
<td>Preterm</td>
<td>5 (7.9)</td>
<td>2 (6.7)</td>
<td>3 (9.1)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Spasticity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

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

*p-independent t-test or Fisher's exact test.

RESULTS

A total of 63 participants were included in the study, 30 of whom were male and 33 were female, with mean ages of 5.11±1.05 years and 5.27±1.14 years, respectively. No significant difference existed in age between the two groups. The average period between the initial FAA and the last follow-up 3D-CT was 43.59±7.74 months (Table 1). A total of 252 3D-CT images were obtained from all patients during the follow-up period, which allowed us to obtain FAA data for 504 limbs according to age (Fig. 3).

![Fig. 3. Changes in femoral anteversion angle (FAA) measured from total three-dimensional computed tomography images according to age.](image-url)
Mean change in FAA and effects of sex on FAA changes
The total initial FAA was 41.42°±8.29°, and the follow up FAA was 33.25°±9.19°, showing a significant decrease in angle (p<0.001). The initial FAA and follow-up FAA for male were 38.53°±8.88° and 30.59°±8.34°, respectively. For female, the initial FAA and follow-up FAA were 44.05°±6.84° and 35.67°±9.37°, respectively. Both males and females showed significant angle changes in the follow-up FAA compared to the initial FAA.

The initial and follow-up FAAs of male and female children differed significantly, with females having larger initial FAA than males. However, no significant difference was found in FAA change between males (-7.95±7.52) and females (-8.38±6.67) based on sex (Table 2).

Differences between the initial and follow-up FPA
Dynamic foot pressure measurement was measured for 57 out of 63 patients, from which the initial and follow-up FPAs were obtained. The mean initial FPA was -10.09°±3.44°, while the follow up FPA was -0.74°±3.76°, indicating a significant difference in the angle between the two time points (p<0.001; Table 3).

Correlation analysis of age and FAA change as well as initial FAA and FAA change
A significant correlation was found between the initial age at the time of 3D-CT imaging and the change in FAA, with a greater change observed in younger children (r=0.248, p=0.005). The change in FAA was found to be significantly greater when the initial FAA was larger (r=-0.333, p<0.001) (Fig. 4).

Change in severity of increased FAA
We classified the initial FAA and the FAA measured at approximately 8 years of age in 63 patients according to the defined severity criteria.

Of the 126 limbs, 71 (56.3%) were classified as severe for initial FAA, while 37 (29.4%) were classified as severe for FAA at approximately 8 years of age. Among the 126 limbs, only 4 (3.2%) were classified into the mild category at the initial age, while 22 (17.5%) were classified into the mild category at the age of approximately 8 years (Table 4).

For males, the severity of the initial FAA was mostly moderate at 55.0%, whereas for females, the severity was most common in the severe category at 71.2%. The difference in the severity rates between males and females was significant (p=0.002).

The severity of FAA at 8 years of age was most commonly in the moderate category for males (65.0%) and females (42.4%). However, when improvement was assessed according to sex, 43.3% of males and 42.4% of females showed improvement, and there was no significant difference between the sexes in the rates of severity change (Fig. 5).

Table 2. Initial and follow-up FFA, and changes in FFA according to sex

<table>
<thead>
<tr>
<th></th>
<th>Initial FAA (°)</th>
<th>Follow-up FAA (°)</th>
<th>FAA change (°)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n=60)</td>
<td>38.53±8.88</td>
<td>30.59±8.34</td>
<td>-7.95±7.52</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Female (n=66)</td>
<td>44.05±6.84</td>
<td>35.67±9.37</td>
<td>-8.38±6.67</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total (n=126)</td>
<td>41.42±8.29</td>
<td>33.25±9.19</td>
<td>-8.18±7.02</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>p-value</td>
<td>0.007*</td>
<td>0.027*</td>
<td>0.806</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.
FPA, femoral anteversion angle; n, numbers of limbs.
Paired t-test (comparing initial and follow-up FAA within each group).
Independent t-test (comparing male and female group differences for initial FAA, follow-up FAA, and FAA changes).
*p<0.05.

Table 3. Initial and follow-up foot progression angle

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Follow-up</th>
<th>Difference in mean (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>-9.65±3.44</td>
<td>-0.48±3.82</td>
<td>-9.17 (-10.32, -8.01)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Right</td>
<td>-10.53±4.22</td>
<td>-1.00±4.56</td>
<td>-9.52 (-10.80, -8.25)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FPA</td>
<td>-10.09±3.44</td>
<td>-0.74±3.76</td>
<td>-9.34 (-10.41, -8.28)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.
FPA, foot progression angle; CI, confidence interval.
Paired t-test.
*p<0.05.
Table 4. The severity of the initial femoral anteversion angle and at 8 years old, according to sex

<table>
<thead>
<tr>
<th>Severity</th>
<th>Initial FAA</th>
<th></th>
<th></th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>FAA at age 8</th>
<th></th>
<th></th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n=60)</td>
<td>Female (n=66)</td>
<td>Total (n=126)</td>
<td></td>
<td>Male (n=60)</td>
<td>Female (n=66)</td>
<td>Total (n=126)</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;25°)</td>
<td>3 (5.0)</td>
<td>1 (1.5)</td>
<td>4 (3.2)</td>
<td>0.002&lt;sup&gt;*&lt;/sup&gt;</td>
<td>11 (18.3)</td>
<td>11 (16.7)</td>
<td>22 (17.5)</td>
<td>0.009&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moderate (25°–40°)</td>
<td>33 (55.0)</td>
<td>18 (27.3)</td>
<td>51 (40.5)</td>
<td></td>
<td>39 (65.0)</td>
<td>28 (42.4)</td>
<td>67 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;40°)</td>
<td>24 (40.0)</td>
<td>47 (71.2)</td>
<td>71 (56.3)</td>
<td></td>
<td>10 (16.7)</td>
<td>27 (40.9)</td>
<td>37 (29.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
<sup>a</sup>Chi-squared test.
<sup>*</sup>p<0.05.

Fig. 4. Femoral anteversion angle (FAA) change was greater in younger children (r=0.248, p=0.005) (A) and in those with higher initial FAA (r=−0.333, p<0.001) (B), according to correlations with age and initial FAA, respectively.

DISCUSSION

We aimed to investigate changes in FAA in children with an intoeing gait using 3D-CT, a reliable and useful tool for measuring FAA [12,14,15,20,21], over a follow-up period of >3 years. We confirmed a significant decrease in the FAA of 126 limbs obtained from 63 subjects over a total period of 43.59±7.74 months, from 41.42°±8.29° to 33.25°±9.19°. This study is significant in that it utilized 3D-CT to follow up on FAA changes in children with an intoeing gait for a relatively long period. Fabry et al. [17] observed changes in 154 limbs from 77 children with an intoeing gait over an average follow-up period of 5 years and 6 months, while Svenningsen et al. [18] conducted a prospective follow-up study on 30 patients for an average of 9 years until a minimum age of 15 years. However, these studies used a biplanar method with simple X-rays, which is known to
demonstrate errors of up to 20° and can occur in living subjects owing to positioning errors [22]. On the other hand, the use of 3D-CT reconstruction allows for an accurate determination of femoral torsion, independent of their positioning, as well as the determination of the femoral neck axis [19,22,23].

In the study by Kong et al., [19] the FAA values of 100 children with intoeing gait were measured using 3D-CT and compared over a follow-up period of 18.0±5.4 months. The study found that FAA decreased significantly in both the 4–6-year and 8–10-year age groups, and that younger age and larger initial FAA angle were associated with a greater decrease in FAA, with females showing a greater FAA decreases than males [19]. Consistent with this, our study showed that the greater the initial FAA, the greater the decrease in FAA. This result may be due to the higher compliance with posture correction and stretching exercises among patients with a higher initial FAA angle, as they may have had more prominent symptoms of intoeing gait when they first presented for treatment. However, in our study, there was no objective evaluation of compliance in the medical records; therefore, this could not be used in the analysis. Future studies, including information on patient compliance using questionnaires, could be help assess the effects of simple postural correction and stretching exercises according to age.

Previous studies indicated that younger children tend to exhibit greater changes in FAA [18,19,24]. In particular, Kong et al. [19] analyzed the correlation between age and FAA changes using a similar method to ours. Although they reported a tendency for greater FAA changes in younger children, it was not statistically significant. However, in this study, we obtained results that support the trend of greater FAA changes at a younger age, with a statistically significant correlation (Fig. 4).

Our results regarding FAA changes according to sex partially differed from those in previous studies [19,25]; we found no difference in FAA change according to sex (Fig. 4). This may be because we observed changes over a longer period compared with the previous studies. Nevertheless, because the initial FAA values were significantly different between males and females in this study, the interpretations should made with caution.

Fabry et al. [17] reported that there was no significant regression of FAA after 8 years of age; thus, active management may not be delayed even if there is severe FAA up to 8 years of age. Accordingly, we investigated the number of limbs that improved to a mild degree of severity at 8 years of age. Our study demonstrated that only a small number of limbs (22 of 126 limbs) were classified as mild in terms of FAA severity at age 8. Although the severity decreased in more than 40% of the patients of both sexes, the majority remained at a moderate to severe degree of FAA. This could be a result of racial differences. In addition, in Asian countries such as Korea and Japan, floor living may result in children adopting positions such as W-sitting more easily. In these cases, improvement may be delayed compared with Western children. Furthermore, contrary to Fabry et al. [17]’s study, some studies reported that FAA continues to regress steadily even after the age of 8 [18,26]; we also observed a somewhat decreasing trend in the graph of FAA obtained from the total 3D-CT images according to age, particularly in the 9–12-year age range. Therefore, if there is a persistent moderate-to-severe degree of excessive FAA even after 8 years of age, continuous follow-up may be necessary during the growth period. However, our results showed a tendency for FAA to decrease with increasing age; therefore, active interventions such as corrective orthosis at a young age may be helpful. Further research is required to confirm these hypotheses.

This study had several limitations. First, owing to its retrospective nature, there may have been selection bias in the included patients. It is possible that parents and children did not visit the hospital if their symptoms improved within three years of their first visit to the outpatient clinic, and even if they did visit, they might have discontinued periodic 3D-CT follow-ups once their condition improved. As a result, children with long-term follow-up 3D-CT who visited the hospital regularly for more than three years may have had severe symptoms from the beginning and may have had little improvement in their condition during the follow-up period, and caution is needed in interpreting the results accordingly. Second, the initial age of the children included in the study was limited to 4–8 years old. Therefore, future studies will need to expand to include larger samples of all ages. Finally, this study only observed changes in FAA in children with intoeing gait who were not actively treated and did not compare the differences between those who received early intervention and those who did not. Future research should compare cases where interventions, such as orthotic devices, are used with cases where no intervention is used to determine the effectiveness of early intervention.

In addition to the limitations of the study design, it is important to consider the practical limitations and potential risks associated with using 3D-CT as a diagnostic tool for evaluating intoeing gait in children. 3D-CT is relatively expensive and can only be performed in relatively large hospitals, which may limit
its accessibility to some patients. Moreover, potential risks are associated with radiation exposure especially in children [27,28]. A CT scan employed to evaluate the lower extremity torsional profile releases an average radiation dose of 0.3–0.5 mSv, which is substantially lower—around 5–15 times less—than the radiation exposure linked to pediatric abdominal and head CT scans [29,30]. Furthermore, scans targeting the arms and legs pose a lower risk of provoking conditions like leukemia and brain tumors in children below 10 years, relative to scans focused on the brain, chest, and abdomen [31]. Nevertheless, it’s important to limit the frequency of scanning to mitigate any elevated risk associated with radiation exposure. Therefore, in clinical practice, it is important to carefully evaluate patients’ conditions and consider factors such as age, medical history, and potential risks associated with radiation exposure. Follow-up 3D-CT scans should only be performed if deemed necessary and at appropriate intervals to minimize the associated risks.

Despite these limitations, FAA measurement using 3D-CT can serve as an objective basis for considering active treatment by accurately assessing the degree of improvement in the anteversion angle. This can assist in preventing long-term complications in children whose FAA does not improve spontaneously. The strength of our study lies in the use of the 3D-CT method, which has high intra- and inter-rater reliabilities in measuring FAA [14], to follow up on FAA changes over a relatively long period. These results could be used as valuable data providing information on FAA changes in children with an intoeing gait.

In conclusion, this retrospective study using 3D-CT imaging showed that younger children with intoeing gait and those with greater initial FAA are more likely to exhibit larger decreases in FAA over a minimum 3-year follow-up period. Furthermore, since most children still have moderate-to-severe FAA even after the age of 8 years, periodic follow-up is necessary even if the intoeing gait appears to have improved visually, and early intervention may be necessary. However, the retrospective design and single-center nature of this study have limitations that should be considered when interpreting the results. Future prospective studies with larger sample sizes and longer follow-up periods are required to confirm these findings.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

None.

AUTHOR CONTRIBUTION

Conceptualization: Shin H. Methodology: Shin H, Park Y. Formal analysis: Kim MJ, Park Y. Project administration: Shin H, Byun H. Visualization: Kim MJ. Writing – original draft: Park Y. Writing – review and editing: Shin H, Byun H, Park Y. Approval of final manuscript: all authors.

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REFERENCES


Correlation Between Articulatory Diadochokinetic Parameters and Dysphagia Parameters in Subacute Stroke Patients

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**Objective:** To determine correlations of alternation motor rate (AMR), sequential motor rate (SMR), and maximum phonation time (MPT) with the severity of dysphagia in subacute stroke patients.

**Methods:** This was a retrospective chart review study. Data of 171 subacute stroke patients were analyzed. Patient's AMR, SMR, and MPT data were collected from their language evaluations. Video fluoroscopic swallowing study (VFSS) was done. Data of dysphagia scales including penetration-aspiration scale (PAS), American Speech-Language-Hearing Association National Outcomes Measurement System (ASHA-NOMS) scale, clinical dysphagia scale (CDS), and videofluoroscopic dysphagia scale (VDS) were obtained. AMR, SMR, and MPT were compared between a non-aspirator group and an aspirator group. Correlations of AMR, SMR, and MPT with dysphagia scales were analyzed.

**Results:** AMR ("ka"), SMR, and modified Rankin Scale were significant associated factors between non-aspirator group and aspirator group, while AMR ("pa"), AMR ("ta"), and MPT were not. AMR, SMR, and MPT showed significant correlations with PAS score, ASHA-NOMS scale, CDS, VDS oral, and VDS pharyngeal scores. The cut-off value for distinguishing non-aspirator group and aspiration group was 18.5 for AMR ("ka") (sensitivity of 74.4%, specificity of 70.8%) and 7.5 for SMR (sensitivity of 89.9%, specificity of 61.0%). AMR and SMR were significantly lower in before-swallow aspiration group.

**Conclusion:** Articulatory diadochokinetic tasks that can be easily performed at the bedside would be particularly helpful in determining the oral feeding possibility of subacute stroke patients who cannot undergo VFSS, which is the gold standard for dysphagia assessment.

**Keywords:** Dysarthria, Deglutition disorders, Phonation, Stroke

**INTRODUCTION**

Dysarthria and dysphagia are common complications after stroke, which are highly related to each other. Many studies have found the co-existence of dysarthria and dysphagia among patients with neuromuscular diseases and ischemic stroke [1-3]. The rate of co-occurrence of dysarthria and dysphagia ranges from 28%-42% in stroke survivors [2-4]. Both speech articula-
tion and swallowing process share some common neuroanatomical structures. For example, muscles of soft palate, larynx, and pharynx are innervated by efferent motor nerves of the vagus rising from the nucleus ambiguus [5]. The upper and lower lips, controlled by facial nerve and tongue, controlled by the hypoglossal nerve, are important oral structures and coordination of these structures are crucial for both speech articulation and swallowing process.

Alternation motor rate (AMR) and sequential motor rate (SMR) are articulatory diadochokinetic parameters that can assess the severity of dysarthria by checking the regularity, rate, and the accuracy of articulators. AMR and SMR are used to evaluate the severity of dysarthria in stroke patients with high validity and reliability [6-8]. AMR includes rapid repetition of monosyllabic sounds such as ‘pa’, ‘ta’, and ‘ka’, while SMR includes repetition of a multisyllabic sound such as ‘pa-ta-ka’. Each sound production evaluates a different articulation point. ‘Pa’ is a bilabial sound produced by the movement of lips. ‘Ta’ sound is an alveolar sound produced by the movement of the tongue tip and alveolar ridge of mouth. ‘Ka’ is a velar sound produced by the movement of dorsum of tongue and soft palate [9]. To perform AMR and SMR correctly, patients need to be able to move their oral structures, such as lips, tongue tip, tong base, dorsum of tongue, and soft palate, in a finely coordinating manner and the integrity of their oral muscles should be intact. Any impairment in coordination or muscles strength of oral structures will result in reduced AMR and SMR [10].

The oral phase of swallowing is a voluntary process that involves the complex movement of the oral structures to mix food with saliva to form a bolus that is propelled into the oropharynx to initiate the swallowing reflex. During the oral preparatory stage, the lips should be closed to prevent anterior leakage, and anterior part of the tongue should maintain contact with the hard palate to hold the bolus at the anterior part of mouth. The posterior part of the oral cavity is sealed by the contact of the dorsum of the tongue and the soft palate to prevent leakage into the pharynx before swallow [11]. During the oral propulsive stage, the anterior tip and sides of the tongue contract against the palate to progressively squeeze the entrapped bolus into the oropharynx. At the same time, the dorsum area of the tongue forms a passage that allows the bolus to enter the oropharynx. If the tongue is weak or paralyzed, the bolus may spill into the oral cavity or into the pharynx, which can lead to aspiration before swallowing [12]. Also, a previous study has shown that tongue base resection showed significant correlation with swallowing dysfunction who underwent oral cancer surgery [13].

However, studies investigating the relationship between AMR, SMR, and the severity of dysphagia in subacute stroke patients have not been reported yet. We hypothesized that stroke patients with impaired AMR and SMR may experience oral stage swallowing difficulties and be at a higher risk for before-swallowing aspiration. We conducted a study to determine whether there is any correlation between AMR and SMR with certain parameters of oral stage dysphagia, and thus explore the relationships between the specific location of the tongue and oral stage swallowing problems.

Moreover, phonation ability has a deep association with swallowing function [14]. The coordination of oral, laryngeal, pharyngeal muscles, and respiratory muscles in the upper airway is important in both phonation and swallowing processes. Maximum phonation time (MPT) is the longest period during which a patient can sustain phonation of a vowel sound. To perform MPT correctly, a patient needs to sustain a prolonged expiratory phase to make sufficient subglottal air pressure to induce the vocal cord vibration, which plays an important role in protecting the airway as well as producing sound by regulating the airflow. MPT can indirectly measure the efficiency of the laryngeal function and vocal cord vibration [15]. Since bronchial airflow is the most important determinant of MPT, we could assume that patients with shorter MPT may have lower subglottal airway pressure, which is one of the important factors for airway protection [16]. In a normal swallowing process, an increase in subglottic pressure occurs to release the air from the subglottic space into the pharynx for airway protection [17].

We hypothesized that patients with shorter MPT may experience difficulty in expelling materials out from the airway, leading to impaired pharyngeal stage swallowing functions and an increased risk of during-swallowing aspiration. Thus, we conducted a study to determine whether there are any correlations between MPT and parameters of the pharyngeal stage swallowing functions, and to investigate the relationship between phonation ability and pharyngeal stage swallowing functions.

METHODS

Participants

This was a retrospective study. Data were collected by reviewing charts of subacute stroke patients who were admitted to Soon-chunhyang University Bucheon Hospital in Korea from January 2018 to December 2021. This study was approved by Institution-
al Review Board (IRB) of Soonchunhyang University Bucheon Hospital (IRB No. SCHBC 2022-07-007).

Inclusion criteria were as follows: (1) patients with first ever stroke, including hemorrhagic stroke, and ischemic stroke; (2) those with subacute stage stroke less than six months of onset; (3) patients who had problems with articulation of speech and had completed a language assessment test; (4) patients who had symptoms of dysphagia and had undergone video fluoroscopic swallowing study (VFSS); and (5) the time difference between dysarthria evaluation and dysphagia evaluation was less than one week.

Exclusion criteria were as follows: (1) patients who had a previous stroke history; (2) those who had other neurologic diseases such as brain tumor, hypoxic brain damage, or Parkinson’s disease; (3) patients who could not properly finish the language assessment test due to various reasons, such as severe cognitive deficit; and (4) patients with a tracheostomy tube.

Mini-mental state examination (MMSE) and modified Rankin Scale (mRS) were collected for the cognitive function and degree of disability of patients, respectively. The stroke lesion location and size were confirmed by neuroimaging studies, including computed tomography or diffusion weighted imaging, at the time of admission. The lesion size was measured as the largest diameter visible on neuroimaging [18].

Initially, data from 269 patients were collected. However, 19 patients with a previous stroke history, 11 patients with other neurologic diseases, 62 patients who could not accomplish speech evaluation test properly, and 6 patients who had a tracheostomy tube were excluded. Finally, data from 171 patients were analyzed.

Dysarthria assessment

During the hospitalized period, all patients finished their language assessment test using the Korean version of Speech Mechanism Screening Test (SMST). The patient’s articulation was tested using AMR and SMR.

To evaluate AMR (“pa”), patients were asked to breathe in air as much as possible and they were asked to make a ‘pa’ sound repeatedly as fast as possible for 5 seconds. The maximum number of ‘pa’ sound made by the patient was counted by a speech therapist. The same were done with a ‘ta’ sound for AMR (“ta”) and a ‘ka’ sound for AMR (“ka”), respectively. The test was repeated three times and the mean value was calculated for each sound.

To evaluate SMR, patients were asked to breathe in air as much as possible and they were asked to make an ‘ah’ sound as long as possible. The speech therapist measured the AMR with a stop watch. The test was repeated three times and the mean value was calculated. During AMR, SMR, and MPT evaluation, the tone and the height of the voice were phonated as comfortable as they could.

VFSS procedure and outcome measures

Patients underwent VFSS to evaluate their swallowing ability. Foods for VFSS were yogurt (International Dysphagia Diet Standardization Initiative [IDDSI] level 4), rice porridge (IDDSI level 5), boiled rice (IDDSI level 7), and water (IDDSI level 0). Barium sulphate suspension was mixed with foods. The order of the food provided was a spoon of yogurt, followed by rice porridge, boiled rice, and 5 mL of water. The last step was cup drinking. It was done only if there was no aspiration during 5 mL of water. The procedure was stopped whenever foods were aspirated. The VFSS procedure was video-recorded. Recorded video was examined by two experienced doctors in the Department of Physical Medicine and Rehabilitation. Based on VFSS study results, we scored Penetration-Aspiration Scale (PAS), clinical dysphagia scale (CDS), videofluoroscopic dysphagia scale (VDS), and American Speech-Language-Hearing Association National Outcomes Measurement System (ASHA-NOMS) scale.

PAS is an 8-point scale to describe penetration and aspiration event during swallowing. It is frequently used to evaluate the severity of dysphagia. Higher PAS scores indicate more severe dysphagia. PAS score 1 indicates normal swallowing function without penetration or aspiration. PAS scores 2 to 5 indicate penetration and PAS scores 6 to 8 indicate aspiration. PAS score for yogurt, rice porridge, boiled rice, 5mL of water, and cup drinking was scored respectively and the highest PAS value of in any diet tested was selected for the analysis.

Also, the timing of aspiration was further divided into before-swallowing, during-swallowing, and after-swallowing aspiration. Aspiration before the swallow was defined as that occurring prior to the beginning of swallowing reflex. Aspiration during the swallow was defined as that occurring during the swallowing reflex. All subsequent aspirations were defined as aspiration after the swallow [19].
CDS has 8 rating items with scores ranging from 0 to 100, with a higher score indicating a more severe dysphagia. CDS is commonly used to evaluate the swallowing function of stroke patients. It has been proven to have a good validity [20]. It evaluates aspiration, lip sealing, chewing and mastication, tongue protrusion, laryngeal elevation, and reflex coughing.

VDS consists of 14 items with scores ranging from 0 to 100, with a higher score indicating a more severe dysphagia. It is composed of VDS oral phase scores and VDS pharyngeal phase scores. The items included in VDS oral phase are lip closure, bolus formation, mastication, apraxia, tongue to palate contact, premature bolus loss, and oral transit time. The items included in VDS pharyngeal phase score are triggering of pharyngeal swallow, vallecular residue, laryngeal elevation, pyriform sinus residue, coating on the pharyngeal wall, pharyngeal transit time, and aspiration. The scores for each item were analyzed. The scoring was done with the worst scores regardless of the type of food we used [21]. It is a quantitative assessment tool for dysphagia and has shown to correlate with VFSS findings with good validity. It can be applied to any dysphagic patients including stroke patients [22].

ASHA-NOMS scale describes the swallowing ability of patients at seven different levels. It assesses how much supervision is required and determines how much diet restriction is needed for safe feeding. Level 1 indicates that an individual cannot swallow anything safely by mouth and that all nutrition and hydration should be received through enteral feeding. Level 7 indicates that an individual's ability to eat independently is not limited by swallowing function and that swallowing would be safe and efficient for all consistencies [23].

**Statistical analysis**

Collected data were analyzed with IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). Test for normality was done for all collected data by Shapiro–Wilk test. Quantitative data are presented as mean±standard deviation or median (interquartile range).

Patients were categorized into two different groups according to their PAS scores. Patients with PAS 1 to 5 were categorized into a non-aspirator group and patients with PAS 6 to 8 were categorized into an aspirator group. To compare the variables between two groups, an independent two sample t-test or Mann–Whitney U-test was conducted as appropriate. Chi-squared test or the Fisher's exact test was performed for categorical variables.

To identify the independent risk factors of outcomes, a step-wise multivariable logistic regression analysis was performed that included all variables with a p-value<0.05 in the univariable analysis. Odd ratio and their 95% confidence interval (CI) were also calculated.

Spearman's partial correlation analysis was conducted to investigate the correlations of AMR, SMR, and MPT with dysphagia parameters. The correlation coefficient was adjusted by other possible effectors such as age, sex, MMSE, mRS, the size of the stroke lesion, the location of stroke lesion, the type of stroke, and the laterality of stroke lesion. The correlation was interpreted as very weak when between 0.00 to 0.19, weak when between 0.20 to 0.39, moderate when between 0.40 to 0.69, strong when between 0.70 to 0.89, and very strong when between 0.90 to 1.00 [24].

The aspirator group was further divided into three different groups according to the timing of aspiration. Aspiration before-swallowing was assigned as group A, aspiration during-swallowing was assigned as group B, and aspiration after-swallowing was assigned as group C. The value of AMR (“pa”), AMR (“ta”), AMR (“ka”), SMR, and MPT were compared between the three groups by Kruskal–Wallis test. Post hoc analysis by Dunn’s procedure was done in the multiple comparison to correct type 1 error.

Receiver operating characteristic (ROC) curve analysis was done to obtain optimal cut-off values for AMR (“ka”) and SMR for distinguishing non-aspirator group and aspiration group by Youden index.

**RESULTS**

Data from a total number of 171 patients were collected. Basic characteristics, AMR, SMR, MPT, and dysphagia parameters of these patients are listed in Table 1. Dysphagia parameters such as ASHA-NOMS, CDS, VDS oral score, and VDS pharyngeal score were significantly different between non-aspirator group and aspirator group. Also, MMSE, mRS, location of the stroke lesion, AMR (“pa”), AMR (“ta”), AMR (“ka”), SMR, and MPT were significantly different between non-aspirator group and aspirator group, which led us to perform stepwise multivariable logistic regression analysis to find out the significant associated risk factors between the two groups.

In Table 2, stepwise multivariable analysis showed that mRS, AMR (“ka”), and SMR were significant associated factors between the two groups. Other variables such as MMSE, location of the stroke lesion, AMR (“pa”), AMR (“ta”), and MPT were
Table 1. Basic characteristics of patients and comparison of AMR, SMR, MPT, and VFSS parameters between two groups (n=171)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-aspirators (n=82)</th>
<th>Aspirators (n=89)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.62±14.52</td>
<td>62.45±14.12</td>
<td>0.937</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.227</td>
</tr>
<tr>
<td>Male</td>
<td>46 (56.10)</td>
<td>58 (65.17)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (43.90)</td>
<td>31 (34.83)</td>
<td></td>
</tr>
<tr>
<td>Onset (mo)</td>
<td>1.56±1.07</td>
<td>1.76±1.25</td>
<td>0.257</td>
</tr>
<tr>
<td>MMSE</td>
<td>22.67±5.49</td>
<td>20.79±5.38</td>
<td>0.027a</td>
</tr>
<tr>
<td>mRS</td>
<td>2.84±0.95</td>
<td>3.30±0.91</td>
<td>0.001c</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td>0.584</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>44 (53.66)</td>
<td>44 (49.44)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>38 (46.34)</td>
<td>45 (50.56)</td>
<td></td>
</tr>
<tr>
<td>Stroke laterality</td>
<td></td>
<td></td>
<td>0.877</td>
</tr>
<tr>
<td>Right</td>
<td>26 (31.71)</td>
<td>29 (32.58)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>37 (45.12)</td>
<td>37 (41.58)</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>19 (23.17)</td>
<td>23 (25.84)</td>
<td></td>
</tr>
<tr>
<td>Stroke lesion</td>
<td></td>
<td></td>
<td>0.003b</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>76 (92.70)</td>
<td>68 (76.41)</td>
<td></td>
</tr>
<tr>
<td>Infratentorial</td>
<td>3 (3.65)</td>
<td>17 (19.10)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>3 (3.65)</td>
<td>4 (4.49)</td>
<td></td>
</tr>
<tr>
<td>Stroke lesion size (mm²)</td>
<td>37.05±35.14</td>
<td>40.56±18.66</td>
<td>0.411</td>
</tr>
<tr>
<td>AMR (&quot;pa&quot;)</td>
<td>23 (19.0–25.0)</td>
<td>16 (10.5–21.0)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>AMR (&quot;ta&quot;)</td>
<td>23 (18.0–25.3)</td>
<td>15 (8.5–20.0)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>AMR (&quot;ka&quot;)</td>
<td>22.5 (18.8–26.0)</td>
<td>14 (7.5–19.5)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>SMR</td>
<td>8 (6–10)</td>
<td>4 (2–6.5)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>MPT</td>
<td>9.16 (6.39–13.06)</td>
<td>5.41 (3.66–7.99)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>ASHA-NOMS</td>
<td>7 (6–7)</td>
<td>5 (3–5)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>CDS</td>
<td>5 (5–15)</td>
<td>45 (35–54)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>VDS_oral</td>
<td>0 (0–5.0)</td>
<td>9 (5.0–18.0)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>VDS_pharyngeal</td>
<td>11 (2–16)</td>
<td>26 (20.0–41.5)</td>
<td>&lt;0.001c</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation, number (%), or median (interquartile range).

AMR, alternation motor rate; SMR, sequential motor rate; MPT, maximum phonation time; VFSS, video fluoroscopic swallowing study; MMSE, mini-mental state examination; mRS, modified Rankin Scale; ASHA-NOMS, American Speech-Language-Hearing Association National Outcomes Measurement System; CDS, clinical dysphagia scale; VDS, videofluoroscopic dysphagia scale.

a) p<0.05 by an independent two sample t-test; b) p<0.05 by chi-squared test or the Fisher’s exact test; and c) p<0.001 by Mann–Whitney U-test.

not significant associated risk factors.

In Table 3, partial correlation was done to find out the correlation between AMR ("pa"), AMR ("ta"), AMR ("ka"), SMR, and MPT with the dysphagia parameters. AMR ("pa"), AMR ("ta"), AMR ("ka"), SMR, and MPT had significant correlation with PAS score, ASHA-NOMS scale, CDS score, PAS score for 5mL liquid and PAS score for cup drinking of water, and velopharyngeal reflux.

AMR ("pa"), AMR ("ta"), AMR ("ka"), and SMR had moderate correlation with VDS oral score and weak correlation with VDS pharyngeal score. All 7 items included in VDS oral score showed significant correlations, while only 2 items included in VDS pharyngeal score showed significant correlation.

MPT had weak correlation with VDS oral score and moderate correlation with VDS pharyngeal score. Only 3 items in VDS oral score had significant correlations, while 5 items in VDS pharyngeal score had significant correlation.

In Table 4, AMR ("pa"), AMR ("ta"), AMR ("ka"), and SMR were significantly lower in the before-swallowing aspiration group compared to the other two groups. However, there was no significant difference in MPT between the three groups.

In Fig. 1, cut-off values of AMR ("ka") and SMR for distinguishing non-aspirator group and aspiration group are shown. The cut-off value was 18.5 for AMR ("ka") with a sensitivity of 74.4% and a specificity of 70.8% on the ROC curve (area under curve [AUC]=0.796, 95%CI=0.730–0.862). The cut-off value...
Table 2. Univariable analysis and stepwise multivariable logistic regression analysis between non-aspirator group and aspirator group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.998 (0.977–1.019)</td>
<td>0.826</td>
</tr>
<tr>
<td>Sex</td>
<td>1.539 (0.829–2.859)</td>
<td>0.172</td>
</tr>
<tr>
<td>Onset</td>
<td>1.165 (0.894–1.519)</td>
<td>0.258</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.939 (0.887–0.993)</td>
<td>0.029&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>mRS</td>
<td>1.706 (1.216–2.395)</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.685 (0.382–1.882)</td>
<td>0.685</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0.719 (0.338–1.529)</td>
<td>0.391</td>
</tr>
<tr>
<td>Stroke lesion laterality</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Right</td>
<td>1.004 (0.992–1.016)</td>
<td>0.473</td>
</tr>
<tr>
<td>Left</td>
<td>0.869 (0.823–0.918)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0.861 (0.815–0.909)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>AMR (&quot;pa&quot;)</td>
<td>0.846 (0.798–0.896)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SMR</td>
<td>0.590 (0.502–0.693)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MPT</td>
<td>0.781 (0.711–0.858)</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; MMSE, mini-mental state examination; mRS, modified Rankin Scale; AMR, alternation motor rate; SMR, sequential motor rate; MPT, maximum phonation time.

<sup>a</sup>p<0.05 by univariable linear logistic analysis; <sup>b</sup>p<0.05 by stepwise multivariable logistic regression analysis; and <sup>c</sup>p<0.001 by stepwise multivariable logistic regression analysis.

Table 3. Partial correlations between AMR, SMR, MPT, and various dysphagia parameters

<table>
<thead>
<tr>
<th></th>
<th>AMR (&quot;pa&quot;)</th>
<th>AMR (&quot;ta&quot;)</th>
<th>AMR (&quot;ka&quot;)</th>
<th>SMR</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDS oral score</td>
<td>R</td>
<td>-0.547</td>
<td>-0.585</td>
<td>-0.608</td>
<td>-0.661</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lip closure</td>
<td>R</td>
<td>-0.476</td>
<td>-0.426</td>
<td>-0.433</td>
<td>-0.428</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bolus formation</td>
<td>R</td>
<td>-0.424</td>
<td>-0.447</td>
<td>-0.444</td>
<td>-0.412</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mastication</td>
<td>R</td>
<td>-0.410</td>
<td>-0.419</td>
<td>-0.445</td>
<td>-0.440</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apraxia</td>
<td>R</td>
<td>-0.239</td>
<td>-0.260</td>
<td>-0.306</td>
<td>-0.199</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.010&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.084</td>
</tr>
<tr>
<td>Tongue to palate contact</td>
<td>R</td>
<td>-0.445</td>
<td>-0.484</td>
<td>-0.505</td>
<td>-0.425</td>
</tr>
<tr>
<td>p-value</td>
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<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Premature bolus loss</td>
<td>R</td>
<td>-0.297</td>
<td>-0.321</td>
<td>-0.403</td>
<td>-0.411</td>
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<tr>
<td>Oral transit time</td>
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<td>-0.450</td>
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</tr>
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(Continued to the next page)
Table 3. Continued

<table>
<thead>
<tr>
<th></th>
<th>AMR (&quot;pa&quot;)</th>
<th>AMR (&quot;ta&quot;)</th>
<th>AMR (&quot;ka&quot;)</th>
<th>SMR</th>
<th>MPT</th>
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<tr>
<td>Pharyngeal phase</td>
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<tr>
<td>VDS pharyngeal score</td>
<td>R</td>
<td>-0.268</td>
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<td>Triggering of pharyngeal swallow</td>
<td>R</td>
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<td>-0.254</td>
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<td>Vallecular residue</td>
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<td>Laryngeal elevation</td>
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<td>Pyriform sinus residue</td>
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<td>p-value</td>
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<td>Coating on the pharyngeal wall</td>
<td>R</td>
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<td>-0.135</td>
<td>-0.131</td>
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<td>Pharyngeal transit time</td>
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<td>-0.075</td>
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<td>Aspiration</td>
<td>R</td>
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<td>-0.391</td>
<td>-0.416</td>
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<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Other dysphagia parameters</td>
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<tr>
<td>PAS score</td>
<td>R</td>
<td>-0.369</td>
<td>-0.376</td>
<td>-0.552</td>
<td>-0.585</td>
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<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>ASHA-NOMS scale</td>
<td>R</td>
<td>0.308</td>
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<td>0.402</td>
<td>0.434</td>
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<td></td>
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<tr>
<td>CDS</td>
<td>R</td>
<td>-0.260</td>
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<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PAS score for yogurt</td>
<td>R</td>
<td>-0.004</td>
<td>-0.041</td>
<td>-0.064</td>
<td>-0.065</td>
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<tr>
<td></td>
<td>p-value</td>
<td>0.962</td>
<td>0.647</td>
<td>0.478</td>
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<tr>
<td>PAS score for rice porridge</td>
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<td>0.013</td>
<td>-0.017</td>
<td>-0.006</td>
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<tr>
<td></td>
<td>p-value</td>
<td>0.597</td>
<td>0.889</td>
<td>0.848</td>
<td>0.950</td>
</tr>
<tr>
<td>PAS score for rice</td>
<td>R</td>
<td>0.039</td>
<td>0.014</td>
<td>-0.012</td>
<td>-0.003</td>
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<tr>
<td></td>
<td>p-value</td>
<td>0.666</td>
<td>0.880</td>
<td>0.894</td>
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<tr>
<td>PAS score for 5 mL water</td>
<td>R</td>
<td>-0.188</td>
<td>-0.248</td>
<td>-0.306</td>
<td>-0.328</td>
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<td>p-value</td>
<td>0.036&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.005&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PAS score for cup drinking of water</td>
<td>R</td>
<td>-0.366</td>
<td>-0.371</td>
<td>-0.425</td>
<td>-0.598</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Velopharyngeal reflux</td>
<td>R</td>
<td>-0.201</td>
<td>-0.267</td>
<td>-0.332</td>
<td>-0.211</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.010&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.007&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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</table>

The correlation coefficient was adjusted by other possible effectors such as age, sex, MMSE, mRS, the size of the stroke lesion, the location of stroke lesion, the type of stroke, and the laterality of stroke lesion.

AMR, alternation motor rate; SMR, sequential motor rate; MPT, maximum phonation time; VDS, videofluoroscopic dysphagia scale; PAS, penetration-aspiration scale; ASHA-NOMS, American Speech-Language-Hearing Association National Outcomes Measurement System; CDS, clinical dysphagia scale.

<sup>a</sup>p<0.001 by Pearson’s partial correlation analysis and <sup>b</sup>p<0.05 by Pearson’s partial correlation analysis.

was 7.5 for SMR with a sensitivity of 89.9% and a specificity of 61.0% on the ROC curve (AUC=0.836, 95% CI=0.776–0.896).

**DISCUSSION**

We went through chart review of 171 subacute stroke patients. Table 1 showed that MMSE, mRS, and brain lesion location were significantly different between the two groups. However, the mean value of MMSE was 22.67±5.49 in non-aspirator group and 20.79±5.38 for aspirator group. Both group had a mean MMSE higher than 20. All patients included in this study were able to accomplish VFSS procedure and speech language eval-
Evaluation test without any problems. Also, stepwise multivariable logistic regression analysis showed that MMSE and brain lesion location were not significant factors between the two groups. In Table 2, mRS, AMR ("pa"), and SMR were the significant factors between non-aspirator group and aspirator group. AMR ("pa"), AMR ("ta"), and MPT were not significant factors between the two groups. Thus, we could suggest that AMR ("ka") and SMR, which represents posterior lingual movements, are the important risk factors between the two groups.

The partial correlation analysis showed that AMR ("pa"), AMR ("ta"), AMR ("ka"), SMR, and MPT had negative correlation with the PAS score, positive correlation with the ASHA-NOMS scale, negative correlation with the CDS. We could suggest that patients with impaired AMR ("pa"), AMR ("ta"), AMR ("ka"), SMR, and MPT are more vulnerable to aspiration, require more diet modification and supervision during oral feeding, and have more severe oropharyngeal dysphagia. We would like to discuss additional results in more detail with VDS oral item scores and VDS pharyngeal item scores according to the different articulation points.

### Table 4. AMR, SMR, and MPT difference between the three groups

<table>
<thead>
<tr>
<th></th>
<th>Before-swallowing aspiration (A)</th>
<th>During-swallowing aspiration (B)</th>
<th>After-swallowing aspiration (C)</th>
<th>p-value</th>
<th>Post hoc analysis (multiple comparison)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR (&quot;pa&quot;)</td>
<td>10.5 (6.75–13.0)</td>
<td>18.0 (13.5–22.0)</td>
<td>20.0 (12.0–23.5)</td>
<td>&lt;0.001a</td>
<td>&lt;0.001b; 0.009b; &gt;0.999</td>
</tr>
<tr>
<td>AMR (&quot;ta&quot;)</td>
<td>8.0 (5.5–10.5)</td>
<td>18.0 (13.0–21.0)</td>
<td>19.0 (7.5–22.5)</td>
<td>&lt;0.001a</td>
<td>&lt;0.001b; 0.015b; &gt;0.999</td>
</tr>
<tr>
<td>AMR (&quot;ka&quot;)</td>
<td>7.5 (3.0–10.0)</td>
<td>17.0 (13.0–20.5)</td>
<td>18.0 (4.5–21.5)</td>
<td>&lt;0.001a</td>
<td>&lt;0.001b; 0.029b; &gt;0.999</td>
</tr>
<tr>
<td>SMR</td>
<td>2.5 (1.0–4.25)</td>
<td>5.0 (3.0–7.0)</td>
<td>6.0 (3.0–7.0)</td>
<td>&lt;0.001a</td>
<td>0.002b; 0.040b; &gt;0.999</td>
</tr>
<tr>
<td>MPT</td>
<td>3.97 (2.58–6.42)</td>
<td>5.47 (3.95–8.40)</td>
<td>6.09 (3.51–10.72)</td>
<td>0.128</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range).
AMR, alternation motor rate; SMR, sequential motor rate; MPT, maximum phonation time.
"p<0.001 by Kruskal–Wallis test and "p<0.05 by Kruskal–Wallis test.

**Fig. 1.** Receiver operating characteristic curves of (A) alternation motor rate ("ka") and (B) sequential motor rate for distinguishing non-aspirator group and aspirator group. AUC, area under curve.
Anterior lingual movements: correlation between AMR ("pa"), AMR ("ta") with oral and pharyngeal dysphagia parameters

Table 3 showed that AMR ("pa") and AMR ("ta") had a moderate correlation with lip closure, bolus formation, mastication, tongue to palate contact, and oral transit time. Also, there was weak correlation with premature bolus loss and apraxia. These parameters are related to problems during the oral preparatory phase as well as the oral propulsive phase.

AMR ("pa") and AMR ("ta") represents the anterior lingual movements. AMR ("pa") is a bilabial sound, representing the movement of the lips. AMR ("ta") is an alveolar sound, representing the anterior tip of tongue motility. Both lips and anterior tip of the tongue are important in oral preparatory phase when lips prevent anterior leakage and the anterior tip of tongue holds the bolus at the anterior part of the mouth against the hard palate. Anterior lingual movements are important when transition from oral preparatory phase in oral propulsive phase occurs. The oral propulsive phase is primarily driven by the tongue when the anterior tongue surface contacts the hard palate just behind the upper incisors, and the area of tongue to palate contact starts to expand backward to squeeze the bolus into the oropharynx [11]. Therefore, patients with impaired AMR ("pa") and AMR ("ta") may have difficulty in preventing anterior leakage, bolus formation, mastication, tongue to palate contact, delayed oral transit time, and premature bolus loss, which increases the risk of aspiration due to reduced anterior lingual motility.

Also, AMR ("pa") and AMR ("ta") had a weak negative correlation with triggering of pharyngeal swallow and aspiration. There were no correlation with vallecular residue, laryngeal elevation, pyriform sinus residue, coating on the pharyngeal wall, and pharyngeal transit time. Therefore, we concluded that anterior lingual movements have a more correlation with oral stage dysphagia than pharyngeal stage dysphagia.

However, the overall correlation coefficient showed only weak or moderate correlations. None of the dysphagia parameters had strong correlation. The correlation coefficient for PAS score and ASHA-NOMS scale showed weak correlations. AMR ("pa") and AMR ("ta") were not significant factors between the non-aspirator group and the aspirator group (Table 2). Therefore anterior lingual motility is thought to have relatively lesser impact on the swallowing process, especially for aspiration.

Posterior lingual movements: correlation between AMR ("ka"), SMR with oral and pharyngeal dysphagia parameters

Table 3 showed that AMR ("ka") and SMR had a moderate correlation with lip closure, bolus formation, mastication, tongue to palate contact, premature bolus loss, and oral transit time. Also, there was a weak correlation with apraxia. These parameters are related to problems during the oral preparatory phase as well as the oral propulsive phase.

AMR ("ka") and SMR represent the posterior lingual motility. AMR ("ka") is a velar sound made by the dorsum of the tongue and soft palate. SMR also has ‘ka’ sound which requires the dorsum of the tongue and soft palate. During the oral preparatory stage, the oral cavity is sealed posteriorly with the dorsum of the tongue and soft palate to prevent the bolus from leaking into the oropharynx before swallowing. During the oral propulsive stage, the area of tongue to palate contact gradually expands backward, squeezing the bolus back along the palate into the oropharynx. The bolus aggregates on the pharyngeal surface of the tongue and in the valleculae to induce a swallowing reflex and start the pharyngeal phase of swallowing.

Therefore, patients with impaired AMR ("ka") and SMR may have difficulties in bolus formation, mastication, tongue to palate contact, delayed oral transit time and be at a higher risk of premature bolus loss, which increases the risk of aspiration.

Also, AMR ("ka") and SMR had a weak correlation with triggering of pharyngeal swallow and a moderate correlation with aspiration. There were no correlation with vallecular residue, laryngeal elevation, pyriform sinus residue, coating on the pharyngeal wall, and pharyngeal transit time.

However, the overall correlation coefficient showed only weak or moderate correlations. None of the dysphagia parameters had a strong correlation. The correlations for the PAS score and the ASHA-NOMS scale were moderate, which were stronger compared with AMR ("pa") and AMR ("ta"). Also, AMR ("ka") and SMR were significant risk factor between the non-aspirator group and the aspirator group (Table 2). Therefore, posterior lingual motility is thought to be an important factor in the swallowing process.

Correlation between MPT with oral and pharyngeal dysphagia parameters

Table 3 showed that MPT had a weak correlation with lip closure, premature bolus loss and oral transit time. There were no correlations with bolus formation, mastication, apraxia, and
tongue to palate contact. However, there were a moderate correlation with triggering of pharyngeal swallow, and a weak correlation with laryngeal elevation, coating on the pharyngeal wall, pharyngeal transit time, and aspiration. From these results, we could suggest that MPT is more related with pharyngeal stage dysphagia compared to oral stage dysphagia.

A previous study found out that MPT is associated with triggering of pharyngeal swallowing and laryngeal elevation in Parkinson’s disease [25]. Another previous study showed that prolonged pharyngeal transit time is a significant predictor of aspiration pneumonia in the elderly [26]. This is consistent with our study results, showing that MPT had a negative correlation with triggering of pharyngeal swallow, delayed pharyngeal transit time, and laryngeal elevation, which are important airway protective mechanism during deglutition. Also, the airway is protected by swallowing apnea, a well-coordinated physiologic response where respiration stops during swallowing by laryngeal elevation and the action of the aryepiglottic folds. This apneic period tends to last about 0.5 to 1.5 seconds serving to prevent aspiration during inspiration by maintaining the higher subglottic pressure [27]

MPT requires a patient to sustain a prolonged expiratory phase to make sufficient subglottal air pressure to induce the vocal cord vibration. MPT is strongly influenced by breathing capacity, expiratory pressure, and subglottic pressure [14]. MPT is known to indirectly measure the efficiency of the laryngeal function and vocal cord vibration [15]. This result is supported by a previous study that showed increase in MPT correlated with improvement in swallowing function in the oral and pharyngeal phase of patients with multiple system atrophy with dysphagia [28].

We concluded that MPT has correlation with pharyngeal phase dysphagia more than oral stage dysphagia. Patients with shorter MPT may have reduced laryngeal elevation, lower subglottic air pressure, have delayed triggering of pharyngeal swallow reflex and delayed pharyngeal transit time, and therefore at an increased risk of aspiration. However the overall correlation coefficient was from weak to moderate and MPT was not a significant factor between the non-aspirator group and the aspirator group (Table 2).

**Correlations with the presence of velopharyngeal reflux**

Table 3 showed that AMR (“pa”), AMR (“ta”), AMR (“ka”), SMR, and MPT had a significant weak correlation with the presence of velopharyngeal reflux. During the normal pharyngeal phase of swallowing, the soft palate is elevated by the contraction of levator veli palatine while the lateral and posterior pharyngeal walls contract medially and anteriorly to close the velopharyngeal port, separating the nasal cavity and oral cavity [11]. This process prevents the bolus from regurgitating into the nasal cavity. Velopharyngeal reflux can occur when the soft palate and pharyngeal walls are unable to form an effective seal.

AMR and SMR utilize oral plosive sounds such as ‘pa’, ‘ta’, and ‘ka’. Oral plosive sounds are created when the air is stopped completely in the oral cavity and then suddenly explodes with its release. Air pressure needs to build up in the oral cavity up to 5–7 mmHg in order to produce there oral plosive sounds [29]. Therefore, in order to perform AMR and SMR correctly, not only lingual movements but also adequate elevation of the soft palate and contraction of the pharyngeal wall are required.

Also, MPT utilizes prolonged phonation process. During phonation, the air passes through the vocal folds and travels through the pharyngeal cavity and then through the oral and nasal cavities, where changes in the space occur due to the various movements of the articulatory organs, resulting in the production of different types of sounds [9]. To make oral sounds, the pathway to the nose is usually blocked by the contraction of the levator veli palatine muscle that elevates the soft palate to attach to the back of the pharyngeal wall, blocking the path to the nasal cavity and allowing the airflow only to the oral cavity. On the other hand, when the soft palate is lowered, the airflow can pass through the nose, resulting in the production of nasal sounds.

MPT utilizes the ‘a’ sound, which is produced without any obstruction in the middle part of the oral cavity, making it a vowel sound. To perform a longer MPT, a patient needs to be able to control their oropharyngeal structures in coordination.

Therefore, we concluded that AMR, SMR, and MPT had significant correlations with the presence of velopharyngeal reflux.

**Correlation between AMR, SMR, MPT, and PAS scores according to type of food**

The partial correlation analysis showed that AMR (“pa”), AMR (“ta”), AMR (“ka”), SMR, and MPT had significant correlations between PAS scores of 5 mL of liquid and cup drinking. However, there were no significant correlations between the PAS scores of yogurt, rice porridge, and rice.

Handling a liquid bolus requires very fast and elaborate movements of the oral structures as well as pharyngeal structures due to its slippery consistency. Liquid has the most vulnerable consistency that increases risk of aspiration. Thus, patients with impaired coordination of oral structures can be more susceptible in handling liquid materials, resulting in premature bolus loss.
and, therefore, a higher risk of aspiration. The study results were consistent with a previous study that showed increasing viscosity of foods would decrease the aspiration for stroke patients [30].

**Correlation between AMR, SMR, MPT, and type of aspiration**

In Table 4, AMR (“pa”), AMR (“ta”), AMR (“ka”), and SMR were significantly lower in group A. Aspiration before the swallow is commonly caused by either the premature entry of liquids into the pharynx due to impaired containment in the oral cavity or by delayed onset of laryngeal closure after a bolus is propelled into the pharynx [11]. A previous study suggested that premature bolus loss is a sign of reduced tongue strength and motility in stroke survivors [31]. Unfortunately, our study did not assess the strength of the tongue. However, tongue motility is reflected by AMR (“pa”), AMR (“ta”), AMR (“ka”), and SMR. Therefore, we could suggest that patients with impaired AMR (“pa”), AMR (“ta”), AMR (“ka”), and SMR were more susceptible to before-swallowing aspiration due to impaired tongue motility, incomplete bolus loss and premature spillage.

MPT were not significantly different between the three groups. Impairments of airway protection can result from reduced laryngeal elevation or inadequate vocal fold closure. These impairments can lead to aspiration, usually during the swallow. Since MPT indirectly reflects laryngeal functions such as vocal cord vibration, bronchial airflow, subglottic air pressure, we expected that Group B would have a lower MPT compared to the other groups [16]. However, we could not find any difference between the tree groups. This may be partially due to some limitations of our study that did not measure intensity of vocalization, and there were no accurate criteria for the height of the voice or tone of the voice. Also, we did not assess vocal cord palsy. These limitations require further studies that encompass all these parameters and in more well-designed study.

To our best knowledge, this is the first study to investigate the correlations of AMR and SMR with dysphagia in subacute stroke patients. There is a previous study that showed the correlation between AMR, SMR, and dysphagia in amyotrophic lateral sclerosis (ALS) patients [32]. The study showed that ALS patients who aspirated in 10 mL liquid bolus had lower AMR (“ka”) compared to the ALS non-aspiration subjects. Also, SMR had a significant negative correlation with pharyngeal residue and aspiration. The authors suggest that alterations in speech production in ALS patients are due to decreased range, rate, and strength of the tongue, decreased oral pharyngeal musculature, decreased lingual coordination and impaired base of tongue movement, which increase the amount of pharyngeal residue and the risk of aspiration. The study suggested that AMR (“ka”) and SMR are related to bolus propulsion through the pharynx in the swallowing process as well as posterior lingual movements during the articulation of speech. Our study showed similar results that posterior lingual movements, represented by AMR (“ka”) and SMR, are important factors in dysphagia of subacute stroke patients. We further found out that the type of aspiration was mainly before-swallowing aspiration.

AMR and SMR are simple to calculate, and they have minimal linguistic burden, which could allow patients with even severe dysarthria to complete the assessment [33]. AMR and SMR can also detect a subtle degree of dysarthria [34].

This study has several limitations. First, for patients with severe aphasia or severe cognitive dysfunction, their articulation ability and phonation ability can be underestimated. Therefore, our study results lack reliability and validity for patients with severe aphasia or severe cognitive impairment, and caution is needed for clinical application of the study result.

Second, we did not evaluate other oral structure related parameters such as maximal tongue protrusion length or maximal tongue base pressure and area that can be assessed by high resolution manometry, which are known to be related with dysphagia [35,36]. Also, we did not evaluate the strength of oral structures such as lips and tongue. Therefore, we could not find the relationship between tongue strength and swallowing functions. Previous studies used Iowa Oral Performance Instrument (IOPI Medical LLC, Woodinville, WA, USA) to measure tongue strength in a quantitative and objective manner. They found out that tongue strength is related with swallowing functions of the stroke survivors [37,38]. Another study found out that lingual strength training provides positive effects on lingual strength and articulator function, such as AMR and SMR, in stroke survivors [39]. We expect that our study results can be helpful in serving as a link to elucidate the relationship between tongue strength, AMR and SMR, and dysphagia of stroke survivors in more detail.

Third, the onset time of stroke was less than six months. We did not enroll chronic stage stroke patients.

Fourth, since this study was designed as a retrospective cross sectional chart review study, it was unable to find out the causal relationship or long-term relationship.

Fifth, when evaluating PAS or VDS scores, we based the scores on the worst findings observed during the examination, regard-
less of the food consistency. It should be noted that the results may differ depending on the consistency of the food.

Lastly, when performing MPT, there were no strict criteria for the tone of the voice, height of the voice and intensity of the voice, which may have led to errors. It would have been more solid if other voice evaluation indices such as richness, roughness, breathiness, pitch, and voice instability were taken into account. Also, we did not assess for the vocal cord palsy or coughing function, such as peak cough flow, of patients [40]. Therefore, subsequent studies with prospective and long-term observation with well-designed studies are required.

Long-term follow-up studies on changes of AMR, SMR, and MPT during speech therapy or pulmonary rehabilitation exercise, in regard with the strength of the oral structures, could provide further information about relationships of AMR, SMR, and MPT with swallowing function in stroke patients.

In conclusion, this study showed that AMR, SMR, and MPT had significant correlations with the severity of dysphagia. AMR (“ka”), SMR, and mRS were significant factors between the non-aspirator group and the aspirator group, while AMR (“pa”), AMR (“ta”), and MPT were not. Extra caution should be taken for dysphagia in patients with AMR less than 18.5 or SMR less than 7.5. Our study results suggest that articulatory diadochokinetic tasks that can be easily performed at the bedside would be particularly helpful in determining the oral feeding possibility of subacute stroke patients who cannot undergo VFSS, which is the gold standard for dysphagia assessment.

CONFLICTS OF INTEREST

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

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None.

AUTHOR CONTRIBUTION

Conceptualization: Seok H, Kim SH, Lee SY, Kim HJ, Oh BM. Methodology: Kim SH, Kim HJ, Oh BM, Park SJ, Kim BJ. Formal analysis: Kim HJ, Oh BM. Project administration: Seok H, Kim SH, Lee SY, Kim HJ, Oh BM. Visualization: Kim HJ, Oh BM, Park SJ, Kim BJ. Writing – original draft: Kim HJ, Oh BM. Writing – review and editing: Seok H, Kim SH, Lee SY, Kim HJ, Oh BM, Park SJ, Kim BJ. Approval of final manuscript: all authors.

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INTRODUCTION

Stroke is well known to significantly impair motor and sensory functions, and the resulting gait disturbance persists even after three months [1]. Therefore, restoring gait ability is the most critical task in post-stroke rehabilitation [2].

In recent years, gait rehabilitation using robot-assisted gait training (RAGT) has been the focus of attention in gait recovery after a stroke. RAGT is a method of training a patient’s lower limbs to move in a gait-like movement using actuators attached to a walking device [3]. RAGT involves the actuator performing the movements of the patient’s lower limbs during walking, thus enabling intensive and repetitive gait practice necessary to re-learn gait [4].

RAGT can be classified into exoskeletal and end-effector types according to how the lower limbs move [5], such as LOKOMAT (Hocoma AG, Volketswil, Switzerland) [6-10] and GaitMaster [11-14], respectively. In a previous report on RAGT for patients with stroke, Schwartz et al. [15] performed RAGT with LOKOMAT in patients with subacute stroke. They showed...
that it was effective in restoring gait ability compared with usual physiotherapy. Tanaka et al. [16] also reported that gait rehabilitation using GaitMaster for patients with subacute stroke resulted in significantly higher gait speed and endurance improvement than conventional gait rehabilitation. Thus, the benefits of RAGT for patients with stroke are promising [17-20]; however, some reports have found no significant difference when compared with conventional gait rehabilitation [21-23]. Therefore, neurophysiological assessment is needed to further understand the effects of RAGT [24].

The neurophysiological effects of RAGT have been studied in lower-limb muscle activity. Hidler and Wall [25] measured muscle activity during RAGT with LOKOMAT and treadmill walking in healthy participants. They reported higher muscle activity in the rectus femoris and vastus lateralis during the free leg phase in RAGT because of pelvic restriction and lower activity in the gastrocnemius and tibialis anterior muscles during the overall walking cycle as a result of passive walking in RAGT. Coenen et al. [26] also measured lower-limb muscle activity during RAGT with LOKOMAT and overground walking in patients with chronic stroke and reported that lower-limb muscle activity in these patients was lower during RAGT than during overground walking. These studies have shown that RAGT reduces lower-limb muscle activity. However, reports so far have not shown how continuous training of RAGT changes muscle activity in patients with stroke. Thus, further studies are needed to assess changes in muscle activity before and after RAGT to improve understanding of the effects of RAGT on muscle activity.

Therefore, this study aimed to measure changes in muscle activity pre- and post-RAGT in patients with stroke and investigate the differences between conventional gait training (CGT) and changes in muscle activity. Concretely, we hypothesized that RAGT with an end-effector-type device would induce ankle joint muscle activity and positively change the ankle muscle activity pattern more than CGT.

**METHODS**

**Participants**

Patients with stroke within 6 months of onset and significant gait disorder (functional ambulatory category [27] of ≤3) on study entry were included. All participants were inpatients. Patients who could not walk independently before onset, patients with severe cardiovascular or pulmonary dysfunction (equivalent to New York Heart Association Classification [28] III or IV), patients with osteoarthritic disease limiting movement, and patients with dementia and difficulty understanding instructions (mini-mental state examination [29] <20) were excluded.

The Ethics Committee of the Tokyo Professional University of Health Sciences approved the study (Approval No. 21-0024). This study was conducted with the consent of all participants or their legal representatives to participate in the study.

**Study protocol**

The participants were assigned to the RAGT group (odd numbers) or CGT (even numbers) using a computer-generated random number table. In the RAGT group, RAGT using a footpad-type locomotion interface was performed five times a week for 4 weeks, and CGT was not performed. The footpad-type locomotion interface used in this study was GaitMaster, which was developed by the Division of Intelligent Interaction Technologies, Faculty of Engineering, Information and Systems, University of Tsukuba [30]. GaitMaster is an end-effector type gait support device that can present gait-like movements by combining back-and-forth and up-and-down movements of the footpads. The participants place their legs on the footpads, and the footpads move along the gait trajectory, enabling the user to perform a gait-like movement [31].

The gait training conditions using the GaitMaster were as follows: the walking speed was the maximum walking speed possible for the participant to perform the gait movement, and the training time was 20 minutes, including rest time. A safety belt was attached to the weight-loading device during gait training to ensure safety, but no weight-unloading was performed. In addition, participants used handrails attached to the GaitMaster as necessary to ensure safety. Patients belonging to RAGT group did not use foot braces during training.

In the CGT group, participants performed CGT to acquire independent gait five times a week for 4 weeks. CGT consisted of stepping exercises, parallel bars, and walking exercises on the floor. The CGT group did not use treadmills or other commonly used gait practice equipment. The physiotherapists modified the content of the gait training for the CGT group according to the patient’s ability and condition. Additionally, the physiotherapist provided gait training in the CGT group using a metal-upright ankle–foot orthosis (n=7), a shoehorn-type ankle–foot orthosis (n=1), and an off-the-shelf soft knee brace (n=1), depending on the patient’s gait ability. The gait training time for the CGT group was 20 min, including rest periods. Neither the
RAGT nor the CGT group had any restrictions on rehabilitation other than walking exercises, such as occupational therapy or speech and language therapy.

Clinical outcomes
Participants’ age, sex, time since onset, stroke type, paralysis side, lower-extremity Fugl–Meyer assessment (LE-FMA), functional ambulation category (FAC), gait speed, and lower-limb muscle strength were baseline assessments. The primary outcome measure was muscle activity in lower-limb muscles by surface electromyography. The electromyogram (EMG) was measured using the wireless electromyography sensor SS-WS2911 (Sports Sensing; Fukuoka, Japan). Gluteus medius, rectus femoris, hamstrings, tibialis anterior, and gastrocnemius muscles on the paralyzed side were evaluated. The electrode attachment positions for each muscle followed the surface EMG for non-invasive assessment of muscles guidelines. A footswitch was also affixed to the heel to measure pressure data. EMG measurements were performed with floor walking. The participant's muscle activity for ten walking cycles was recorded at a sampling frequency of 1,000 Hz. The acquired data were processed with a bandpass filter at 10–500 Hz and smoothed by root mean square (RMS) every 100 ms. The RMS-processed waveforms were normalized to 100% of the maximum myopotential for each muscle. The normalized ten walking cycles of the waveform data were converted to one walking cycle (0%–100%) by additive averaging using footswitch data. The converted data for one gait cycle was divided into the initial contact phase (0%–1%), loading response phase (2%–12%), mid-stance phase (13%–31%), terminal stance phase (32%–50%), preswing phase (51%–62%), initial swing phase (63%–75%), mid-swing phase (76%–87%), and terminal swing phase (88%–100%) [33].

The secondary assessment outcome was the gait speed. Gait speed was defined as the maximum walking speed in floor walking. Gait speed was measured by having the participants walk as fast as possible on a 10-m walking path and calculating their walking speed using the number of seconds required to do the walk. Two measurements were made for the gait speed. The faster gait speed was adopted as the maximum gait speed. When measuring walking speed, the use of common walking aids was permitted, and walking assistance by a physiotherapist was allowed if necessary. These assessments were measured before the study began and at the end.

Statistical analysis
Comparisons between the RAGT and CGT groups for age, time since onset, LE-FMA, FAC, gait velocity, and lower-limb muscle strength at the baseline were made using an unpaired t-test for those following a normal distribution after conducting the Shapiro–Wilk test or the Mann–Whitney U-test for those not following a normal distribution. Comparisons were made for sex, stroke type, and paralyzed side using Fisher’s direct significant difference establishment.

Pre- and post-comparisons of gait speed and muscle activity in each group were made using the Shapiro–Wilk test followed by a paired t-test for those following a normal distribution and the Wilcoxon signed rank test for those not following a normal distribution. The changes before and after the intervention were calculated for between-group comparisons of walking speed and muscle activity. After performing the Shapiro–Wilk test, those following a normal distribution were compared using an unpaired t-test, and those not following a normal distribution were compared using the Mann–Whitney U-test. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), with a statistical significance set at 0.05.

RESULTS
Participant characteristics
We enrolled 32 participants in this study; however, 1 participant having FAC of ≥3 and 1 participant who could not perform gait training were excluded from the study, leaving a total of 30 participants. The enrolled participants were divided into RAGT groups (n=17) for odd numbers and CGT groups (n=13) for even numbers, using a computer-generated random number table. All participants completed the study. However, five participants in the RAGT group and five in the CGT group were excluded from the analysis because their muscle activity could not be measured. As a result, 12 patients in the RAGT group and 8 in the CGT group were included in the analysis (Fig. 1). The participant demographics at baseline showed no significant differences between the two groups (Table 1).

Clinical outcomes after gait training
Gait speed increased significantly in both groups (RAGT: pre, 0.45±0.28 m/s vs. post, 0.73±0.55 m/s; p=0.027; CGT: pre, 0.28±0.25 m/s vs. post, 0.56±0.47 m/s; p=0.017).

Regarding muscle activity changes within the groups, the
Fig. 1. Consort flow chart. FAC, functional ambulation category.

Table 1. Demographic characteristics of the RAGT and CGT groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAGT group (n=12)</th>
<th>CGT group (n=8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.83±11.42</td>
<td>64.50±10.30</td>
<td>0.507a</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (75.0)</td>
<td>5 (62.5)</td>
<td>0.455</td>
</tr>
<tr>
<td>Female</td>
<td>3 (25.0)</td>
<td>3 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Duration of stroke (day)</td>
<td>60.83±23.54</td>
<td>61.38±26.32</td>
<td>0.963a</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarction</td>
<td>7 (58.3)</td>
<td>5 (62.5)</td>
<td>0.612</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5 (41.7)</td>
<td>3 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Lesion side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6 (50.0)</td>
<td>7 (87.5)</td>
<td>0.106</td>
</tr>
<tr>
<td>Right</td>
<td>6 (50.0)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>LE-FMA</td>
<td>16.75±7.91</td>
<td>14.63±5.53</td>
<td>0.489b</td>
</tr>
<tr>
<td>Initial FAC</td>
<td>2.08±0.79</td>
<td>1.63±0.52</td>
<td>0.179b</td>
</tr>
<tr>
<td>Initial gait speed (m/s)</td>
<td>0.45±0.28</td>
<td>0.28±0.25</td>
<td>0.263b</td>
</tr>
<tr>
<td>Initial muscle strength (kg/f)</td>
<td></td>
<td></td>
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<tr>
<td>Paretic side</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip extension</td>
<td>3.94±4.49</td>
<td>6.59±7.03</td>
<td>0.624b</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>4.33±4.29</td>
<td>7.08±10.75</td>
<td>0.910b</td>
</tr>
<tr>
<td>Knee extension</td>
<td>8.12±9.53</td>
<td>9.23±16.22</td>
<td>0.678b</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>3.02±5.70</td>
<td>3.18±6.81</td>
<td>0.678b</td>
</tr>
<tr>
<td>Non paretic side</td>
<td></td>
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<td></td>
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<tr>
<td>Hip extension</td>
<td>9.27±5.09</td>
<td>12.95±3.72</td>
<td>0.057b</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>15.10±10.04</td>
<td>21.00±13.00</td>
<td>0.208b</td>
</tr>
<tr>
<td>Knee extension</td>
<td>18.09±12.31</td>
<td>23.63±10.37</td>
<td>0.238b</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>10.23±6.07</td>
<td>12.40±4.53</td>
<td>0.270b</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
RAGT, robot-assisted gait training; CGT, conventional gait training; LE-FMA, lower-extremity Fugl-Meyer assessment; FAC, functional ambulation category. 

*RAGT and CGT comparisons in unpaired t-tests and **RAGT and CGT comparisons in Mann-Whitney U-test.
RAGT group showed a significant increase in muscle activity in the gastrocnemius throughout the gait cycle. In the CGT group, a significant increase in muscle activity was found in the early stance phase in the rectus femoris (Table 2).

**Group comparison of clinical outcomes**

The change in the walking speed between the RGAT and CGT groups before and after training showed no significant differences between the two groups (RAGT, 0.27±0.37 m/s vs. CGT, 0.28±0.26 m/s; p=0.337).

A comparison of muscle activity between the RAGT and CGT groups showed an increase in the muscle activity in the CGT group at the initial contact and terminal swing in the rectus femoris and a higher increase in muscle activity in the RAGT group at the terminal stance and an initial swing in the gastrocnemius (Table 2).

**DISCUSSION**

This study compared the changes in lower-limb muscle activity between gait rehabilitation with RAGT using GaitMaster and CGT in patients with stroke and gait disorders. To the best of our knowledge, no longitudinal study has examined changes in muscle activity following RAGT-based interventions. This study is probably the first study in that category. In the RAGT group, a significant increase in muscle activity in the gastrocnemius muscles was found, particularly in the terminal stance phase, after 4 weeks of RAGT intervention with GaitMaster. By contrast, after 4 weeks of intervention, the CGT group showed a significant increase in muscle activity in the early stance phase of the rectus femoris.

In a previous study of the effects of RAGT on muscle activity, Hidler and Wall [25] reported that muscle activity during walking with an exoskeletal LOKOMAT was generally higher in the quadriceps and gluteus maximus than during treadmill walking but lower in the gastrocnemius, long adductor, and tibialis anterior. The results of the present study were inconsistent with those of previous studies. The disagreement is probably due to differences in the induction method of the skeletal and end-effector lower limbs. RAGT with GaitMaster differs from CGT in that the ankle joint is in a gait position with the ankle joint fixed to the footpad [31]. The plantar surface of the foot always touches the footpad, which means that the lower-limb is loaded proportionately, even during the swing phase. In addition, RAGT with GaitMaster can induce the terminal stance phase of the lower-limb on the stance side through the backward movement of the footpad. Compared with CGT, this combined effect may have led to an increase in gastrocnemius muscle activity throughout the gait cycle, particularly in the terminal stance phase. In contrast, CGT significantly increased muscle activity in the early stance phase of the rectus femoris. As Prosser et al. [34] reported similar muscle activity patterns for ground and treadmill walking, so we consider that muscle activity during treadmill walking can be used as a reference. Regarding treadmill walking in stroke patients, van Kammen et al. [35] reported higher muscle activity in the lateral vastus muscles during the early stance phase of treadmill walking compared with LOKOMAT and walking. Repeated CGT may have increased the muscle activity of the rectus femoris in the early stance phase. However, as described by Semaan et al. [36], the relationship between CGT and increased muscle activity in the rectus femoris should be further investigated, as treadmill walking and ground walking has similar muscle activity patterns differ in the amplitude of muscle activity and kinematic measures. Moreover, the CGT group used foot braces during gait training. Further investigation into the relationship between foot braces and rectus femoris muscle activity is needed, as ankle joint immobilization with foot braces may have increased stability during the stance phase and influenced the activity of the rectus femoris muscles.

Post-stroke gait disorders are affected by reduced propulsion from the paralyzed side [37], leading to reduced walking speed and asymmetry [38]. Therefore, propulsion improvement on the paralyzed side may be necessary for recovery from gait disorders after a stroke [39]. The gastrocnemius muscles mainly generate the propulsive force of walking. Therefore, it is crucial to improve the strength of the gastrocnemius. Varoqui et al. [40] reported that repetitive gait movements with the LOKOMAT did not worsen the plantar flexor ankle muscles’ muscle tone but improved their strength. Therefore, here, the increase in gait speed of the RAGT group in this study can be attributed to increased muscle activity in the gastrocnemius due to repetitive gait movements using the GaitMaster, which increases muscle strength. However, this study did not assess ankle plantar flexion muscle strength and gastrocnemius muscle tone. These factors should be assessed in future studies. Additionally, as this study only assessed the paralyzed side, future research on improving symmetry is required.

We observed no significant difference in the gait speed improvement between the RAGT and CGT groups. However, a previous report by Tanaka et al. [16] found that RAGT with
### Table 2. Changes in muscle activity between pre- and post-training for each group

<table>
<thead>
<tr>
<th>Variable</th>
<th>RAGT group</th>
<th></th>
<th></th>
<th>CGT group</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>pre</td>
<td>post</td>
<td>pre</td>
<td>post</td>
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<tr>
<td>Gluteus medius</td>
<td></td>
<td></td>
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<tr>
<td>Initial contact</td>
<td>32.67±18.86</td>
<td>43.08±24.76</td>
<td>20.27±14.57</td>
<td>28.72±17.50</td>
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<td></td>
</tr>
<tr>
<td>Loading response</td>
<td>36.99±19.03</td>
<td>37.25±23.48</td>
<td>23.30±16.25</td>
<td>33.18±20.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid stance</td>
<td>34.91±19.51</td>
<td>25.46±16.24</td>
<td>24.70±13.66</td>
<td>24.97±14.67</td>
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<td></td>
</tr>
<tr>
<td>Terminal stance</td>
<td>23.42±15.05</td>
<td>14.46±9.48</td>
<td>17.77±10.35</td>
<td>21.55±10.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-swing</td>
<td>17.55±9.95</td>
<td>12.81±9.59</td>
<td>14.61±10.79</td>
<td>19.94±9.91</td>
<td></td>
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</tr>
<tr>
<td>Mid-swing</td>
<td>17.38±8.37</td>
<td>10.91±7.02 (b)</td>
<td>14.52±10.91</td>
<td>20.16±10.44</td>
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</tr>
<tr>
<td>Terminal swing</td>
<td>15.73±9.15</td>
<td>10.07±6.00 (b)</td>
<td>13.90±10.43</td>
<td>21.19±11.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectus femoris</td>
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<tr>
<td>Initial contact</td>
<td>39.47±13.04</td>
<td>37.60±17.53</td>
<td>24.09±10.75</td>
<td>35.37±13.54</td>
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<td></td>
</tr>
<tr>
<td>Loading response</td>
<td>36.49±13.63</td>
<td>36.64±17.34</td>
<td>26.83±14.60</td>
<td>38.62±14.31</td>
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</tr>
<tr>
<td>Mid stance</td>
<td>30.48±16.22</td>
<td>24.84±17.75</td>
<td>22.57±13.77</td>
<td>23.99±8.56</td>
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<td>Terminal stance</td>
<td>22.79±13.00</td>
<td>18.82±14.00</td>
<td>17.39±10.22</td>
<td>19.55±9.65</td>
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<tr>
<td>Pre-swing</td>
<td>16.95±8.95</td>
<td>13.83±8.80</td>
<td>15.82±9.83</td>
<td>22.90±14.50</td>
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<td>Initial swing</td>
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<tr>
<td>Mid-swing</td>
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<td>14.46±10.41 (b)</td>
<td>17.18±14.61</td>
<td>24.84±12.91</td>
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<tr>
<td>Terminal swing</td>
<td>27.18±9.93</td>
<td>19.43±10.47</td>
<td>14.11±9.61</td>
<td>22.82±12.33</td>
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<tr>
<td>Hamstrings</td>
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<tr>
<td>Initial contact</td>
<td>32.83±17.47</td>
<td>44.77±20.29</td>
<td>23.25±14.16</td>
<td>30.05±21.03</td>
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<tr>
<td>Loading response</td>
<td>39.08±15.77</td>
<td>44.79±19.41</td>
<td>28.75±16.51</td>
<td>32.92±20.08</td>
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<tr>
<td>Mid-stance</td>
<td>31.05±19.58</td>
<td>37.75±14.63</td>
<td>27.70±17.58</td>
<td>26.23±19.30</td>
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<tr>
<td>Terminal stance</td>
<td>18.94±15.30</td>
<td>22.10±12.57</td>
<td>18.97±15.10</td>
<td>16.96±10.64</td>
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<td>Initial swing</td>
<td>8.79±6.84</td>
<td>14.79±11.42</td>
<td>11.40±8.02</td>
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<td>Terminal swing</td>
<td>20.90±13.66</td>
<td>31.94±13.94 (b)</td>
<td>16.12±8.27</td>
<td>22.64±14.02</td>
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<tr>
<td>Tibialis anterior</td>
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<td>Initial contact</td>
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<td>35.12±20.21</td>
<td>23.34±14.57</td>
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<td>21.53±12.58</td>
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<td>Mid-stance</td>
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<td>16.60±15.76</td>
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<tr>
<td>Pre-swing</td>
<td>17.13±10.76</td>
<td>24.95±18.00</td>
<td>16.88±13.15</td>
<td>22.99±15.25</td>
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<tr>
<td>Initial swing</td>
<td>23.45±13.44</td>
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<td>20.17±11.10</td>
<td>27.79±15.80</td>
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<tr>
<td>Mid-swing</td>
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<td>25.01±16.06</td>
<td>24.13±12.55</td>
<td>29.28±13.49</td>
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<tr>
<td>Terminal swing</td>
<td>20.40±11.22</td>
<td>24.20±13.73</td>
<td>20.98±9.74</td>
<td>25.03±14.60</td>
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<tr>
<td>Gastrocnemius</td>
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<tr>
<td>Initial contact</td>
<td>25.31±20.49</td>
<td>37.85±17.51 (b)</td>
<td>32.16±16.43</td>
<td>40.29±18.90</td>
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</tr>
<tr>
<td>Loading response</td>
<td>21.82±15.92</td>
<td>35.63±12.41 (b)</td>
<td>28.52±14.43</td>
<td>35.44±13.34</td>
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<tr>
<td>Mid-stance</td>
<td>23.34±18.07</td>
<td>35.63±12.42 (b)</td>
<td>29.41±18.14</td>
<td>30.40±10.99</td>
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</tr>
<tr>
<td>Terminal stance</td>
<td>29.92±21.87</td>
<td>35.63±12.43 (b)</td>
<td>27.07±17.66</td>
<td>21.43±11.02</td>
<td></td>
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<tr>
<td>Pre-swing</td>
<td>20.93±17.11</td>
<td>35.63±12.44</td>
<td>22.16±15.83</td>
<td>13.73±5.89</td>
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<tr>
<td>Initial swing</td>
<td>14.38±10.56</td>
<td>35.63±12.45 (b)</td>
<td>18.19±13.75</td>
<td>12.27±6.52</td>
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<tr>
<td>Terminal swing</td>
<td>18.86±12.92</td>
<td>35.63±12.47 (b)</td>
<td>20.17±10.19</td>
<td>24.70±11.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.

RAGT, robot-assisted gait training; CGT, conventional gait training.

(a)p<0.05, RAGT and CGT comparisons in unpaired t-tests; (b)p<0.05, pre- and post-training comparisons in paired t-test; and (c)p<0.05, pre- and post-training comparisons in Wilcoxon signed rank test.
GaitMaster had greater gait speed improvement than that in the CGT group. In this study, lower-limb muscle strength in the CGT group tended to be higher than that in the RAGT group at the beginning of the study, although this difference was not significant. However, it is possible that this difference in muscle strength could have influenced the increase in gait speed.

This study found that RAGT and CGT elicit muscle activities in different regions. This finding indicates that RAGT and CGT have different mechanisms of gait disorder recovery. Many previous RAGT studies have focused on improving gait ability; however, very few have focused on the mechanism of gait recovery. Therefore, future studies should examine the effects of RAGT from the aspect of gait recovery mechanisms.

This study has several limitations. First, the statistical power was low because of the small number of participants and analysis because of errors in EMG measurements. Second, the results are limited to RAGT using GaitMaster and therefore cannot be generalized to all robot gait devices, as many robot gait device types perform RAGT, and the mechanism for performing RAGT differs from one type to another. Therefore, future studies should generalize the effects of RAGT on muscle activity by increasing the number of participants and identifying differences in the results on muscle activity among robotic gait devices.

In conclusion, the results suggest that RAGT with GaitMaster is more effective than CGT in increasing muscle activity in the gastrocnemius muscle, which is involved in the propulsive force of the gait.

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

ACKNOWLEDGEMENTS
We thank the patients who participated in this study. In addition, we are very grateful to the rehabilitation staff at Hitachinaka General Hospital for their cooperation in data collection.

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Delirium After Traumatic Brain Injury: Prediction by Location and Size of Brain Lesion

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Department of Rehabilitation Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

Objective: To examine (1) the location of brain lesion that would predict post-traumatic delirium and (2) the association between volume of brain lesion and occurrence of delirium in patients with traumatic brain injury (TBI).

Methods: A retrospective study was conducted by reviewing medical records of 68 TBI patients, categorized into two groups: the delirious group (n=38) and non-delirious group (n=30). The location and volume of TBI were investigated with the 3D Slicer software.

Results: The TBI region in the delirious group mainly involved the frontal or temporal lobe (p=0.038). All 36 delirious patients had brain injury on the right side (p=0.046). The volume of hemorrhage in the delirious group was larger by about 95 mL compared to the non-delirious group, but this difference was not statistically significant (p=0.382).

Conclusion: Patients with delirium after TBI had significantly different injury site and side, but not lesion size compared to patients without delirium.

Keywords: Traumatic brain injury, Delirium, Intracranial hemorrhages

INTRODUCTION

Traumatic brain injury (TBI) is defined as an alteration in brain function and consciousness that results in physical and cognitive impairments caused by an external force [1]. TBI is now perceived as a global public health epidemic and is expected to become the world’s leading cause of neurological disability across all age groups, according to the World Health Organization. It has been reported that on average 1.7 million traumatic brain injuries occur annually in the United States, approximately 275,000 are on admission, 52,000 die, and approximately 76 billion dollars in annual costs arise directly or indirectly from TBI. It can lead to both short- and long-term cognitive functional decline, with a subsequent burden on patients and their relatives.

One of the common early cognitive dysfunction is post-traumatic delirium (PTD). Delirium is an acute disturbance of consciousness and cognition that can occur after a traumatic event such as TBI. Nakase-Thompson et al. [2] revealed delirium in 69.4% of patients with TBI. The cardinal features of delirium include a rapid onset or fluctuating course, inattention, disturbance in the sleep-wake cycle, disorientation, altered level of consciousness, disorganized thoughts with perceptual disturbances, and incoherent speech [3]. Currently, the evaluation of delirium in patients adheres to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classification, and its diagnostic criteria consist of manifestations such as sleep-wake cycle disturbance, abnormal motor behavior, lability of mood, perceptual disturbance, delusions, and hallucinations [4].
Despite the prevalence of TBI and the significant impact that delirium can have on patient outcomes, the association between the site or severity of brain lesions as a result of trauma and the PTD is not well understood. Delirium in TBI can be derived from several anatomical and functional disruptions, such as altered interregional connectivity among large-scale brain networks for higher cognitive functions, such as attention, emotional integration, and behavioral coherence [4]. Thus, structural brain changes after TBI, which result in cognitive and physical performance following injury, should be considered in the evaluation of PTD. However, there is a lack of research that has systematically explored the relationship between brain lesions and the development and progression of delirium in patients with TBI.

Therefore, this study aimed to determine the correlation between the location and size of brain lesions after TBI and the clinical course of PTD. The following hypotheses were considered: (1) the location of brain lesions would be predictive of diagnosing delirium and (2) the volume of brain lesions would be correlated with the degree of cognitive or physical dysfunction in delirious patients with TBI.

**METHODS**

**Subjects**

Medical records of patients with TBI admitted to the rehabilitation unit of Ewha Womans University Mokdong Hospital, Seoul, Korea from March 2011 to October 2021 were retrospectively collected. All included patients were older than 18 years and were diagnosed with intracranial hemorrhage after trauma using computerized tomography. The exclusion criteria were the presence of a history of previous stroke or brain injury and a disorder of dementia or mental illness that would confound delirium. We also excluded patients who were not eligible for estimating intellectual ability due to their remaining minimally conscious status. A total of 88 patients with TBI were recruited, and 68 patients who met the criteria were reviewed. The characteristics of these patients, such as age, sex, years of education, trauma type, and brain surgery, were evaluated.

Prior to the start of the study, ethical approval was obtained from a Institutional Review Board (IRB) of Ewha Womans University Mokdong Hospital, Seoul, Korea (IRB No. 2022-03-013) and informed consent was waived due to the retrospective nature of the medical record review. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association Declaration. It was performed in accordance with the approved guidelines.

**Clinical assessments**

In this retrospective study, the presence of delirium in patients with TBI was investigated from transfer to the rehabilitation unit until discharge. An experienced rehabilitation medicine physician evaluated the cases and sorted them into two groups based on the DSM-5 criteria: the delirious group and the non-delirious group. Additionally, in the delirious group, Delirium Rating Scale-Revised-98 (DRS-R-98) was used to assess delirium severity and track its progression, dependent on each TBI patient’s medical records including hospitalization course, nursing chart, application of physical restraint, and history of antipsychotics use. The DRS-R-98 non-cognitive (items 1–8) and cognitive (items 9–13) subscale scores were computed. Eight symptoms of the DRS-R-98, which belong to the non-cognitive domain, were sleep–wake cycle disturbance, perceptual disturbances and hallucinations, delusions, lability of affect, language, thought process abnormalities, motor agitation, and motor retardation. The five symptoms of the DRS-R-98 cognitive domain were orientation, attention, short-term memory, long-term memory, and visuospatial ability. The DRS-R-98 scale consisted of these 16 items, including three diagnostic item scores (e.g., temporal onset, physical disorder and fluctuation of symptom severity), and a maximum total scale score of 46, where each symptom ranged from 0 to 3, normal to severe, or the most disturbed behaviors [5].

The comparison between the delirious and non-delirious groups among patients with TBI was routinely performed using the Mini Mental State Exam (MMSE), Clinical Dementia Rating (CDR), Modified Barthel Index (MBI), to determine the cognitive and Medical Research Council (MRC)-sum score. These measures were used to determine the cognitive and physical functional outcomes of each group from transfer to discharge, based on trauma date. Two physical therapists with more than 5 years of experience evaluated the MMSE, CDR, and MBI. Four physical therapists with more than 5 years of experience evaluated the MRC-sum score. All enrolled patients underwent these examinations, and there was no missing data.

The location of traumatic brain lesions is divided into frontal, temporal, parietal, and occipital lesion derived from the brain's four basic lobes. And the volume of TBI were demarcated using the 3D Slicer software (Fig. 1). 3D Slicer is a free open-source software platform for biomedical research (http://www.slicer.org).
We measured intracranial hemorrhage volume with the 3D Slicer, which could count all pixels compromising the hemorrhage beyond the configuration of the hematoma, in comparison with the traditional planimetric method. Hemorrhage was automatically identified pixel-by-pixel in each slice after setting a threshold range of 50–100 Hounsfield units. In this manner, it went beyond the limits of the size-dependent and shape-dependent estimation errors of the Tada (ABC/2) formula. The validity of 3D Slicer has been demonstrated in other studies.

**Statistical analysis**
We performed statistical analysis using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA), using parametric methods. The distribution of continuous outcomes was evaluated using the Shapiro–Wilk test, while the Student's t-test or Mann–Whitney U-test were employed when necessary. Mean±standard deviation or median (1st quartile–3rd quartile) was reported for parametric and non-parametric data, respectively. The categorical data was expressed as frequency and percentage and the chi-square test was conducted to compare categorical variables. If the number of cells with an expected frequency of less than 5 was over 20%, we used Fisher’s exact test.

**RESULTS**
In this study, 68 patients with TBI were recruited. These patients were classified into two groups according to the DSM-5 criteria: the delirious group (n=38) and the non-delirious group (n=30). We found a statistically significant difference between the two groups in the TBI site and side (Table 1). Most TBI lesions in the frontal or temporal lobe revealed delirious features (p=0.038). Thirty-seven patients with delirious TBI had frontal or temporal lobe lesion, whereas 13 patients had non-delirious TBI lesions. In addition, all 36 delirious patients after TBI had brain injury on the right side (p=0.046). Six delirious patients had pure right-sided TBI, and 30 delirious patients had TBI on both sides. Meanwhile, in the non-delirious group, only two patients had right-sided TBI, 10 patients had it on left side, and 18 patients had injury on both sides. There were no statistical differences in age, sex, education, trauma type, brain surgical procedure, CDR, MBI, MMSE, and MRC-sum score between the two groups (Table 1).

The TBI volume in delirious group was expected to be...
Table 1. Comparison between the characteristics of delirious group and non-delirious group after TBI

<table>
<thead>
<tr>
<th></th>
<th>Delirious group (n=38)</th>
<th>Non-delirious group (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.84±10.98</td>
<td>66.82±13.48</td>
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</tr>
<tr>
<td>Age group</td>
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<td></td>
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<tr>
<td>&lt;65 yr</td>
<td>12 (31.6)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>26 (68.4)</td>
<td>20 (66.7)</td>
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</tr>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (76.3)</td>
<td>17 (56.7)</td>
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<tr>
<td>Female</td>
<td>9 (23.7)</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Education (yr)</td>
<td>10.41±4.38</td>
<td>10.67±3.74</td>
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<td>Trauma type</td>
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<td>Traffic accident</td>
<td>14 (36.8)</td>
<td>12 (40.0)</td>
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</tr>
<tr>
<td>Fall</td>
<td>17 (44.7)</td>
<td>12 (40.0)</td>
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<tr>
<td>Unknown</td>
<td>7 (18.5)</td>
<td>6 (20.0)</td>
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<tr>
<td>Surgical procedure</td>
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<tr>
<td>Brain surgery</td>
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<td>17 (56.7)</td>
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<td>No brain surgery</td>
<td>14 (36.8)</td>
<td>13 (43.3)</td>
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<td>TBI site</td>
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<td>Frontal lobe</td>
<td>20 (52.6)</td>
<td>7 (23.3)</td>
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<tr>
<td>Temporal</td>
<td>17 (44.7)</td>
<td>6 (20.0)</td>
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<tr>
<td>Parietal</td>
<td>3 (7.9)</td>
<td>8 (26.7)</td>
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<tr>
<td>Occipital</td>
<td>2 (5.3)</td>
<td>7 (23.3)</td>
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<tr>
<td>Others</td>
<td>4 (10.5)</td>
<td>2 (6.7)</td>
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<tr>
<td>TBI side</td>
<td>0.046*</td>
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<tr>
<td>Right</td>
<td>6 (15.8)</td>
<td>2 (6.7)</td>
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<tr>
<td>Left</td>
<td>2 (5.3)</td>
<td>10 (33.3)</td>
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<tr>
<td>Both</td>
<td>30 (78.9)</td>
<td>18 (60.0)</td>
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<tr>
<td>TBI volume (mL)</td>
<td>495.90±220.62</td>
<td>400.81±210.98</td>
<td>0.382</td>
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<td>Clinical Dementia Rating</td>
<td>2 (1–2)</td>
<td>1 (1–3)</td>
<td>0.421</td>
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<td>MBI score</td>
<td>38.66±22.40</td>
<td>40.44±28.69</td>
<td>0.779</td>
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<td>MMSE score</td>
<td>13.04±8.14</td>
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<tr>
<td>MRC-sum score</td>
<td>46.01±7.13</td>
<td>42.14±10.88</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation, number (%), or median (1st quartile–3rd quartile).
TBI, traumatic brain injury; MBI, Modified Barthel Index; MMSE, Mini Mental State Exam; MRC, Medical Research Council.
*p<0.05.

larger than that in non-delirious group. The TBI volume was 495.90±220.62 mL in the delirious group and 400.81±210.98 mL in the non-delirious group in brain computed tomography obtained within one day after trauma via 3D Slicer; the hemorrhage volume of the delirious group was larger by about 95 mL than that of the non-delirious group, but the relationship was not statistically significant (p=0.382; Table 1).

As brain hemorrhage resolved, there were statistically significant improvements in DRS-R-98 total, cognitive, and non-cognitive scores in delirious patients with TBI (p=0.014, 0.008, and 0.015, respectively; Table 2). Orientation, attention, and long-term memory were enhanced in the cognitive domain in delirious patients with TBI other than non-delirious patients with TBI from transfer until discharge, based on injury date (Table 2).

The medications used for delirium in the delirious patients with TBI included quetiapine (n=29), trazodone (n=8), risperidone (n=7), paroxetine (n=6), triazolam (n=4), lorazepam (n=5), peridol (n=2), alprazolam (n=2), and benzatropine (n=2). The most commonly used drug was quetiapine, with an average daily dose of 25.34 mg, and the second most commonly used drug was trazodone, with an average daily dose of 15.13 mg. On average, these two drugs were used for 45 days. The use of these drugs might have affected the clinical course of delirium in patients with TBI. There were no adverse or side effects reported during the administration period of antipsychotics in these patients.
Table 2. Comparison between the initial and follow-up DRS-R-98 scores in the delirious group after traumatic brain injury

<table>
<thead>
<tr>
<th></th>
<th>Delirious group (n=38)</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Initial score</td>
<td>Follow-up score</td>
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<tr>
<td>DRS-R-98</td>
<td></td>
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<tr>
<td>Total (n=38)</td>
<td>20.67±8.43</td>
<td>13.55±2.85</td>
</tr>
<tr>
<td>Cognitive</td>
<td>13.68±5.51</td>
<td>6.33±4.22</td>
</tr>
<tr>
<td>Non-cognitive</td>
<td>4.88±2.75</td>
<td>4.83±0.82</td>
</tr>
<tr>
<td>Cognitive domain</td>
<td></td>
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</tr>
<tr>
<td>Orientation</td>
<td>2.13±0.74</td>
<td>1.23±0.84</td>
</tr>
<tr>
<td>Attention</td>
<td>2.51±0.78</td>
<td>1.60±0.76</td>
</tr>
<tr>
<td>Short-term memory</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Long-term memory</td>
<td>2.43±0.52</td>
<td>1.72±1.60</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>2.10±1.39</td>
<td>1.83±1.02</td>
</tr>
<tr>
<td>Non-cognitive domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep–wake cycle disturbance</td>
<td>2.35±1.14</td>
<td>0.98±0.68</td>
</tr>
<tr>
<td>Perceptual disturbances</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Delusions</td>
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<td>0 (0–1)</td>
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<tr>
<td>Lability of affect</td>
<td>1 (1–2)</td>
<td>0 (0–2)</td>
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<tr>
<td>Thought process abnormalities</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Motor agitation</td>
<td>2 (1–3)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Motor retardation</td>
<td>0.38±0.88</td>
<td>0.25±0.41</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or median (1st quartile–3rd quartile).

*DRS-R-98, Delirium Rating Scale-Revised-98.
*p<0.05.

DISCUSSION

Understanding the pathophysiology of delirium in TBI is crucial for improving patient outcomes and reducing the burden of TBI on individuals and society as a whole. We found that damage to the frontal or temporal lobe was frequently found in delirious patients with TBI. The frontal lobe and limbic system are closely linked structures that are involved in attention, emotional regulation, and stress response. Limbic structures, such as the hippocampus, modulate attention and conscious awareness, which helps organisms maintain arousal [10,11]. The temporal lobe including hippocampus and parahippocampal gyrus have been implicated in awareness specifically with respect to operations supporting declarative memory [12]. Abnormalities in these areas can paint the clinical picture of a delirious patient: disturbance in attention and awareness with changed cognition or the development of perceptual disturbance [12,13]. The location of the brain injury could have a significant prognostic value in predicting delirium. Indeed, the delirious patients with TBI in this study had damage in orientation and attention, which improved as delirium resolves, as shown in the results of DRS-R-98.

Furthermore, delirious features were observed in patients with TBI, particularly in those with lesions in the right hemisphere. Previous studies have analyzed the odds ratio of delirium in patients with brain lesions, but these studies were mainly limited to patients with stroke rather than trauma. While there were more stroke patients who did not develop delirium among all stroke patients, patients with TBI had a higher rate of delirium, with more than half of them developing delirium in other studies [14]. This study is noteworthy because it specifically focused on patients with TBI, where delirium is common. According to our study outcomes, the presence of delirium in TBI is not related to age, sex, education, trauma type, brain surgery, or size of brain injury, but rather to the location and side of the brain injury. These clinical characteristics, including TBI volume, have not offered a plausible explanation for delirium in patients with traumatic brain hemorrhage, whereas the site of hemorrhage may provide an attractive explanation.

In TBI, focal hemorrhagic contusions have preference sights in the frontal and temporal lobes [15]. A study by van der Naalt et al. [16] suggests that twice as many lesions were seen in patients with restless and agitation, mainly localized in the frontotemporal region after head injury. These previous studies
investigated the delirious features of patients with TBI and the location of the TBI site, but they did not measure the TBI volume or differentiate the TBI side, unlike our study. Moreover, the delirious features were described using the Glasgow Coma Scale, which is a traditional tool to measure consciousness, rather than a screening tool for delirium. In contrast, our study examined the presence of delirium by using the DSM-5 criteria and evaluated the severity of delirium in patients with TBI in detail, using the DRS-R-98.

The susceptibility of certain anatomical regions to stroke or of certain types of neurological deficits to delirium has been reported in several studies and case reports. Previous studies have revealed that post-stroke delirium may correlate with issues in the right hemisphere, right frontal straight gyrus, or medial occipitotemporal lobe [14]. Specific brain structures involved in delirium are elucidated, like the prefrontal cortex, thalamus, and basal ganglia, especially in the non-dominant hemisphere [17]. Oldenbeuving et al. [18] suggested that post-stroke delirium is more frequent in patients with right hemispheric stroke than in those with left. Our study concluded that right-hemispheric TBI has a stronger association with delirium. Attention, the impairment of which is an important feature of delirium, is predominantly right hemisphere-dependent [19]. Identifying TBI lesion site and side could contribute to predicting a higher risk for delirium.

Existing studies have addressed delirium by measuring the volume of the remaining brain volume or intracerebral hematoma (ICH) volume. The ABC/2 formula has been widely used for volume assessment of ICH; nonetheless, it cannot analyze other types of intracranial hemorrhages, such as epidural hemorrhage, subdural hemorrhage, and subarachnoid hemorrhage, which are linked to the possibility of delirium in TBI. Furthermore, the ABC/2 formula is crude for irregularly shaped hematomas, and hematomas are often irregular rather than ellipsoid. Its accuracy decreases with large, irregular or lobar hematomas that are more likely to occur in traumatic conditions [7].

Accurate measurement of hemorrhage volume is a chief concern since hematoma volume alters treatment strategy, functional outcome, and mortality. In our study, various hemorrhage types and volumes were included and calculated using radiologic 3D Slicer, which is different from other studies. Other studies have reported no significant difference between hematoma volumes in ever-delirious and never-delirious patients [11,20]. A study reported that delirious patients had an ICH volume approximately twice that of non-delirious patients [21]. However, the above-mentioned studies merely dealt with ICH and did not consider other types of intracranial hematomas. Our study suggests that the degree of hematoma volume, including all types of cerebral hemorrhage, is independent of delirious symptoms.

If delirium is present, it is difficult to proceed with rehabilitation treatment and TBI patients with delirium are often excluded from rehabilitation treatment. In this study, orientation, attention, and long-term memory were enhanced in the cognitive domain in delirious patients with TBI other than non-delirious patients with TBI. All patients included in this study underwent rehabilitation treatment. In previous study, delirium and physical function are closely related, since disability, immobility and declined function are identified as risk factors of delirium [22]. In this study, the improvement in cognition of TBI patients with delirium could be the effect of active rehabilitation treatment. Therefore, it would be helpful to include TBI patients with delirium in active rehabilitation to improve prognosis.

Limitations
We have several limitations in this study. First, our study results cannot be generalized to all patients with TBI because the study population was derived from a single ward that met the selection criteria. Second, there were variations in the risk factors for delirium such as alcohol use, comorbidities, hospital length of stay, that were not included. Therefore, further study with a larger sample size or a longer period of survey is recommended to understand the pathophysiology of PTD. Due to its retrospective manner, this study lacked various evaluation tools.

In conclusion, patients with TBI developed delirium, most of whom had frontal or temporal lobe lesion and right-sided brain injury. Compared with non-delirious group, the delirious group after TBI had significantly different injury site and side without a difference in lesion size. The findings of this study have the potential to improve understanding of the pathophysiology of delirium in TBI. In this study, orientation, attention, and long-term memory were enhanced in the cognitive domain in delirious patients with TBI other than non-delirious patients with TBI. Therefore, it would be helpful to include patients with PTD in active rehabilitation to improve prognosis.

CONFLICTS OF INTEREST
No potential conflict of interest relevant to this article was reported.
FUNDING INFORMATION

None.

AUTHOR CONTRIBUTION

Conceptualization: Han SJ, Suh JH, Kim SJ, Lee JY. Methodology: Han SJ, Suh JH, Kim SJ, Lee JY. Formal analysis: Han SJ, Suh JH, Kim SJ. Project administration: Han SJ. Visualization: Kim SJ. Writing – original draft: Kim SJ. Writing – review and editing: Han SJ, Lee JY, Suh JH. Approval of final manuscript: all authors.

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REFERENCES


INTRODUCTION

Pes planus (flatfoot) and pes cavus (high-arched foot) are types of foot deformity that may cause foot or ankle injury [1]. Patients with pes planus have a collapse of the medial longitudinal arch, foot abduction at the talonavicular joint, and hindfoot valgus. By contrast, patients with pes cavus have a midfoot cavius, prominence of lateral midfoot, forefoot adduction, and hindfoot varus. Patient symptoms include foot or ankle pain, foot or ankle deformity, gait instability, and frequent falling etc [2,3].

Pes planus and pes cavus are usually diagnosed by physical examination, radiographic evaluation, and footprint measurement.
Patients were referred to the orthotic and prosthetic clinic, by individual physicians. The physical examinations include a medial longitudinal arch height measurement, foot-ankle alignment especially forefoot abduction angle and heel angle measurements [1,4,5]. The radiographic evaluation includes measurements of lateral talo-first metatarsal angle, a talocalcaneal angle, a calcaneal pitch, and a metatarsus adduction angle [4-6]. Among these, a lateral talo-first metatarsal angle defined by Meary, is the most widely used for pes planus and pes cavus evaluation using a weight-bearing lateral radiograph [7]. The talo-first metatarsal angle is highly sensitive and specific to describe the arch of the foot [4,8]. However, radiographic measurement needs an experienced physician for interpretation.

Footprint measurement can include the Harris imprint index (HII), Chippaux-Smirak index (CSI), Staehli index (SI), Clarke’s angle, footprint index, arch index, length index, and truncated arch index. The HII, CSI, and SI measure a distance or calculate a distance ratio by using a simple measuring instrument such as a vernier caliper [5,9-11].

In the orthotic and prosthetic clinic, rehabilitation department, Thammasat University Hospital, the rehabilitation physician and the orthotist usually use physical examination and the footprint measurement to diagnose pes planus and pes cavus. The footprint measurements for HII, CSI, and SI are frequently performed in our clinic because of ease-of-use, rapidity, low cost and low tech in terms of instruments [12]. Furthermore, the footprint shows not only a foot shape but also reveals a high-pressure area of the foot that is useful in making a customized foot orthosis. However, a foot shape determined from the footprint measurement sometimes does not relate with the patient’s symptoms or radiographic evaluation. Therefore, this study aims to determine the diagnostic accuracy and reliability of the footprint measurements expressed as HII, CSI, and SI compared with the radiographic measurement of the talo-first metatarsal angle for screening the arch of the foot.

### METHODS

This retrospective study was approved by the Human Research Ethics Committee of Thammasat University (Medicine) (approval number: MTU-EC-RM-2-205/63), on October 17, 2020 and registered in the Thai Clinical Trials Registry (TCTR 202209190003).

#### Participants

Patients were referred to the orthotic and prosthetic clinic, rehabilitation department, Thammasat University Hospital between January 1, 2016 and August 31, 2020. Data was collected from the medical record. Inclusion criteria were (1) age between 18–80 years and (2) the footprint measurement and the radiographic evaluation in lateral foot weight-bearing position were recorded. Patients with history of fracture and/or surgery in ankle and foot were excluded.

Data from all patients who had undergone the footprint measurement and the radiographic evaluation in lateral foot weight-bearing position was recruited and dedicated to this study.

#### Test methods

The reference method used the talo-first metatarsal angle in lateral foot weight-bearing radiograph. This angle has been used to identify the foot deformity in patients with pes planus and pes cavus. The talo-first metatarsal angle is formed between a line drawn along the longitudinal axis of the talus and the first metatarsal bone (Fig. 1A). The arch of foot is classified as pes cavus when convex upward angle >4 degrees, a normal arched foot has convex upward to downward angle within 4 degrees, and pes planus has convex downward angle >4 degrees [7,13]. The talo-first metatarsal angle compared with symptoms of the patient shows sensitivity and specificity of 88% and 94% respectively in pes cavus, and 100% and 87% respectively in pes planus [14]. This angle has a good intra-observer reliability (intraclass correlation coefficient [ICC]=0.96) and inter-observer reliability (ICC=0.69) [8]. The talo-first metatarsal angle in radiograph was measured at a single time using a goniometer by the one experienced foot and ankle orthopaedist who blinded for the clinical diagnosis.

The footprints were performed by the Harris mat footprint method and documented in the medical record. The 3 index tests of HII, CSI, and SI were conducted with computer-assisted program. (1) The HII measured a distance from the origin of two perpendicular lines in centimeter. The y-axis is a midline foot axis from tip of 2nd toe to the midpoint of hindfoot and the x-axis is a perpendicular line drawn medially and laterally at the widest and narrowest point of the arch (Fig. 1B). HII score is based on distance from the origin of the x-axis where the lateral side of arch is negative and medial side of arch is positive. HII score defined as pes cavus is (-4, -3, -2), normal arched foot is (-1, 0, +1), and pes planus is (+2, +3, +4) [5,9]. (2) The CSI is the ratio between the narrowest width of the midfoot (line b) to the widest width of the forefoot (line a) (CSI=b/ a×100; Fig.
CSI≤24% is classified as pes cavus, 25% to 45% as normal arched foot and ≥46% as pes planus [9]. (3) The SI is the ratio between the narrowest width of the midfoot (line b) to the widest width of the hindfoot (line c) (SI=b/c; Fig. 1C). SI≤0.4 is categorized as pes cavus, 0.5–0.7 normal arched foot and ≥0.8 as pes planus [9,15]. All 3 index tests were measured two times with an interval of 2 weeks to determine the intra-observer reliability by the rehabilitation physician. Furthermore, the orthotist who blinded to the results of the other tests measured the index tests at one time to calculate the inter-observer reliability.

**Statistical methods**

Categorical data is presented as frequency and percentages. Continuous data is presented as mean, median, standard deviation, and minimal-maximal values dependent on nature of data. The sensitivity, specificity, likelihood ratio of a positive test and a negative test (LR+, LR-), positive and negative predictive values (PPV, NPV), and the area under the receiver operating characteristic curve (AUROC) with 95% confidence interval (95% CI) of the index tests were calculated by 2×2 table. The intra-observer and inter-observer reliability were determined by Cohen’s Kappa [16]. The data was analyzed via STATA version 15.1 (Stata, College Station, TX, USA).

**RESULTS**

One hundred and ninety-eight patients with 274 feet were included. The average age was 60.7±14.5 years. Female and male were 79.3% and 20.7% (Table 1). Foot type classified by radiographic evaluation and footprint measurements were divided into pes planus, normal arched foot, and pes cavus (Fig. 2).

The diagnostic accuracy of HII, CSI, and SI compared to talar-first metatarsal angle for pes planus diagnosis is shown in Table 2. The frequency of pes planus was 82.8%. Table 3 shows the diagnostic accuracy of HII, CSI, and SI compared to talar-first metatarsal angle for pes cavus diagnosis. The frequency of pes cavus was 4.7%.

In pes planus, the intra-observer reliability of HII, CSI, and SI shown by Cohen's Kappa were 0.92, 0.97, and 0.93, respectively. In addition, the inter-observer reliability of HII, CSI, and SI were 0.82, 0.85, and 0.70, respectively. In pes cavus, the intra-observer reliability of HII, CSI, and SI shown by Cohen's Kappa were 0.89, 0.95, and 0.79, respectively, and the inter-observer reliability of HII, CSI, and SI were 0.76, 0.77, and 0.66, respectively (Table 4).

**DISCUSSION**

The diagnostic accuracy of the footprint showed that CSI was the most accurate in pes planus prediction, followed by HII and SI (AUROC=0.73, 0.68, 0.68, respectively). In pes cavus prediction, HII was the most accurate, followed by SI and CSI.
Fig. 2. Foot type classified by radiographic evaluation and footprint measurement (%).

Table 2. The diagnostic accuracy of HII, CSI, and SI for pes planus

<table>
<thead>
<tr>
<th>Footprint</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HII</td>
<td>0.68 (0.64–0.71)</td>
<td>37.4% (31.1–44.1)</td>
<td>97.9% (88.7–99.9)</td>
<td>17.6 (2.5–123.2)</td>
<td>0.6 (0.6–0.7)</td>
<td>98.8% (93.7–100.0)</td>
<td>24.5% (18.5–31.3)</td>
</tr>
<tr>
<td>CSI</td>
<td>0.73 (0.69–0.77)</td>
<td>47.6% (40.9–54.3)</td>
<td>97.9% (88.7–99.9)</td>
<td>22.4 (3.2–156.2)</td>
<td>0.5 (0.5–0.6)</td>
<td>99.1% (95.0–100.0)</td>
<td>27.9% (21.2–35.4)</td>
</tr>
<tr>
<td>SI</td>
<td>0.68 (0.61–0.75)</td>
<td>61.7% (55.0–68.0)</td>
<td>74.5% (59.7–86.1)</td>
<td>2.4 (1.5–3.9)</td>
<td>0.5 (0.4–0.7)</td>
<td>92.1% (86.6–95.9)</td>
<td>28.7% (20.9–37.6)</td>
</tr>
</tbody>
</table>

At frequency 82.8%.

HII, Harris imprint index; CSI, Chippaux-Smirak index; SI, Staheli index; AUROC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; LR+, likelihood ratio of a positive test; LR-, likelihood ratio of a negative test; PPV, positive predictive value; NPV, negative predictive value.

Table 3. The diagnostic accuracy of HII, CSI, and SI for pes cavus

<table>
<thead>
<tr>
<th>Footprint</th>
<th>AUROC (95% CI)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
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<tbody>
<tr>
<td>HII</td>
<td>0.71 (0.57–0.85)</td>
<td>61.5% (31.6–86.1)</td>
<td>80.8% (75.5–85.4)</td>
<td>3.2 (1.9–5.3)</td>
<td>0.5 (0.2–0.9)</td>
<td>13.8% (6.1–25.4)</td>
<td>97.7% (94.7–99.2)</td>
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<tr>
<td>CSI</td>
<td>0.60 (0.48–0.72)</td>
<td>23.1% (5.0–53.8)</td>
<td>96.9% (94.1–98.7)</td>
<td>7.5 (2.3–25.1)</td>
<td>0.8 (0.6–1.1)</td>
<td>27.3% (6.0–61.0)</td>
<td>96.2% (93.1–98.2)</td>
</tr>
<tr>
<td>SI</td>
<td>0.61 (0.49–0.73)</td>
<td>23.1% (5.0–53.8)</td>
<td>98.1% (95.6–99.4)</td>
<td>12.1 (3.2–45.0)</td>
<td>0.8 (0.6–1.1)</td>
<td>37.5% (8.5–75.5)</td>
<td>96.2% (93.2–98.2)</td>
</tr>
</tbody>
</table>

At frequency 4.7%.

HII, Harris imprint index; CSI, Chippaux-Smirak index; SI, Staheli index; AUROC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; LR+, likelihood ratio of a positive test; LR-, likelihood ratio of a negative test; PPV, positive predictive value; NPV, negative predictive value.

(AUROC=0.71, 0.61, 0.60, respectively). For pes planus, the intra-observer reliability was almost perfect by Cohen’s Kappa (HII=0.92, CSI=0.97, SI=0.93) and the inter-observer reliability was moderate to strong (HII=0.82, CSI=0.85, SI=0.70). For pes cavus, the intra-observer reliability was moderate to almost perfect (HII=0.89, CSI=0.95, SI=0.79) and the inter-observer reliability was moderate (HII=0.76, CSI=0.77, SI=0.66).

The diagnostic accuracy of HII shows an overall useful test by AUROC (0.68 in pes planus and 0.71 in pes cavus). HII displayed low sensitivity but high specificity in diagnosis of both pes planus and pes cavus. Previous research showed HII has a medium correlation with the talar-first metatarsal angle.
Overweightness and excessive calcaneal prominence of lateral midfoot in pes cavus may increase the narrowest width of the midfoot distance to the point that CSI might not be in pes cavus range in a similar way as y-axis of HII. The HII revealed (1) almost perfect intra-observer reliability and strong inter-observer reliability in pes planus, and (2) strong intra-observer reliability and moderate inter-observer reliability in pes cavus. The rehabilitation physician and the orthotist returned differing measurements of the hollowed arch, and that may be the reason for moderate inter-observer reliability.

The diagnostic accuracy of CSI showed an overall useful test by AUROC (0.73 in pes planus and 0.60 in pes cavus). The CSI displayed low sensitivity but high specificity in diagnosis both pes planus and pes cavus. Previous research found CSI compared with pes planus symptoms showed high sensitivity (94.2%) but low specificity (56.1%) [6], confirming that correlation between CSI and pes planus condition was high (r=−0.663) [4]. In addition, CSI was influenced by obesity and calcaneal alignment [17,18]. CSI measures the ratio of the narrowest width of the midfoot to the widest width of the forefoot. The prominence of lateral midfoot in pes cavus may increase the narrowest width of the midfoot distance to the point that CSI might not be in a pes cavus range [2]. This CSI revealed (1) almost perfect intra-observer reliability and strong inter-observer reliability in pes planus, and (2) almost perfect intra-observer reliability and moderate inter-observer reliability in pes cavus. Previous work in pes planus revealed excellent intra-observer and inter-observer reliability by ICC (>0.9) [19,20]. Measurement of the narrowest width of the midfoot point returned unequal distances between rehabilitation physician and orthotist which may possibly have caused moderate inter-observer reliability.

The diagnostic accuracy of SI shows an overall useful test by AUROC (0.68 in pes planus and 0.61 in pes cavus). The sensitivity (61.7%) and specificity (74.5%) of SI for pes planus (cut point≥0.8) are close to that of Plumarom et al. [21] (sensitivity=70.2%, specificity=73%, cut point≥0.77). Nevertheless, the work of Pita-Fernández et al. [6] showed high sensitivity (81.8%) but low specificity (58.7%) in relation to pes planus symptom, probably because the correlation between SI and pes planus symptom was high (r=−0.662) [4]. Overweightness and excessive foot soft tissue may likely cause a false positive pes planus symptom [21]. In contrast, this study shows SI in pes cavus to have low sensitivity but high specificity. SI measures the ratio of the narrowest width of the midfoot to the widest width of the hindfoot. The prominence of lateral midfoot in pes cavus may increase the narrowest width of the midfoot distance to the point that SI might not be in pes cavus range in a similar way to CSI [2]. This SI reveals (1) almost perfect intra-observer reliability and moderate inter-observer reliability in pes planus, and (2) moderate intra-observer reliability and inter-observer reliability in pes cavus. The previous studies in pes planus revealed excellent intra-observer and inter-observer reliability (ICC>0.9) [19,20]. The rehabilitation physician and orthotist returned unequal measurements of the narrowest width of the midfoot which may possibly have caused moderate inter-observer reliability.

There are several limitations to this study. First, this study was a retrospective study in which the prevalence of pes planus and pes cavus were unequal. Second, some patients were excluded because the footprint or radiographic evaluation were not done. Future studies will be designed in a prospective study and will attempt to recruit every patient passing through the clinic.

In conclusion, the accuracy of the HII, CSI, and SI was fair in screening of pes planus and pes cavus. The intra- and inter-observer reliability of the three footprints were in the moderate to almost perfect range by Cohen’s Kappa.

**CONFLICTS OF INTEREST**

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

Conceptualization: Paecharoen S. Methodology: Paecharoen S, Arunakul M, Tantivangphaisal N. Formal analysis: Paecharoen S. Funding acquisition: Paecharoen S, Arunakul M, Tantivangphaisal N. Project administration: Paecharoen S. Visualization: Paecharoen S. Writing – original draft: Paecharoen S. Writing – review and editing: Paecharoen S, Arunakul M. Approval of final manuscript: all authors.

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Correction: Reliability and Validity of the Korean Version of the Duchenne Muscular Dystrophy Functional Ability Self-Assessment Tool

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

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After publication of the article, we found one sentence was published incorrectly in the Appendix 3 section.

Before correction:


<table>
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<th>Task</th>
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<th>Option 3</th>
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*Current affiliation: Hye Min Ji (Department of Physical Medicine and Rehabilitation, Veterans Health Service Medical Center, Seoul, Korea)
The original article has been modified also.
We sincerely apologize for any confusions that we may have caused.
Instructions for authors

Enacted in May, 2011
Revised on January 31, 2013
Revised on August 1, 2018
Revised on Mar 11, 2019
Revised on Mar 16, 2020

1. AIMS & SCOPE

Annals of Rehabilitation Medicine (ARM) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, nearly 8,000 physiatrists receive this journal every two months as a member benefit. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM). International members comprise approximately half the editorial board and conduct peer-review of submitted manuscripts.

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

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1) CATEGORIES OF MANUSCRIPTS

Manuscripts include original articles, review articles, brief reports, case reports, images in this issue, and letters to the editor.

(1) Original articles
This form of publication represents original research articles reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers.

(2) Review articles
Invited review articles provide a comprehensive review of a subject of importance to clinicians and researchers and are commissioned by the editorial board to an invited expert in the field.

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These manuscripts are short but important reports to provide preliminary communications with less complete data sets than would be appropriate for original contributions that present novel and impactful clinical and basic research of a more preliminary nature.

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Case reports are considered for publication when at least one of the following criteria is met: (a) a rare condition is reported, (b) atypical symptoms and signs are observed, (c) new diagnostic or therapeutic methods are introduced, (d) atypical clinical and lab-
4. RESEARCH AND PUBLICATION ETHICS

All manuscripts should be written with strict adherence to the “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (http://www.icmje.org/recommendations/; updated December 2019) and the “Good Publication Practice Guidelines for Medical Journals, 3rd” (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13&per_page=). For all studies involving human subjects, the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) should be upheld, informed consent must be obtained from all participants, and must be approved by a recognized Institutional Review Board (IRB) or research ethics committee. The editor may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. Experiments involving animals should comply with the NIH guidelines for the use of laboratory animals (https://www.nlm.nih.gov/services/research_report_guide.html) and/or be reviewed by an appropriate committee (e.g., Institutional Animal Care and Use Committee, IACUC) to ensure the ethical treatment of animals in research. ARM will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org/) for settlement of any misconduct.

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ARM follows the “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” (http://www.icmje.org/recommendations/; updated December 2019) and the “Good Publication Practice Guidelines for Medical Journals, 3rd” (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13&per_page=). Authorship is credited to those who have direct involvement in the study and have made significant contributions to (a) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (b) drafting the work or revising it critically for important intellectual content; AND (c) final approval of the version to be published; AND (d) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved as recommended by ICMJE. The primary investigator is designated the first author of the study, unless contested by the other authors. The corresponding author is directly responsible for communication and revision of the submitted manuscript. All persons who have made substan-
tional contribution, but who are not eligible as authors should be named in the acknowledgments. In the case of change of authorship, a written explanation must be submitted. Change in either the first author or the corresponding author requires approval by the editorial board, and any changes in the other authors require approval by the editor-in-chief.

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All submissions are made online at the journal’s online manuscript submission site (http://www.e-arm.org/submission) by the corresponding author. Submitted manuscripts are initially examined for format, and then appointed a submission number. For nonbiased peer review, authors’ names and institutional affiliations should not be mentioned in the text. The revised manuscript should be submitted through the same web system under the same identification numbers. The date of final review for the manuscript will be the date of acceptance for publication. If you have any questions about the online submission process, contact the Editorial Office by e-mail at edit@e-arm.org.

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1) DESK REJECT POLICY
Conformity of the submitted manuscript to the submission instructions is examined upon submission. The Editorial Board may reject the manuscript or request the author to resubmit in the following cases: 1) Topic clearly out of scope / insufficient perceptual content 2) Work clearly does not meet sufficient standards of novelty or quality 3) Manuscript incomplete or incorrectly formatted 4) Suspected plagiarism in the manuscript.

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Submitted manuscripts will be reviewed by two or more peer reviewers selected from the board’s database of expert reviewers. In addition, if deemed necessary, a review of statistics may be requested. Following review, the editorial board will decide whether the manuscript will be 1) accepted for publication, 2) subject to minor revision, 3) subject to major revision, or 4) denied publication. For manuscripts which are either subject to minor revision or subject to major revision, the corresponding author must resubmit the revised manuscript online. The revised manuscript should have the changes highlighted by using the Track Changes tool in Microsoft Office Word. In addition, the corresponding author must reply to both reviewers’ comments point by point, and explain in detail what changes were made in the manuscript. When considered necessary, the editorial board may make changes to the structure and phrases of the manuscript without compromising the integrity of the original paper. After completion of the peer review process, the editorial board will determine acceptance for publication and notify the corresponding author by e-mail. Manuscripts which do not comply with the present guidelines will be notified for correction or withheld from publication. 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.

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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, 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. All the words in the title should be in capital letters except for prepositions, articles, and conjunctions. Provide a short running title containing less than 10 words.

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Original papers should be structured in the following order: Abstract, Introduction, Methods, Results, Discussion, 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).

(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, city (state), and country in parentheses, e.g., Flow Cytometer (Coulter Electronic Inc., New York, NY, USA). 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.

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) 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.

(7) 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].
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Journals

Book & Chapter of book
4. Esquenazi A. Upper limb amputee rehabilitation and prosthetic

Proceedings of academic conference

Thesis (Dissertation)

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

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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.

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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.

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