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REVIEW

Effects of Physical Agents on Muscle Healing with a Focus on Animal Model Research

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ABSTRACT. Skeletal muscle injury is caused by a variety of events, such as muscle laceration, contusions, or strain. Muscle fibers respond to minor damage with immediate repair mechanisms that reseal the cell membrane. On the other hand, repair of irreversibly damaged fibers is achieved by activation of muscle precursor cells. Muscle repair is not always perfect, especially after severe damage, and can lead to excessive fibroblast proliferation that results in the formation of scar tissue within muscle fibers. Remaining scar tissue can impair joint movement, reduce muscular strength, and inhibit exercise ability; therefore, to restore muscle function, minimizing the extent of injury and promoting muscle regeneration are necessary. Various physical agents, such as cold, thermal, electrical stimulation, and low-intensity pulsed ultrasound therapy, have been reported as treatments for muscle healing. Although approaches based on the muscle regeneration process have been under development, the most efficacious physiological treatment for muscle injury remains unclear. In this review, the influence of these physical agents on muscle injury is described with a focus on research using animal models.

Key words: Muscle injury, Muscle regeneration, Physical agents

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Skeletal muscle injury is caused by a variety of events, such as muscle laceration, contusions, or strain[1]. Muscle injuries are one of the most common injuries in relation to sports[2]. Muscle fibers respond to minor damage by utilizing limited immediate repair mechanisms to reseal the cell membrane. On the other hand, repair and replacement of irreversibly damaged fibers is achieved by activating muscle precursor cells that are predetermined to differentiate into skeletal muscle[3,4]. Satellite cells are the major source of myogenic cells in adult skeletal muscle. They are located between the plasma and basement membranes of muscle fibers[5] and play a key role in muscle repair[6]. Satellite cells are normally quiescent in undamaged adult muscle, only being activated in response to injury. When activated, these cells can proliferate, move to the area of damage, and fuse with preexisting fibers and the surviving segments of damaged fibers. However, muscle repair does not always perfectly align the surviving fiber stump with the newly forming repair segment, and thus, many fibers can become branched after regeneration[4], especially after severe or extensive damage, such as deep wounds, leading to the excessive proliferation of fibroblasts and the formation of scar tissue within muscle fibers. Scar tissue exhibits no contractile function and has low extensibility; therefore, remaining scar tissue can impair joint movement, reduce muscular strength, and inhibit exercise ability[7]. For these reasons, minimizing the extent of injury and promoting muscle regeneration is necessary to restore muscle function.

Skeletal muscle regeneration is stimulated by muscle injury, after which, it undergoes sequential phases of degeneration, inflammation, regeneration, and the formation of new myofibers or fibrosis[1,8] (Table 1). The inflammatory response is essential to the effective repair of tissue, and the inhibition of these events inhibits the repair phases that follow[9,10]. Therefore, to apply optimal physical agents, it is necessary to understand the muscle regeneration process. In the case of pharmacological treatments, anti-inflammatory drugs, growth factors, and fibrosis inhibitors are prescribed as appropriate in accordance with the healing process[1,11]. Regarding physiotherapy interventions, various physical

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Table 1. Phases of skeletal muscle healing[8].

Healing phase	Changes within the muscle
Degeneration/inflammation phase	Characterized by rupture and necrosis of myofibers, formation of a hematoma, and important inflammatory reactions
Regeneration phase	Phagocytosis of damaged tissue, followed by myofiber regeneration, leading to satellite cell activation
Remodeling phase	Maturation of regenerated myofibers with recovery of muscle functional capacity, fibrosis, and scar tissue formation

agents, including cold, thermal, electrical stimulation, and low-intensity pulsed ultrasound therapy (LIPUS), have been used as treatments for muscle healing. The purposes of applying physical agents are to diminish pain following injury and to accelerate muscle healing. In this review, the influence of these physical agents on muscle injury is described with a focus on research using animal models.

Cryotherapy

Cryotherapy, defined as the use of cold modalities, such as icing, cold packs, and cold water immersion, is widely applied as a treatment in the acute phase of muscle injury. The physiological responses to cryotherapy include decreased blood flow, tissue metabolism, and nerve conduction velocity, which diminish bleeding and acute inflammation symptoms[12,13] such as swelling[14] and pain[15-17]. Ischemia due to bleeding and increased enzyme activity following the primary injury can cause additional damage to uninjured tissues around the injury site, which are referred to as secondary injuries. Cryotherapy suppresses secondary injuries because it reduces local metabolism and cellular energy demands for surviving tissues[18,19], and is therefore considered valuable in minimizing the extent of muscle damage.

While cryotherapy has been reported to exert a beneficial effect for posttraumatic symptoms, it has also been shown to retard muscle regeneration (Table 2). Takagi et al.[20] showed that ice applied immediately after a muscle crush injury can retard muscle regeneration and induce collagen deposition. They also found that the expression of both transforming growth factor (TGF)-β1 and insulin-like growth factor-1 was retarded in the icing group, which suggested that these growth factors, which were produced by macrophages, regulated the proliferation and differentiation of satellite cells and collagen synthesis, thereby indicating that icing delayed muscle regeneration. Shibaguchi et al.[21] investigated the effects of icing after bupivacaine-induced muscle injury. Their results also showed an increasing collagen area, which might be related to the delay in the timing of the inhibited expression of TGF-β during regeneration. Ito et al.[22] also investigated the effects of cryotherapy using a cardiotoxin-induced muscle injury model. They found that the wet weight of regenerated muscle and the cross-sectional area of myofibers were decreased after cryotherapy. Cryotherapy applied immediately after injury inhibited the accumulation of macrophages in the inflammatory process[20,23]. As inflammatory cells play essential roles in regulating the muscle repair response and development of fibrosis after muscle injury[9,10,24]; if these inflammatory events are impaired by cryotherapy, muscle regeneration is also affected.

On the other hand, it has been reported that cryotherapy inhibits the inflammatory process without changing the expression of myogenic regulatory factors, such as desmin and myoD, or collagen deposition[13]. Singh et al.[25] demonstrated that icing attenuated or delayed the infiltration of inflammatory cells and the expression of proangiogenic factors in regenerating muscle. Despite these differences, no significant differences were observed in the capillary density or myofiber cross-sectional area between the icing and no icing groups. Ikezaki et al.[26] investigated the effects of icing on the muscle regeneration process, including molecules related to pain, and found that icing was effective for alleviating muscle soreness; however, icing had no influence on histological features, such as the cross-sectional area of regenerated muscle fibers or the ratio of central nucleated fibers. Cryotherapy is generally used in the acute phase of muscle injury to alleviate inflammatory symptoms and secondary injuries. However, the results of studies investigating the effectiveness of cryotherapy on muscle regeneration have been inconsistent, as described above, which suggests that cryotherapy should be administered after muscle injury only after careful consideration.

Thermal Therapy

Several thermal modalities are available for heat application to tissues. Thermal therapy is categorized into superficial heating, such as hot packs, warm whirlpool and paraffin, and deep heating, such as continued ultrasound and diathermy. The physiological effects of elevating tissue temperature results in an increase in blood flow to the area, attributable in part to the vasodilatory response in surface blood vessels. In addition, increasing tissue temperature is associated with an increasing metabolic rate[27]. Based on these responses, heat stress appears to play a beneficial role in wound healing after the acute phase as a result of in-

Table 2. Studies on cold therapy for muscle injury in animal models.

Reference	Injury type	Method of cryotherapy	Timing of cryotherapy	Effects in the cryotherapy compared with the injured without cryotherapy group
Ramos et al.[13]	Freezing injury	Ice pack (plastic bag filled with crushed ice) 3 sessions of 30 min, 2 h apart	Immediately after injury, 24 h and 48 h after injury	Decreased macrophage infiltration and accumulation of TNF-α, NF-κB, and TGF-β No influence injury area, expression of desmin and MyoD, and collagen I and III protein levels.
Takagi et al.[20]	Crush injury	Ice pack, 0.3~1.3 °C (plastic bag filled with crushed ice) 20 min	5 min after injury	Retarded number of macrophages and immunohistochemical expression of TGF-β1 and IGF-I Decreased muscle fiber cross-sectional area Increased collagen fiber area
Shibaguchi et al.[21]	Bupivacaine-induced muscle injury	Ice pack, 0 °C 20 min	Immediately after injury	Delayed the timing of disappearance of TGF-β Increased collagen deposition
Ito et al.[22]	Cardiotoxin-induced muscle injury	Ice-cold water 20 min	IE group: 1 h after injury ID group: 8 days after injury	IE group: decreased muscle wet weight and muscle fiber cross-sectional area ID group: no influence of muscle wet weight and muscle fiber cross-sectional area
Miyakawa et al.[23]	Crush injury	Ice pack, 0.3~1.3 °C (plastic bag filled with crushed ice) 20 min	5 min after injury	Inhibited accumulation of macrophages. Delayed neutrophil and monocyte chemoattractant protein-1 + cells.
Singh et al.[25]	Contusion injury	Icing 20 min	5 min after injury	Attenuated and/or delayed neutrophil and macrophage infiltration, expression of vWF, VEGF, and nestin No influence on capillary density or muscle fiber cross-sectional area
Ikezaki et al.[26]	Bupivacaine-induced muscle injury	Ice pack, 0 °C 20 min	Immediately or 3 days after injury	No influence on muscle fiber cross-sectional area Decreased expression of myoD and BKB2 receptor mRNA

TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TGF-β, transforming growth factor-β; IGF-1, insulin growth factor-1, factor; vWF, von Willebrand factor; VEGF, vascular endothelial growth factor; BKB2 receptor, Bradykinin B2 receptor; IE group, icing at early stage of muscle injury group; ID group, icing at delayed stage of muscle injury group.

creased blood flow, which improves wound and periwound tissue perfusion and increases both oxygen and wound oxygen tension[27]. In addition, thermal therapy is generally contraindicated in acute phase injuries because heat stimulation increases the inflammation response and metabolic rate excessively, and can aggravate secondary injuries. However, heat stress has also been reported to exert a beneficial effect in the acute stage of muscle damage (Table 3). Kojima et al.[28] showed that whole-body heat stress immediately after injury stimulated the proliferation of satellite cells and protein synthesis during the regeneration process in a cardiotoxin-induced muscle injury model. In addition, the application of hot water immersion has been shown to accelerate the recovery of fiber size and myonuclear number, and to increase the numbers of total and activated satellite cells[29]. Hatade et al.[30] applied a hot pack to a muscle crush injury and found that heat stress immediately after the injury could enhance the proliferation and differentiation of myogenic cells and the expression of muscle regulatory factors MyoD and myogenin. In addition, heat stress was shown to facilitate the migration of macrophages to the injury site, the proliferation and differentiation of satellite cells, the growth of muscle fiber, and the inhibition of collagen synthesis in the regenerating muscle in other thermal stimulation experiments using hot packs after a muscle crush injury[31]. Moreover, in a rat model, no painful behavior responses were exhibited after heat treating. Shibaguchi et al.[21] examined the effects of intermittent heat stress compared with icing on the regeneration process in a bupivacaine-induced muscle injury. The results indicated that heat stress suppressed the increasing fibrosis and partially promoted the recovery of muscle mass, protein content, and size of the muscle fibers in injured skeletal muscle. In addition, enhanced macrophage infiltration, the pro-

Table 3. Studies on thermal therapy for muscle injury in animal models.

Reference	Injury type	Method of thermotherapy	Timing of thermotherapy	Effects in the thermotherapy compared with the injured without thermotherapy groups
Shibaguchi et al.[21]	Bupivacaine-induced muscle injury	Hot water immersion 42 °C 30 min	Initiated 48 h after injury and continued every other day	Reduced the development of fibrosis Increased muscle mass, myofibrillar protein content, muscle fiber cross-sectional area, and expression of Pax-7-positive satellite cells and heat shock protein
Kojima et al.[28]	Cardiotoxin-induced muscle injury	Whole-body heat stress 41 °C 60 min	Immediately after injury	Increased protein content, Pax-7-positive satellite cells, and heat shock protein 72
Oishi et al.[29]	Bupivacaine-induced muscle injury	Hot water immersion 42±1 °C 30 min	Initiated 48 h after injury and continued every other day	Increased myonuclear number, numbers of Pax-7- and MyoD-positive satellite cells, and heat shock protein 72
Hatade et al.[30]	Crush injury	Hot pack 42 °C 20 min	5 min after injury	Earlier expression of MyoD and myogenin protein
Takeuchi et al.[31]	Crush injury	Hot pack 42 °C 20 min	5 min after injury	Increased muscle fiber cross sectional area Faster expression of ED1-positive macrophages Increased number of Pax-7-positive satellite cells Less collagen fiber area

liferation and differentiation of satellite cells, and the expression of heat shock protein (HSP) 72 were also observed under a heat stress condition. As a mechanism of these effects, the involvement of HSPs, some intracellular signaling pathways related to protein synthesis, and gene expression associated with muscle growth has been suggested. HSPs are proteins that respond to stress within the body and play important roles in preventing protein denaturation, the regulation of cell signaling, and the maintenance of cell homeostasis[32,33]. It has also been reported that heat stress attenuates skeletal muscle atrophy[34,35] and induces hypertrophy[29,36-38]. These previous studies also report that thermal stimulation is effective for muscle regeneration. However, thermal therapy has not been applied to acute phase injuries in the clinical setting because it may increase pain and bleeding. If thermal therapy is used in the acute phase of muscle injury in clinical settings, the therapeutic protocol might need to be modified to deal with acute phase symptoms such as pain.

Microcurrent Electrical Neuromuscular Stimulation (MENS)

Microcurrent electrical neuromuscular stimulation (MENS) was developed as a physical therapy modality capable of delivering a current with an amplitude less than 1 mA. The human epidermis exhibits a natural endogenous battery that generates a small electric current when wounded[39,40]. Applying electrical stimulation produces current flow in the tissues that mimics the natural skin battery, and thereby, promotes tissue healing. MENS has been shown to have beneficial effects in terms of wound healing[40,41], pressure ulcer healing[42], tendon or ligament repair[43,44], the alleviation of muscle soreness[45,46], and muscle regrowth[47]. The therapeutic effects of MENS on muscle injury have been evaluated in regard to muscle weight, muscle protein content, mean muscle fiber cross-sectional area, and number of muscle satellite cells[48] (Table 4). The results showed that MENS may facilitate the regeneration of injured skeletal muscle by activating its regenerative potential[48]. Yoshida et al.[49] investigated the effects of MENS with or without icing on the injured muscle regeneration process and found that both treatments had similar beneficial effects on the recovery of muscle protein content and muscle fiber cross-sectional area. However, judging from the fiber morphology and expression level of phosphorylated Akt, MENS combined icing stimulated regeneration of the injured muscle more effectively than did MENS alone. Another treatment attempt combined MENS and hyperbaric oxygen (HBO) therapy in a cardiotoxin-induced muscle damage model[50]. Although MENS or HBO alone was not effective, MENS combined with HBO increased the muscle fiber cross-sectional area. With regard to the mechanisms underlying the effects of MENS, an increase in the generation of adenosine triphosphate has been reported[51]. Another study demonstrated that MENS increased the protein content in C2C12 myotubes. MENS has also been found to upregulate the expression of caveolin-3, tripartite motif-containing 72, and creatine kinase isoenzyme MM. It has also been suggested that MENS stimulates not

Table 4. Studies on microcurrent electrical neuromuscular stimulation or therapeutic ultrasound for muscle injury using animal models.

Reference	Injury type	MENS or TPU treatment condition	Timing of MENS or TPU treatment	Effects in the treated compared with the injured without treatment groups
Fujiya et al.[48]	Cardiotoxin-induced muscle injury	MENS: intensity 10 μA frequency 0.3 Hz pulse width 250 ms stimulation time 60 min	Initiated 48 h after injury and 3 days a week	Increased muscle dry weight, protein content, muscle fiber cross-sectional areas, and number of Pax7-positive muscle satellite cells
Nagata et al.[58]	Cardiotoxin-induced muscle injury	TPU: intensity 30 mW/cm^2 frequency 1 MHz duty cycle 20% stimulation time 15 min	Initiated 24 h after injury and continued daily exposure	Increased muscle fiber cross-sectional. Downregulated expression of COX-2 protein Decreased number of inflammatory infiltrated cells Increased expression of myogenin and myosin heavy-chain protein Increased number of Pax-7-positive cells
Shu et al.[59]	Contusion injury	TPU: intensity 0.25, 0.5, or 0.75 W/cm^2 frequency 3 MHz duty cycle 20% stimulation time 5 min	Initiated 24 h after injury and continued daily exposure	Increased numbers of muscle satellite cells and myotubes, increased desmin expression Greater muscle protein, maximum load, and tensile strength
Chongsatientam et al.[60]	Contusion injury	TPU: intensity 0.3 W/cm^2 frequency 1 MHz duty cycle 20% stimulation time 5 min	Initiated 24 h after injury and continued daily exposure	Increased muscle fiber cross-sectional area and muscle contraction force Increased VEGF mRNA expression and capillary density No influence on mRNA expression of nitric oxide synthase
Chan et al.[61]	Laceration injury	TPU: intensity 30 mW/cm^2 frequency 1.5 MHz duty cycle 20% stimulation time 20 min	Initiated 24 h after injury and continued daily exposure	Increased muscle contraction force (fast-twitch and tetanic strength)
Rantanen et al.[62]	Laceration injury	TPU: intensity 1.5 W/cm^2 frequency 3 MHz duty cycle 20% stimulation time 6 min	Initiated 6 h or 3 days after injury and 2 consecutive days of treatment, followed by 1 day of "rest".	Enhanced myogenic precursor cell and fibroblast proliferation No influence on myotube production
Piedade et al.[63]	Contusion injury	TPU: intensity 0.57 W/cm^2 frequency 1 MHz duty cycle 50% stimulation time 5 min	Initiated 48 h after injury and continued daily exposure	Increased the differentiation of muscular lineage cells Larger deposition of collagenous fibers
Wilkin et al.[64]	Contusion injury	TPU: intensity 1 W/cm^2 frequency 3.3 MHz duty cycle 20% stimulation time 5 min	Initiated 6 h after injury and continued daily exposure	No influence on myonuclear number or cross-sectional area
Markert et al.[65]	Contusion injury	TPU: intensity 0.1 W/cm^2 frequency 3 MHz duty cycle 100% (continuous) stimulation time 5 min	Initiated 24 h after injury and continued daily exposure	No influence on muscle mass, protein content, or muscle fiber cross-sectional area

MENS, microcurrent electrical neuromuscular stimulation; TPU, therapeutic ultrasound; COX-2, Cyclooxygenase-2; VEGF, vascular endothelial growth factor.

only protein synthesis, but also membrane repair in regenerated skeletal muscle[52]. These studies suggest that MENS has a beneficial effect on regeneration after muscle injury. In future research, it will be necessary to examine the most effective treatment parameters of MENS and to elucidate its underlying mechanism in terms of muscle regeneration.

Therapeutic Ultrasound

Ultrasound is a form of acoustic energy that involves mechanical pressure waves. Sound energy at frequencies > 20 kHz is defined as ultrasound. Ultrasound can be used for therapeutic purposes in both the low- and high-intensity ranges. Therapeutic ultrasound for muscle damage is applied at a low intensity or by pulsing[53]. Therapeutic ultrasound has been shown to induce biological activities related to tissue recovery, such as the stimulation of protein and collagen synthesis[54,55], and to increase the production of vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and interleukin-8[56]. Therapeutic ultrasound has been shown to increase the production of nitric oxide[57]. These mechanisms may help promote tissue healing. The reported effects of therapeutic ultrasound on injured muscle include the modulation of the inflammatory response and the upregulation of myogenic differentiation in inflammatory conditions both in *in vitro* and *in vivo*[58]. In addition, it may increase the number of activated satellite cells, upregulate myogenic regulatory factors and skeletal muscle structural proteins, and increase the muscle fiber cross-sectional area in injured skeletal muscle[58-60]. Moreover, therapeutic ultrasound promotes VEGF mRNA expression and revascularization in injured muscle[60]. Regarding physiologic performance, therapeutic ultrasound may improve contractive properties after laceration injury[60,61], as well as maximum load and tensile strength[59]. By contrast, it has also been found to enhance myogenic precursor cell and fibroblast proliferation without affecting myotube production[62]. Piedade et al.[63] reported that therapeutic ultrasound after laceration injury increases the differentiation of muscular lineage cells and the deposition of collagenous fibers. Those results[62,63] suggest that ultrasound treatment also prolongs the proliferation phase of fibroblasts during muscle regeneration, which can increase the amount of permanent scar tissue production, leading to worse muscle function. Moreover, the results of other studies[64,65] suggest that ultrasound does not improve muscle regeneration. The cause of such discrepancies is related to a variety of factors, such as differences in muscle injury models and the irradiation conditions of therapeutic ultrasound, including frequency and intensity (Table 4). As mentioned above, evidence for the therapeutic effects of LIPUS on muscle injury is insufficient, and the mechanisms underlying ultrasound therapies remain unclear. Using C2C12 cells, Salgarella et al.[66] reported the effects of LIPUS at different frequencies and intensities. Their results indicated the most effective parameters for maximizing proliferation and differentiation, and could therefore be useful for conducting in vivo experiments in a future study.

Conclusion

Muscle healing is sometimes delayed, and scar tissue may remain within muscle fibers. As a result, the residual muscle injury itself might inhibit the progress of rehabilitation and delay discharge from hospital. For these reasons, muscle function needs to be restored as soon as possible. This review described the effects of physical agents on muscle healing with a focus on research using animal models. The application of physical agents for the treatment of muscle injury aims to diminish pain, promote muscle regeneration, and prevent sequela such as the formation of scar tissue in muscle. Although appropriate physical approaches have been attempted to be developed according to the muscle healing process, the most efficacious treatment for muscle injury remains unclear. Therefore, further research, including clinical studies, is needed to identify the most efficacious therapeutic conditions.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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REVIEW

Respiratory Impairment, Limited Activity, and Pulmonary Rehabilitation in Patients with Interstitial Lung Disease

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ABSTRACT. Interstitial lung disease (ILD) is a diverse group of chronic lung conditions characterized by dyspnea, exercise-induced hypoxemia (EIH), and exercise intolerance. Since activity limitations and impaired health-related quality of life (HRQoL) in ILD are similar to those in other chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), pulmonary rehabilitation is also indicated for patients with ILD. This rehabilitation program mainly comprises exercise training and self-management education. Exercise training is the most important component of pulmonary rehabilitation. It significantly improves dyspnea and enhances exercise capacity and HRQoL in patients with ILD. The standard exercise prescription used for COPD is also effective for ILD. However, considering that disease progression and exercise-limiting factors are different in patients with COPD is necessary. Severe EIH, the adverse effects of corticosteroid administration, and comorbidities often lead to difficulty in employing a sufficient exercise intensity. Some modifications in the exercise prescription for individual patients or strategies to minimize EIH and dyspnea are required to optimize training intensity. Since EIH is common and severe in patients with ILD, supplemental oxygen should be provided. In advanced and more severe patients, who have difficulty in performing exercises, energy conservation techniques and the use of energy-saving devices to improve and maintain the patients' activities of daily living may be effective.

Key words: Interstitial lung disease, Exercise capacity, Dyspnea, Hypoxemia, Exercise training

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Interstitial lung disease (ILD) is a diverse group of chronic lung conditions comprising more than 200 disease entities. It is characterized by lung inflammation and/or scarring, inducing restrictive ventilatory disorders. Pulmonary rehabilitation has become an accepted treatment for ILDs because of respiratory impairment, dyspnea on exertion, and exercise-induced hypoxemia (EIH), affecting the patients' activities of daily living (ADLs) and health-related quality of life (HRQoL). Although significant short-term improvements in patients with ILD following pulmonary rehabilitation have been demonstrated, clinical problems in which the progressive nature of the disease and its characteristics, such as marked EIH, limit the progression of rehabilitation programs have not been elucidated yet. Therefore, this review describes the clinical features of ILD and the consideration and practical guidance for pulmonary rehabilitation, focusing on exercise training.

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Clinical Features and Problems of ILD

Disease specificity of ILD

ILD is a heterogeneous group of clinical disorders characterized by inflammation and fibrosis of the lung parenchyma. Pathological images are diverse and classified into various independent disease groups based on the histopathological pattern. Therefore, the clinical course and treatment responsiveness differ depending on the disease group. Specifically, idiopathic pulmonary fibrosis (IPF), the

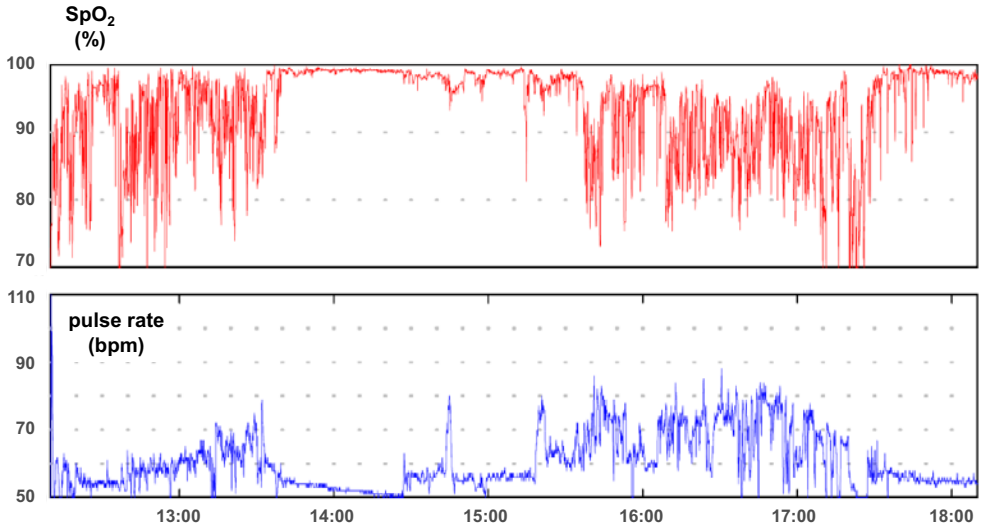

Fig. 1. Continuous oxygen saturation monitoring during daily activities in a 70-year-old man with ILD.

most common type of idiopathic interstitial pneumonia, is progressive and refractory and has a poor prognosis. The disease trajectory is heterogeneous, including patients who follow a slow and stable course, those who experience an acute exacerbation of IPF, and those who progress rapidly in a short-term period[1]. Recognizing that ILD is a "refractory and progressive disease" is necessary. This is an important factor in not only managing but also considering the patients for selection and evaluation of the effects of exercise training. In addition, we should acknowledge ILD as the most distinct respiratory impairment and activity-limiting disease compared with other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD).

Respiratory impairment

In ILD, interstitial fibrosis reduces lung compliance. Restrictive ventilatory disorders, indicated by decreased total lung capacity and vital capacity, are usually observed in pulmonary function tests. Vital capacity significantly declines, and this decline progresses over time. As a result, breathing effort increases, and the patient has a rapid and shallow breathing pattern to ensure ventilation by increasing the respiratory rate. This breathing pattern becomes prominent during exercise, as the dead space ventilation increases.

Gas exchange in ILD is characterized by diffusion limitation (decreased diffusing capacity of the lungs for carbon monoxide [DL_{CO}]), which may be seen before lung capacity decreases. A decreased DL_{CO} is a predictor of EIH owing to their strong correlation. It becomes remarkable when the DL_{CO} decreases to approximately 40% of the predicted value. Oxygen therapy is the control management for diffusion disorders and is essential, especially during exertion.

Dyspnea

Dyspnea on exertion is a common and disabling symptom and is observed in more than 80% of patients with symptomatic ILD[2]. It is also associated with pulmonary function and depression. Moreover, it limits the patient's physical activity and significantly impairs exercise tolerance and ADL performance, markedly impacting their HRQoL[3]. However, the relationship between dyspnea and EIH often differs among individual patients. In some patients, the sensation of dyspnea is poor even with significant EIH, and thus, assessments of both dyspnea and EIH are required.

Exercise-induced hypoxemia

Hypoxemia is often absent at rest in the early stages of ILD (Fig. 1). However, EIH appears relatively early in the course of the disease. EIH is a critical impairment and more advanced than other chronic respiratory diseases, such as COPD[4]. Furthermore, it is identified as a prognostic predictor of mortality[5].

Since the pulmonary capillary bed is reduced, pulmonary diffusing limitation and ventilation perfusion mismatch show remarkable EIH. Hypoxemia induces a rapid and shallow breathing pattern and, as a result, increases the effort for breathing[6]. Furthermore, it limits the supply of oxygen to peripheral skeletal muscles and causes hypoxic pulmonary vasoconstriction, limiting the cardiac output. The reduction in diffusing capacity and hypoxemia during exercise depends on cardiac output[7]. Thus, the prevalence of pulmonary hypertension is increased in patients with EIH.

Skeletal muscle dysfunction

Respiratory impairment, gas exchange disorders, and circulatory limitations are major factors limiting exercise

tolerance and capacity of patients with ILD. In addition, skeletal muscle dysfunction contributes to exercise intolerance[8]. Weakness of the quadriceps muscle is associated with reduced functional exercise capacity[9,10], and quadriceps force is reduced in patients with ILD, which is significantly lower than in healthy controls[11]. Moreover, lower muscle strength was associated with a greater activity limitation. Possible causes of skeletal muscle dysfunction include deconditioning due to physical inactivity, malnutrition, oxidative stress, disease-specific systemic inflammation, and adverse drug reactions. Particularly, long-term corticosteroid administration causes skeletal muscle weakness, such as steroid-induced myopathy. Hanada[12] has reported that quadriceps and hand grip forces were significantly lower in subjects receiving corticosteroids than those in controls, and muscle weakness is inversely correlated with the total amount of corticosteroids administered. Furthermore, muscle weakness and exercise incapacity in patients with ILD and mild dyspnea were associated with corticosteroid treatment[13]. The effects of exercise training on patients receiving corticosteroids were less than those on patients not treated with corticosteroids[14].

Impairment of exercise capacity

Exercise limitation is a common feature of ILD, and its direct causes include dyspnea and deconditioning due to physical inactivity. It contributes to poor functional status and reduced HRQoL. The pathological mechanism of ILD is similar to those in chronic respiratory diseases, such as COPD. However, it differs from other respiratory diseases, in which gas exchange disorders and circulatory limitations are important contributors to exercise limitation in ILD[15]. Peak oxygen uptake as an indicator of exercise tolerance is better associated with circulatory limitation than respiratory dysfunction in patients with ILD[16,17]. Oxygen pulse, an indirect marker of stroke volume, is restricted to increasing from the early stage of exercise, and in some patients, it remains at a plateau or decreases even if exercise intensity is increased[18]. As a result, the heart rate tends to increase for a given exercise intensity compared with healthy individuals. Circulatory limitations promote hypoxia in peripheral tissues, lower mixed venous oxygen saturation, and worsen EIH.

Basic and Special Considerations for Pulmonary Rehabilitation in Patients with ILD

In ILD, particularly IPF, reducing symptoms and improving the patients' HRQoL are difficult even with management, including pharmacological treatment. Pulmonary rehabilitation reduces dyspnea and improves the patients' HRQoL. Exercise training, a core component of pulmonary rehabilitation, significantly improves dyspnea and enhances exercise capacity and HRQoL of patients with ILD[19]. However, these effects are short-term and long-term effects longer than six months have not been observed. Studies on exercise training for patients with ILD are based on the rehabilitation program for COPD, indicating that the same program can be implemented in patients with ILD.

Although activity limitation in patients with ILD is similar to that in patients with COPD, disease progression and exercise-limiting factors are different among these patients. In severe EIH, the adverse effects of corticosteroid administration and comorbidities often make sufficient exercise intensity difficult to employ. Patients with ILD present with various comorbidities that may also affect exercise capacity. Therefore, disease-specific and/or individual differences, including comorbidities, should be considered in developing exercise programs. In addition, the timing of exercise training should be considered. Early referral to exercise training should be considered in all patients, particularly those with IPF, because of the difficulty in implementing exercises in advanced or severe patients with uncontrollable symptoms. Exercise training may be more effective when offered earlier in the disease trajectory.

In patients with advanced and severe ILD, considering the referral to palliative care and trying to reduce the burden in performing ADLs by teaching the patients' energy conservation techniques and using energy-saving devices are necessary[20].

Practical Approach of Pulmonary Rehabilitation

Patient selection, assessment, and program component

Several studies have examined the effects of exercise training on patients diagnosed with ILD. A diagnosis is not an indication for exercise training. In patient selection, disease severity and progression rate are the most important criteria for patient selection. Patients with ILD show several disease trajectories, including long periods of stability, gradual or rapid progression, and acute exacerbation. Implementing exercise training programs and obtaining its effects on patients with severe or advanced disease or rapid progression are difficult. The feasibility, safety, and benefits of exercise training during and early after acute exacerbation of ILD are unclear.

Patient assessment is required when employing exercise training. Symptoms (e.g., dyspnea and cough), exercise capacity, and the patients' HRQoL are the main elements of pulmonary rehabilitation (Table 1) and are similar to those of COPD. Assessment of desaturation (EIH) with dyspnea is essential for evaluating exercise capacity. In some patients with ILD, a discrepancy exists between dyspnea and the degree of EIH, and identifying these patients is necessary because of safety management for exercise training. Many patients with ILD have various comorbidities, which may also impact exercise capacity, functional status, and HRQoL. These comorbidities include ischemic heart dis-

Table 1. Assessment tools for respiratory impairment, activity limitation and impairment of quality of life in patients with ILD

dyspnea	cough	exercise capacity	HRQoL
modified Borg scale	cough visual analogue scale	6MWT	SGRQ
MRC dyspnea scale	LCQ	ISWT	CRQ
BDI/TDI	Cough quality-of-life questionnaire	CPET	IPF-specific version of the SGRQ
Dyspnoea-12			KBILD

6MWT, 6-min walk test; BDI/TDI, baseline/transitional dyspnea index; CPET, cardiopulmonary exercise testing; CRQ, Chronic Respiratory Questionnaire; HRQoL, health-related quality of life; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ISWT, incremental shuttle walk test; KBILD, King's Brief Interstitial Lung Disease Questionnaire; LCQ, Leicester Cough Questionnaire; MRC, Medical Research Council; SGRQ, St George's Respiratory Questionnaire

ease, pulmonary hypertension, pulmonary fibrosis, and emphysema.

Pulmonary rehabilitation programs consist of exercise training as the core component and self-management education. Breathing retraining or controlled breathing techniques were applied, and a systematic review[21] has shown that this technique appears to complement exercise training in improving dyspnea and enhancing the HRQoL of patients with IPF. However, slow and deep breathing patterns are difficult for patients with ILD and have not been shown to be useful. Pursed lip breathing, proven to be useful in patients with COPD, did not acutely improve dyspnea on exertion, walking distance, and gas exchange in patients with ILD[22]. The effects of chest wall mobilization techniques and respiratory muscle relaxation to reduce the effort of breathing have not been investigated in patients with ILD. Moreover, the effects of inspiratory muscle training on these patients are currently unknown.

Efficacy and characteristics of exercise training for patients with ILD

Although randomized controlled trials examining the effects of exercise training on ILD are limited, a systematic review[19] has shown that exercise training improves exercise capacity, dyspnea, and the patients' HRQoL. In addition, no significant adverse events have been reported, and exercise training can be safely performed in this patient group. These programs are based on those employed in patients with COPD. However, many studies did not have a detailed description of exercise prescription, and the disease-specific program and progress criteria remain unclear.

Dowman et al.[23] have examined the effects of an 8-week exercise training program as a randomized controlled trial involving 142 patients with ILD by disease classification. As a result, although the effects of the program were observed in all disease groups, they were particularly larger in patients with IPF and asbestosis than those with connective tissue disease-related ILD. These results indicate that exercise training is effective regardless of ILD disease classification.

Obtaining the effects of exercise training is difficult in severe patients, and exercise training should be started earlier in the disease course for all patients, particularly in patients with IPF[20,24]. A major cause of the poor efficacy of exercise training in severe patients is the inability to adequately increase the exercise intensity due to severe dyspnea and EIH, and controlling these symptoms is essential in exercise training. Furthermore, in exercise training, understanding the pathophysiology and characteristics of impairment in each subject is important; furthermore, observing the changes in symptoms during the clinical course is crucial as well. The dynamic changes in the respiratory status during exercise compared with during rest may lead to early detection of complications, such as acute exacerbation, pneumothorax, and progression of pulmonary hypertension in clinical practice.

Practice of exercise training for ILD

Exercise training for patients with ILD mainly consists of whole-body endurance and upper and lower limb resistance exercises, similar to that for patients with COPD. Endurance training includes cycling and walking. The standard exercise prescription used for COPD is also effective on ILD, including 8-12 weeks of the training. The exercise intensity should be 60-80% of the maximum oxygen consumption, maximum work rate, or maximum walking speed obtained from various exercise tests. The target exercise duration should be set to more than 20 min. However, patients with ILD are heterogeneous and require modifications in exercise prescriptions according to each individual patient.

Limb resistance training was performed using a free weight, an elastic band, and a training machine. The exercise intensity started low, which gradually increased. All these should be performed three times a week, preferably daily. During exercise training, percutaneous oxygen saturation (SpO_2) and dyspnea should be monitored. If controlling EIH or dyspnea is difficult, the following strategies or methods of training should be considered. Several strategies to minimize EIH and dyspnea and to optimize training intensity have been proposed for patients with COPD and ILD.

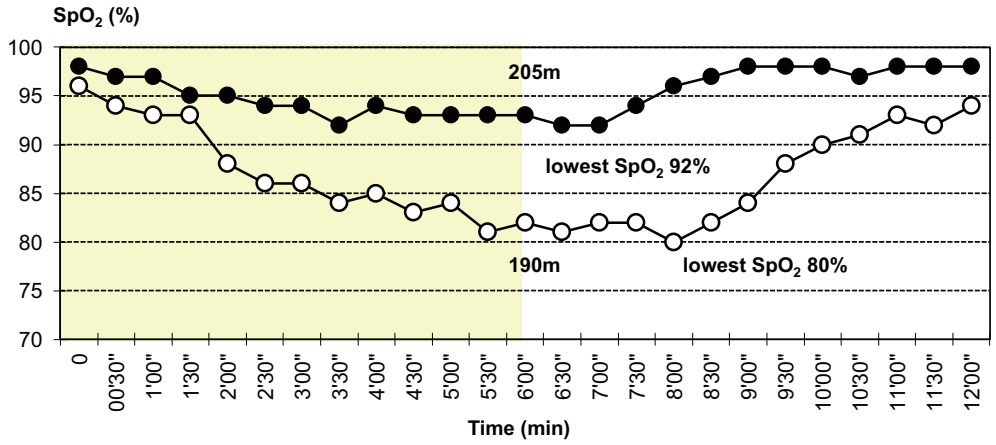

Fig. 2. Effect of wearing a surgical mask over the nasal cannula on oxygen saturation during and after 6 min walk test compared to a nasal cannula alone in which the test was performed at the same oxygen flow rate (5L/min). A 70-year-old woman with IPF. Solid circles = surgical mask. Open circles = nasal cannula alone.

1) Interval training

Interval training is a type of discontinuous exercise involving a series of high-intensity exercises interspersed with rest or recovery periods. A systematic review comparing interval training compared with continuous training in patients with varying degrees of COPD has shown that functional capacity, dyspnea, and HRQoL significantly improved in both groups, with no significant difference between the groups[25]. In the clinical setting, few patients with ILD can perform continuous training for 20 min; thus, discontinuous training is often indicated. Interval training was demonstrated to be well tolerated and preferred by patients with advanced ILD[26] and may be considered an alternative to continuous training in patients with ILD, especially in those with severe EIH or dyspnea.

2) Supplemental oxygen

In patients with ILD, the use of supplemental oxygen during exercise training may lead to optimization or superior training outcomes. If the patients who experience marked desaturation during exercise have difficulty achieving the required training intensity, instead of reducing the training intensity, a necessary and sufficient amount of oxygen should be administered. It may be useful to help patients achieve effective training intensity[27].

Since high-flow rates of oxygen are often required in this patient group, selecting appropriate oxygen delivery devices (e.g., nasal cannula and simple face mask) is important. When a higher concentration of oxygen is needed, a simple face mask or non-rebreather mask should be indicated according to relevant institutional protocols. However, during the coronavirus disease 2019 (COVID-19) pandemic, the combined use of a surgical mask over the nasal cannula is empirically useful in maintaining adequate SpO_2 in some patients (Fig. 2).

Therefore, evaluating the effects of supplemental oxygen on each subject is necessary, rather than uniformly administering oxygen only due to the presence of EIH and dyspnea[28]. The purposes of supplemental oxygen are to assess exercise tolerance (6-minute walk test and constant-load exercise test) with and without oxygen administration; to compare changes in indicators, such as dyspnea, walking distance, and exercise duration; and to evaluate the patients' response. Exercise endurance time is sensitive to changes due to these interventions[29]. Moreover, it is also suitable for assessing the effects of oxygen use.

Although exercise capacity was increased, a systematic review evaluating the impact of supplemental oxygen on training outcomes in patients with ILD has shown that oxygen therapy has no effects on dyspnea during exercise[30]. Future trials are warranted to evaluate whether improvements in exercise capacity with oxygen use can affect the HRQoL and physical activity of patients with ILD.

3) High-flow nasal cannula oxygen therapy

High-flow nasal cannula (HFNC) oxygen therapy is a recently introduced high-flow oxygen delivery system. This consists of an air-oxygen blender and heated humidification system and generates a gas flow up to 60 L/min and fraction of inspired oxygen (FIO_2) up to 100%, allowing the administration of oxygen at accurate concentrations. In addition, HFNC has several effects such as washout of anatomical dead space and improved gas mixing in large airways, high nasal inspiratory flow, and generation of a low-level positive airway pressure. It is expected that these effects are useful for preventing severe EIH and reducing the effort of breathing during exercise (Fig. 3).

Cirio et al.[31] have evaluated the effects of the administration of oxygen using HFNC in patients with COPD during exercise and reported that EIH and dyspnea were sig-

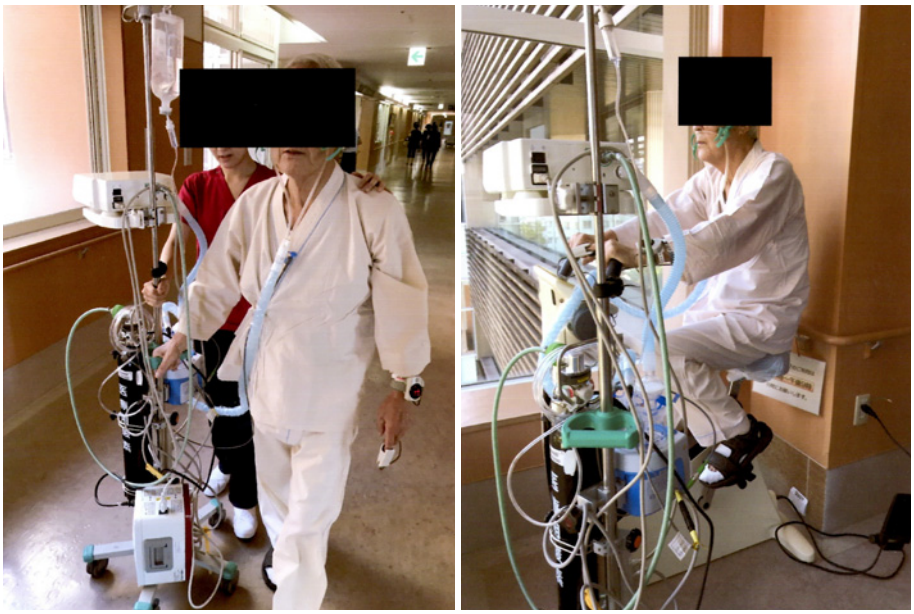

Fig. 3. Exercise training using high-flow nasal cannula oxygen therapy.

nificantly reduced and oxygen therapy using HFNC allowed the patients to exercise for a longer time with a higher exercise intensity.

A randomized controlled crossover trial[32] was conducted to compare the effects of HFNC (50 L/min; FIO_2 0.5) on exercise endurance time, SpO_2, and dyspnea with those of oxygen therapy using a Venturi mask (15 L/min; FIO_2 0.5) in patients with fibrotic ILD. They reported no significant differences in endurance time, SpO_2, and dyspnea between HFNC and Venturi mask. In this study, the FIO_2 setting may have been insufficient during exercise. The effects of HFNC with FIO_2 may be shown according to the degree of EIH in each patient. This may be due to the benefit of using this device in patients with severe EIH. Further large-scale studies are needed.

4) Noninvasive ventilation

The combination of exercise training and noninvasive positive pressure ventilation (NPPV) enables high exercise load and improves exercise tolerance in patients with moderate to severe COPD. In patients with IPF, the use of NPPV during exercise reduced EID and dyspnea, improved exercise tolerance, and decreased the heart rate[33], indicating its usefulness. However, tachypnea is likely to occur during exercise in patients with ILD, which often makes synchronization with the ventilator difficult. Oxygen administration using HFNC is more tolerated than NPPV in patients with synchrony[34].

5) Alternative exercise interventions

Some strategies have been proposed to optimize training intensity and decrease dyspnea in patients with COPD during exercise training. These interventions in clinical settings include single-limb partitioning[35], Nordic walking[36], and downhill walking[37]. These strategies may be useful in patients who cannot tolerate high-intensity exercises due to EIH or dyspnea. In patients with COPD, these strategies showed some positive effects on exercise capacity and/or HRQoL compared with conventional training. However, the feasibility and outcomes of these interventions have not been investigated in patients with ILD. Further research is required to compare the effects of these interventions with those of conventional training.

Energy conservation techniques and the use of energy-saving devices in performing ADLs

Improving and maintaining a patient's ADL is crucial, which is conducted for patients with COPD[38,39]. This intervention aims to reduce energy expenditure and includes methods such as pacing, coordinating breathing with tasks, sitting to perform activities, performing ADLs slowly, using lightweight equipment, and regular rest breaks. Although energy conservation techniques and the use of energy-saving devices may be useful for improving ADL performance, their effectiveness has not been proven in patients with ILD.

First, essential or important activities to the patient are restricted due to dyspnea and EIH should be identified. In addition, the physiotherapist and patient should consider the pace of movement and timing of breaks in performing activities in burden.

Patients with advanced ILD often develop severe dyspnea and EIH, even in performing basic ADLs. The living environment at home should be set to reduce the physical burden by using self-help tools and equipment to facilitate the performance of activities, installing handrails for standing up, and reducing steps. Because indoor walking is also limited in patients with severe ILD, placing a few

chairs to take a break while moving from the living room to the toilet or bedroom is beneficial. In addition, being careful not to entangle or get caught in the oxygen extension tube is important.

A fundamental intervention for reducing the burden in the performance of ADLs is to slowly perform activities, and reviewing how to spend the day and establishing routines are also important. Daytime activities are often concentrated in the morning after waking up; thus, distributing activities throughout the day should be considered. In addition, planning ADLs is crucial.

These interventions are empirically useful for patients with advanced ILD who have difficulty performing exercise training. Strategies to enhance and maintain the performance of ADLs as part of patient education and self-management in pulmonary rehabilitation programs should be provided.

Conclusion

Pulmonary rehabilitation is an important component of comprehensive care for patients with ILD. Exercise training can improve exercise capacity, symptoms, and HRQoL of these patients. Although the standard exercise prescription for patients with COPD is also effective in patients with ILD, the mechanism of exercise limitation and clinical course of ILD is different from that of COPD; therefore, special consideration is required. Particularly, EIH is common; therefore, supplemental oxygen is recommended, and other methods for reducing EIH should be considered.

An approach that considers disease specificity and the clinical course is important. Hence, understanding the characteristics of the subject's dysfunction, disease severity, progression rate, and clinical course is essential. Moreover, to constantly discuss the role and potential of pulmonary rehabilitation, exercise training is important. In clinical practice, the effects of antifibrotic treatment on patients with IPF and progressive fibrosing ILD are expected; thus, the timing, roles, and significance of pulmonary rehabilitation may change in the future.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Association of objectively measured physical activity with combined bilateral knee and low-back pain in older adults with knee osteoarthritis: A cross-sectional study

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ABSTRACT. Objective: Knee pain (KP) and low-back pain (LBP) are common sites of pain and major public health issues among older adults. We investigated the combined association of bilateral KP and LBP with objectively measured physical activity (PA) among adults with knee osteoarthritis (OA). Methods: We recruited 150 knee OA adults and measured steps and PA intensity, including sedentary behavior (SB), low PA (LPA), and moderate-to-vigorous PA, using an accelerometer. KP and LBP were measured using a numerical rating scale. They were classified into 4 groups based on the presence of KP and LBP: with the only unilateral KP (UKP), with the combined UKP and LBP (UKP and LBP), with the bilateral KP (BKP), and with the combined bilateral KP and LBP (BKP and LBP). One-way analysis of covariance was performed to compare physical activity variables (intensity or steps) between the four groups. Results: Overall, 126 patients were enrolled. The prevalence of UKP, BKP, UKP and LBP, and BKP and LBP were 29.4%, 23.8%, 18.3%, and 28.6%. The proportion of SB was higher in the BKP and LBP group than in the other groups ($F = 6.51$, $p < 0.01$). The proportion of LPA was lower in the BKP and LBP group than in the other groups ($F = 6.21$, $p < 0.01$). Conclusions: The proportions of SB and LPA were significantly worse in knee OA adults with BKP and LBP than in those with UKP. Our findings may be a basis for considering knee OA adults for improving PA.

Key words: knee osteoarthritis, knee pain, low-back pain, objectively measured physical activity

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Knee osteoarthritis (OA) is a common orthopedic disease in older adults. There are approximately 25 million adults with knee OA, including the potential population diagnosed by X-ray imaging in Japan[1)]. Knee OA adults are likely to be inactive and do not meet the physical activity (PA) recommendations[2)]. Decreasing PA in knee OA adults not only increases the risk of heart disease and diabetes mellitus but also worsens physical function[3,4)]. Consistent with this, increasing PA in knee OA adults has been shown to improve muscle strength and health-related quality of life[5,6)]. Thus, it is extremely important to improve PA in knee OA adults.

Knee pain (KP) and low-back pain (LBP) are common sites of pain and major public health issues among older adults. The prevalence of KP and LBP were higher in knee OA adults than in healthy adults[7-9)], and knee OA adults are likely to have bilateral KP because of symmetrical varus deformity. KP and LBP are associated with functional limitations and disabilities among knee OA adults[10,11)]. Additionally, previous studies examined the association with KP and PA in knee OA adults[12,13)]. These studies reported that KP was not associated with recommended PA levels[12)] and steps[13)] in knee OA adults. However, they could not investi-

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gate the association with KP and the intensity of PA such as sedentary behavior (SB), low physical activity (LPA). It is necessary to evaluate the intensity of PA because worsening SB and LPA have been shown to be associated with increasing risk of diabetes mellitus and decreasing motor function in older adults[14,15]. Besides, LBP was associated with disability in knee OA adults[16]. However, little is known of the association with LBP and PA. Considering them, it is clinically significant to investigate the association of objectively measured PA including the intensity of PA with combined bilateral KP and LBP.

Therefore, we aimed to investigate the association of combined bilateral KP and LBP with objectively measured PA (including steps and PA intensity) among knee OA adults.

Materials and Methods

Study design and participants eligibility

This study used a cross-sectional design. One hundred fifty knee OA adults who received pharmacological therapy and physical therapy at an orthopedic outpatient clinic in Kobe City, Hyogo Prefecture, Japan, were recruited between October 2017 and April 2018. These participants were diagnosed as grade 3 or 4 on the basis of the Kellgren and Lawrence radiographic grading system (K/L grade). The inclusion criteria were as follows: (i) the numerical rating scale during walking is more than 4 at the worse side of the knee, (ii) over 65 years old, (iii) able to walk freely or with assisting gait tools, and (iv) no symptoms in the hip and ankle joint during walking. The exclusion criteria were as follows: (i) neurological conditions affecting gait ability, such as Parkinson's disease or cerebrovascular disease, (ii) total joint arthroplasty in the lower joints, and (iii) invalid data on the accelerometer (details described later). The ethics committee of the Anshin Hospital approved all procedures before commencing the study (approval protocol number; No.61), and all participants provided written informed consent in accordance with the Declaration of Helsinki before participating.

Measurements of physical activity

We measured steps and PA intensity by using an accelerometer (Active Style Pro HJA-350IT; Omron Healthcare, Kyoto, Japan). The algorithm and validity of the accelerometer device have been previously described[17-19]. The device was used to measure anteroposterior (x-axis), mediolateral (y-axis), and vertical (z-axis) acceleration signals. Patients were instructed to wear the accelerometer on their waist for ≥7 days, except when sleeping or during water-based activities such as bathing, showering, and swimming. The device estimates the intensity of activity by metabolic equivalents (METs). The algorithm for the prediction of METs was established using the Douglas bag method in a controlled laboratory setting[18,19]. The intensity of PA was classified into 3 categories based on METs: SB (≤1.5 METs), LPA (>1.5 to <3.0 METs), and moderate-to-vigorous physical activity (MVPA) (≥3.0 METs). The data were collected in 60-s epochs. Non-wear time was defined as at least consecutive 60 min of 0 counts per minute (cpm), with allowance of up to 2 min of some limited movement (<50 cpm) within those periods[20]. To provide a sufficient estimation of PA on the basis of the accelerometer, patients needed to wear the accelerometer for >4 valid days, with ≥ 10 wear hours per day[21].

Measurements of pain and physical function

Knee pain and low-back pain

We used the numerical rating scale to evaluate KP and LBP. Numerical rating scale is a valid and reliable instrument used in clinical practice because of its sensitivity[22]. KP and LBP were evaluated by the average pain in the last month on a scale ranging from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable. Patients were classified by whether they have KP or LBP. Patients who provided a numerical rating scale score of ≥4 were defined as having pain, and that score was used as the cut-off point in terms of pain-related interference with functioning in patients with chronic musculoskeletal pain[23].

Physical function

Knee extensor strength

The maximal isometric strength of knee extensors was measured using a hand-held dynamometer (μTas F1; ANIMA, Chofu, Japan). Details of the measurements have been described previously[24]. The peak torque (N m) was estimated as the product of force and lever-arm length. Two attempts at maximal contraction were performed, and the greater value was recorded and normalized according to the body weight (N m/kg).

Knee range of motion

The range of motion (ROM) of the knee joint, during flexion and extension, was measured using a standard two-arm plastic goniometer. Measurement of knee flexion and extension ROM followed the methods recommended by the Japanese Orthopedic Association and the Japanese Association of Rehabilitation Medicine. Passive ROM of the involved limb was measured every 5 degrees in the supine position. All measurements were performed twice by trained physical therapists and were selected a value of the good one.

Knee-specific functional outcomes

The new knee society score (KSS) questionnaire was used to assess knee-specific functional outcomes[25]. The new KSS consists of four categories: symptoms (3 items, 25 points), patient satisfaction (5 items, 40 points), patient

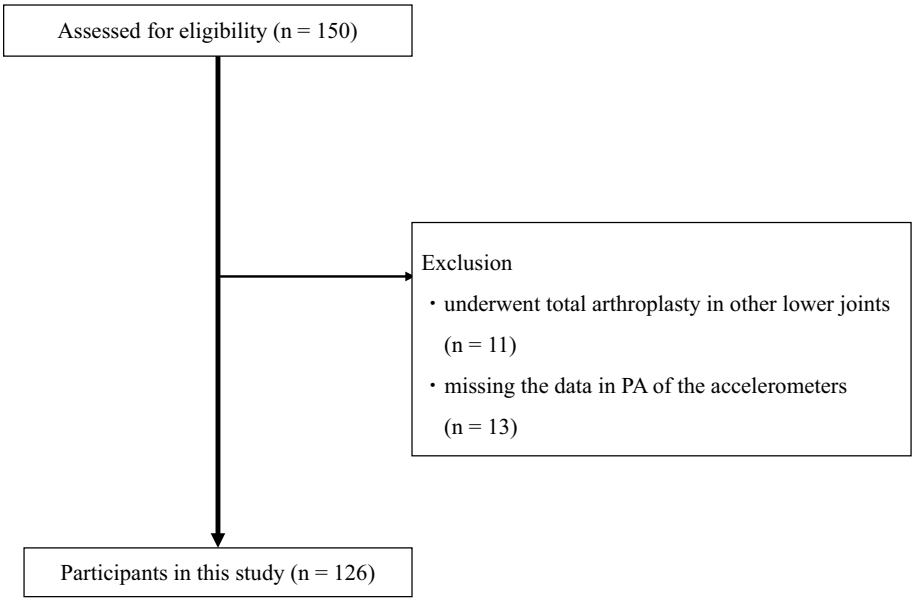

Figure 1. Flow chart for selection and assessment of the participants

expectations (3 items, 15 points), and functional activities (19 items, 100 points). High scores represent less pain and greater patient satisfaction, expectations, and physical functioning. The new KSS is a validated and reliable instrument used before and after TKA[26].

Gait function

The timed-up-and-go (TUG) test was used to evaluate the time taken to rise from a chair, walk 3 meters, turn around, and return to a seated position. Participants were instructed to walk as fast as possible, and they completed two trials each; the fastest time was used for analysis[27].

Other measurements

We collected demographic data such as sex, age, weight, height, body mass index, and the K/L grade in bilateral side from medical records. Patients answered whether they ever diagnosed as the depression.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and nominal variables were expressed as number (%).

The patients were classified into 4 groups based on the presence of KP and LBP: with the only unilateral KP (UKP group), with the combined UKP and LBP (UKP and LBP group), with the bilateral KP (BKP group), and with the combined bilateral KP and LBP (BKP and LBP group). One-way analysis of variance was performed for continuous variables, and the χ^2 test was performed for categorical variables to compare demographic data, physical function, and pain parameters. For physical activity variables (intensity or steps), one-way analysis of covariance (ANCOVA) was performed to compare the variables between the four groups. Age, body mass index, sex, and K/L grade on the bilateral side were considered potential confounders. When significance was determined by one-way analysis of variance and covariance, the Bonferroni test was performed for post-hoc comparisons.

The statistical significance level was set at $p < 0.05$ for all analyses. All analyses were performed using SPSS for Windows 21.0.0 version (IBM, Tokyo, Japan).

Results

Of the 150 patients, 11 underwent total arthroplasty in other lower joints, and 13 were missing the accelerometer PA data. These patients were excluded from the study. Finally, a total of 126 patients were enrolled in this analysis (figure1). We confirmed that the measured baseline characteristics and physical function of our remaining participants and those of the dropouts were not significantly different (Supplemental Table).

Patient characteristics, physical function, and pain among the four groups are summarized in Table 1. The prevalence of UKP, UKP and LBP, BKP, and BKP and LBP were 29.4%, 23.8%, 18.3%, and 28.6%, respectively. The KSS in the BKP group, and BKP and LBP groups, were lower than those in the UKP group and the UKP and LBP group (F = 4.47 vs UKP group, $P < 0.01$ vs UKP and LBP group, $P < 0.01$, separately).

The results of comparing the physical activity variables among the four groups are summarized in Table 2. The proportion of SB was higher in the BKP and LBP group than in the other groups (F = 6.51 vs UKP group, $P < 0.01$ vs UKP and LBP group, $P = 0.03$ vs BKP group, $P = 0.03$). The proportion of LPA was lower in the BKP and LBP group than in the other groups (F = 6.21 vs UKP

Table 1. Patient characteristics, physical function, and pain among the four groups

Variable	All patients (n = 126)	UKP group (n = 37)	UKP + LBP group (n =23)	BKP group (n = 30)	BKP + LBP group (n =36)	F value	*p* value
Sex (female), n (%)	98 (78.0)	29 (78.4)	18 (78.3)	23 (76.7)	28 (77.8)	-	0.63
Age, years	72.3 ± 6.2	71.5 ± 7.1	69.1 ± 5.8	74.3 ± 4.4	72.5 ± 6.3	2.41	0.07
Height, cm	153.0 ± 7.7	152.9 ± 8.2	151.5 ± 8.0	152.2 ± 5.7	154.4 ± 8.6	0.75	0.53
Weight, kg	60.4 ± 13.0	60.5 ± 11.4	57.5 ± 8.9	63.4 ± 18.6	60.0 ± 9.2	0.91	0.44
BMI, kg/m^2	25.8 ± 5.9	25.8 ± 4.1	25.2 ± 3.9	27.7 ± 9.6	24.7 ± 4.2	1.4	0.25
The presence of depression, n	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	-	0.9
Grade of knee OA in the involved limb						-	0.56
grade 3, n (%)	38 (30.2)	13 (35.1)	8 (34.8)	8 (26.7)	9 (25.0)		
grade 4, n (%)	88 (69.8)	24 (64.9)	15 (65.2)	22 (73.3)	27 (75.0)		
Grade of knee OA in the uninvolved limb						-	0.12
grade 1, n (%)	17 (13.5)	7 (18.9)	5 (21.7)	3 (10.0)	2 (5.6)		
grade 2, n (%)	40 (31.7)	12 (32.4)	8 (34.8)	9 (30.0)	11 (30.6)		
grade 3, n (%)	38 (30.2)	9 (24.3)	6 (26.1)	11 (36.7)	12 (33.4)		
grade 4, n (%)	31 (24.6)	9 (24.3)	4 (17.4)	7 (23.3)	11 (30.6)		
Range of motion							
Flexion, degree	120.1 ± 13.8	120.5 ± 17.0	124.7 ± 11.7	118.8 ± 11.6	118.5 ± 12.0	0.87	0.46
Extension, degree	−10.2 ± 6.8	−8.5 ± 5.6	−11.8 ± 10.6	−10.0 ± 7.6	−11.3 ± 5.6	1.27	0.29
Knee extensor strength, N m/kg	0.82 ± 0.36	0.76 ± 0.23	0.97 ± 0.30	0.74 ± 0.25	0.88 ± 0.51	2.23	0.09
New knee society score, score	79.7 ± 29.0	87.3 ± 32.6	90.6 ± 17.9	73.0 ± 26.3*, †	70.6 ± 26.3*, †	4.47	<0.01
Timed up and go test, s	10.4 ± 3.7	9.5 ± 2.8	9.5 ± 2.9	10.5 ± 2.6	11.7 ± 3.6	2.38	0.08
Knee pain, NRS	5.9 ± 2.1	4.9 ± 2.7	5.0 ± 2.0	6.5 ± 1.8*, †	6.9 ± 2.0*, †	6.2	<0.01
Knee pain (contralateral side), NRS	3.1 ± 2.5	0.9 ± 0.8	1.1 ± 0.8	5.1 ± 2.2*, †	5.2 ± 1.8*, †	63.44	<0.01
Low-back pain, NRS	2.3 ± 2.6	0.5 ± 0.8	5.2 ± 2.2*, ‡	0.7 ± 0.9	5.0 ± 1.7*, ‡	94.69	<0.01

Continuous variables are expressed as mean ± standard deviation, and ordinal variables are expressed as number (%). One-way analysis of variance was performed for continuous variables and the χ^2 test was performed for categorical variables.

BKP, bilateral knee pain; BMI, body mass index; LBP, low-back pain; NRS, numerical rating scale; OA, osteoarthritis; UKP, unilateral knee pain.

* $p < 0.01$ vs UKP group.

† $p < 0.01$ vs UKP and LBP group.

‡ $p < 0.01$ vs BKP group.

group, $P < 0.01$ vs UKP and LBP group, $P = 0.02$ vs BKP group, $P < 0.01$). The proportion of MVPA and number of steps were not significantly different among the 4 groups.

Discussion

In this study, we investigated the association of combined bilateral KP and LBP with PA, including steps and PA intensity in knee OA adults. The main findings showed that the proportions of SB and LPA were significantly worse in knee OA adults with combined bilateral KP and LBP than in those with UKP, UKP and LBP, and BKP, even after adjusting for potential confounders. This study is the first to clarify the association of combined bilateral KP and LBP with objectively measured PA in knee OA adults.

This study showed that PA in the BKP group or the UKP and LBP group was not worse than that in the UKP group, which supports the results of previous research in community-dwelling adults[28,29]. These studies have reported an insignificant association of PA with KP or LBP. However, interestingly, PA was significantly worse in the BKP and LBP group than in the other groups, which suggests that combined bilateral KP and LBP had a negative effect on PA. A potential explanation for these results is the effect of multisite pain on PA. Murata et al. reported that chronic musculoskeletal multisite pain was negatively associated

Table 2. Results of comparing physical activity among the four groups

Variable	All patients (n = 126)	UKP group (n = 37)	UKP and LBP group (n =23)	BKP group (n = 30)	BKP and LBP group (n =36)	F-value	*p* value
Valid days (days)	9.3 ± 2.1	9.2 ± 2.6	9.6 ± 1.8	9.6 ± 2.3	8.9 ± 2.3	0.76	0.55
Waking wear time (min/day)	811.4 ± 107.4	809.6 ± 91.0	812.8 ± 106.0	837.6 ± 126.2	790.9 ± 111.6	0.44	0.82
SB							
Time (min/day)	446.3 ± 118.9	424.8 ± 119.3	436.5 ± 130.7	442.0 ± 140.4	487.2 ± 134.0	-	-
Time/waking wear time (%)	55.3 ± 11.4	52.5 ± 11.3	53.7 ± 10.9	53.9 ± 9.7	61.6 ± 9.3*, †, ‡	6.51	< 0.01
LPA							
Time (min/day)	331.9 ± 94.7	345.7 ± 110.6	338.4 ± 84.8	366.1 ± 97.2	279.2 ± 105.8	-	-
Time/waking wear time (%)	40.9 ± 10.4	43.0 ± 10.9	41.8 ± 10.8	43.1 ± 8.8	35.3 ± 8.8*, †, §	6.21	< 0.01
MVPA							
Time (min/day)	31.1 ± 30.3	37.3 ± 31.0	35.0 ± 31.2	25.7 ± 35.9	24.5 ± 37.7	-	-
Time/waking wear time (%)	3.8 ± 3.0	4.5 ± 4.1	4.3 ± 3.8	3.1 ± 3.4	3.1 ± 3.6	1.37	0.26
Step counts (number/day)	4019 ± 2692	4735 ± 2942	4179 ± 2656	3357 ± 2585	3660 ± 2364	1.13	0.34

Data are expressed as means ± standard deviations. One-way analysis of covariance was performed to compare physical activity variables between the 4 groups. Age, body mass index, sex, and K/L grade on the bilateral side were considered as potential confounders. SB: sedentary behavior; LPA: light physical activity intensity; MVPA: moderate-to-vigorous physical activity intensity

* $p < 0.01$ vs UKP group.

† $p < 0.05$ vs UKP and LBP group.

‡ $p < 0.05$ vs BKP group.

§ $p < 0.01$ vs BKP group.

with PA[30]. Therefore, it was considered that the BKP and LBP group, which had multisite pain, had significantly worse PA than the other groups. For this reason, it was considered that PA was significantly worse in the combined BKP and LBP group than in other groups.

Other important findings were that the proportion of MVPA and step counts were not associated among 4 groups, whereas increasing the proportion of SB and decreasing the proportion of LPA were negatively associated with combined bilateral KP and LBP. One possible reason for these results is that participants were inactive and had more severe knee OA. Our participants had severe knee OA classified as KL grade 3 or 4 at worse side of KP, and the proportion of MVPA and step counts were relatively small (3.8 ± 3.0%, 3688 ± 2736 steps/day, respectively). The severity of knee OA in our study was higher (the KL grade of our participants was III-IV) and the step counts were lower (the mean step count of our participants was 3688 ± 2736) than those in the study by Chmelo et al. (KL grade: II-III; mean step count: 6209 ± 2554)[31]. The proportion of MVPA was not found because no information about total wear time in that previous study was available; therefore, it was difficult to compare that study with ours. Our results suggest that the influence of knee OA severity at the worse side of KP on MVPA and step count was higher than that of KP and LBP.

Future research that studies knee OA adults with mild knee OA and a high proportion of MVPA is needed to clarify the association of combined bilateral KP and LBP with MVPA or step count.

The results of one-way analysis of covariance indicated that the proportion of SB was 8-9% higher in knee OA adults with combined bilateral KP and LBP than in those with UKP, UKP and LBP, and BKP. Mitchell et al. reported that a 1-h increase in total sedentary time was associated with a 35%-44% increase in the odds of metabolic syndrome in older adults[12]. Additionally, Mekary et al. reported that a 1-h increase in SB was associated with an 18% increase in the odds of depression[32]. The 10% of total waking wear time in our study was equal to more than 1 hour. Therefore, a 10% increase in SB could be a clinically meaningful effect size in terms of the health of knee OA adults.

Several limitations were identified in our study. First, we used a cross-sectional study design; therefore, we were unable to explain the cause and effect relationship. Future longitudinal studies are needed to clarify the cause and effect relationship between combined bilateral KP and LBP with PA. Second, we cannot evaluate the periods of pain. The periods of pain may affect physical activity. Third, the accelerometer used in this study could not capture water-based activities such as bathing, swimming, and underwater walking. These activities may have affected our results by causing the underestimation of PA. Finally, we did not evaluate depression status, which can be a confounding factor. Previous study has reported the association of depression with PA and pain[33]. Further research should investigate the influence of depression on PA and pain perception.

Conclusion

This study explored the association of PA with combined bilateral KP and LBP in knee OA adults. The proportions of SB and LPA were significantly worse in knee OA adults with combined bilateral KP and LBP than in those with UKP, UKP and LBP, and BKP, even after adjusting for potential confounders.

Our findings may be a basis for considering knee OA adults about for improving PA and developing strategies for relieving pain in sedentary knee OA adults.

Conflict of Interest: None.

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Appendix

baseline characteristics and physical function between the patients who remained and those who dropped out.

PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Effect of types of proximal femoral fractures on physical function such as lower limb function and Activities of Daily Living

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ABSTRACT. Objectives: This study aimed to assess physical function such as lower limb function and Activities of Daily Living after surgery for proximal femoral fractures (unstable medial femoral neck fracture and trochanteric fracture). Methods: This study enrolled 68 patients with proximal femoral fractures. Isometric knee extension strength (IKES), the Japanese Orthopedic Association (JOA) hip score, and the number of days required to develop straight leg raising, transfer, and T-caneassisted gait abilities to become independent were assessed. Patients were classified based on the types of proximal femoral fractures, namely unstable medial femoral neck fracture (bipolar hip arthroplasty [BHA] group), stable trochanteric fracture (S group), and unstable trochanteric fracture (US group). Results: IKES and the JOA hip score were significantly better in the BHA group than in the S and US groups. IKES and the JOA hip score were significantly worse in the US group than in the BHA and S groups. Both transfer and T-cane-assisted gait abilities of patients in the BHA and S groups were indifferent. However, all physical functions were significantly worse in the US group. Conclusions: Our study results suggested that physical therapists plan the different rehabilitation program for the patients with proximal femoral fractures who were classified into three types, namely unstable medial femoral neck fracture, stable trochanteric fracture, and unstable trochanteric fracture, instead of two types.

Key words: Proximal Femoral Fractures, Surgical Approach, Lower Limb Function, Activities of Daily Living (ADL), Physical Function

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Proximal femoral fractures are one of the most devastating injuries among the elderly individuals. Loss of gait ability and quality of life after proximal femoral fracture are more severe among majority of the patients[1-3)]. Furthermore, the inability to walk after hospital discharge and presence of delirium are independent predictors of 1-year mortality. In addition, the possibility of not recovering gait ability at hospital discharge and 1-year mortality after proximal femoral fracture were higher among older patients who had severe cognitive impairment, lower functional level before injury, and those who experienced postoperative delirium and pressure ulcers[3)]. Therefore, early recovery of gait ability is crucial for the patients.

Proximal femoral fractures are divided into two fracture types: medial femoral neck fracture and trochanteric fracture. Researchers have previously reported that the clinical prognosis of medial femoral neck fracture was con-

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siderably better than that of trochanteric fracture[4-7]. According to Evans classification, trochanteric fractures were divided into the stable and unstable types[8]. The short-term clinical results of individuals with stable type were better than of those with unstable type for gait ability[9]. Therefore, considering these reports, it is important to subdivide proximal femoral fractures into the three-fracture type. However, no studies have reported physical function such as lower limb function and Activities of Daily Living in the three-fracture type of the proximal femoral fracture. We hypothesized that physical function such as lower limb function and Activities of Daily Living decrease in the following order: medial femoral neck fracture, stable type of trochanteric fracture, and unstable type of trochanteric fracture.

This study aimed to assess physical function such as lower limb function and Activities of Daily Living after surgery for proximal femoral fractures (unstable medial femoral neck fracture and trochanteric fracture).

Material and Methods

1. Patients

This study recruited 382 patients who experienced proximal femoral fractures from March 2016 to February 2019. The inclusion criteria were independent gait ability with or without T-cane-assistance before the fracture. And the period of hospitalization for the patients was for more than 4 weeks. The exclusion criteria were presence of dementia (Mini Mental State Examination score: <23) and a history of cerebrovascular or osteoarthritis disorder that caused gait disorder. In this study, the period of hospitalization for the patients with proximal femoral fractures who underwent intramedullary nail fixation (hanson pin or cannulated cancellous screw) was within two weeks. Therefore, they were excluded in this study. In total, 68 patients with proximal femoral fractures who underwent bipolar hip arthroplasty (BHA; BHA group) or intramedullary nail fixation (gamma locking nail; gamma group) met the inclusion criteria and were enrolled in this study. After surgery, all the patients were divided based on the surgery type. The BHA group comprised 34 patients and the gamma group comprised 34 patients. Moreover, the gamma group patients were divided into the stable type (S group; 21 patients) and the unstable type (US group; 13 patients)[8]. This study was approved by the institutional review board and conformed to the Declaration of Helsinki. All the procedures in this study were approved by the Ethics Committee of the Heisei Memorial Hospital (H15-1). No infection was observed in the hip during the entire postoperative course.

All the patients followed the same postoperative rehabilitation protocol and they did not drop out for this protocol. They were instructed to increase the range of hip motion starting the day after the surgery and to bear as much weight as they could tolerate starting the day after the treatment.

2. Assessment of outcome

Relevant descriptive characteristics such as age, height, weight, and body mass index (BMI) were extracted from the medical records of the patients. We evaluated isometric knee extension strength (IKES) and the Japanese Orthopedic Association (JOA) hip score at 1, 2, 3, and 4 weeks after the surgery and discharge.

IKES was measured using a hand-held dynamometer (μ-tas F-1, ANIMA Corp., Japan) with patients in a seated position and the knee flexed at a 90° angle, as described previously[10]. Patients were instructed to gradually increase the intensity of knee extension against the dynamometer for approximately 2 seconds, avoiding an explosive contraction, and to maintain their maximal force output for approximately 3 seconds. Two measurements were obtained and the maximum values were used for analysis. Furthermore, the laterality (affected side per non-affected side) was calculated.

Medical doctor, nurse, and physical therapist evaluated the number of days required to develop straight leg raising (SLR), transfer, and T-cane-assisted gait abilities to become independent. The independent criteria were more than 6 points on Functional Independence Measure.

3. Statistical analyses

IKES and the JOA hip score were analyzed using two-way analysis of variance (ANOVA) with repeated measurements to evaluate the fracture types and assessment time points (after 1, 2, 3, and 4 weeks of surgery and discharge).

The number of days required to develop SLR, transfer, and T-cane-assisted gait abilities by each group were compared using one-way ANOVA with repeated measures. Bonferroni corrections were applied to account for multiple comparisons. The significance level for all analyses was set at 5%. SPSS version 18.0J for Windows (SPSS, Chicago, IL, USA) was used for analysis.

Results

Characteristics of patients of all the three groups are summarized in Table 1. No significant differences were noted in the mean age, height, weight, and BMI of patients of all the three groups.

The two-way ANOVA for both IKES and the JOA hip score showed a significant main effect of fracture types ($p < 0.001$), their interaction ($p < 0.01$), and the assessment timepoint ($p < 0.001$). According to Post hoc analyses, the BHA group had significantly better IKES (after 1, 2, 3, and 4 weeks of surgery) and JOA hip score (after 2, 3, and 4 weeks of surgery and discharge) compared with the S group. In addition, significantly better IKES (after 1, 2, 3, and 4 weeks of surgery and discharge) and JOA hip score

Table 1. Patients' characteristics

	BHA group	S group	US group	p value
Age (year)	78.3±8.4	81.2±6.1	84.7±4.0	n.s.
Height (cm)	153.2±6.7	152.2±8.2	150.1±4.8	n.s.
Weight (kg)	59.1±9.3	49.0±9.3	45.5±9.2	n.s.
BMI (kg/m^2)	16.3±2.8	16.0±2.4	15.1±2.7	n.s.

Data expressed as means ± standard deviations.

(after 1, 2, 3, and 4 weeks of surgery and discharge) were noted in the BHA group than in the US group ($p < 0.001$) according to the post hoc analyses. The IKES results (after 1, 2, 3, and 4 weeks of surgery) of the S group were significantly better than those of the US group ($p < 0.05$). No differences were noted in the JOA hip scores of the S and US groups. The results are summarized in Table 2.

To become independent, the BHA, S, and US groups required 3.3 ± 1.8, 6.0 ± 4.7, and 17.1 ± 6.2 days, respectively, to develop SLR ability; 4.1 ± 1.7, 4.4 ± 2.3, and 8.0 ± 4.7 days, respectively, to develop transfer ability; and 19.5 ± 9.4, 23.2 ± 5.6, and 38.6 ± 10.8 days, respectively, to develop T-cane-assisted gait ability. The BHA group required significantly less number of days to develop SLR ability than both the S and US groups. The BHA and S groups required the same number of days to develop both transfer and T-cane-assisted gait abilities. However, all physical functions were significantly worse in the US group. The results are summarized in Figure 1, 2, and 3.

Discussion

This study revealed the differences in physical function such as lower limb function and Activities of Daily Living after surgery by types of proximal femoral fractures, namely unstable medial femoral neck fracture and stable and unstable trochanteric fractures. Clinical prognosis was significantly worse in the US group. Therefore, considering the clinical prognosis, proximal femoral fractures should be subdivided into three types.

IKES was significantly higher after 1, 2, 3, and 4 weeks of surgery in the BHA group than in the S and US groups. However, at discharge, no differences were noted in IKES between the BHA and S groups. IKES was significantly worse in the US group at all assessment time points. Previously, researchers have reported that patients with trochanteric fracture experience a large of amount of bleeding[11,12]. Furthermore, patients in the US group have been reported to experience more bleeding than those in the S group[13,14]. Thus, increased amount of bleeding resulted in swelling or edema in the thigh that in turn increased the internal pressure in the thigh, causing muscle weakness and limiting knee extension. In addition, the gamma locking nail invaded the vastus lateralis and knee extension is asso-

Table 2. The Results of chronological data and two-way ANOVA (IKES and JOA hip score)

	1 week		2 weeks		3 weeks		4 weeks		discharge
IKES (kgf/kgf) a)									
BHA group	0.64±0.14	**	0.69±0.16	***	0.74±0.14	***	0.76±0.14	***	0.77±0.16
S group	0.50±0.14	*	0.52±0.14	**	0.55±0.10	*	0.59±0.11	*	0.66±0.19 **
US group	0.35±0.08	***	0.35±0.07	***	0.40±0.07	***	0.45±0.08	***	0.59±0.17
JOA hip score (points) b)									
BHA group	36.67±11.70		49.70±14.58	***	58.67±12.63	***	64.05±14.13	**	77.52±7.90 **
S group	32.09±5.88		36.57±6.52	***	46.19±13.13	***	53.09±12.19	***	66.09±14.90 *
US group	29.38±4.49		34.30±6.7		38.07±4.19		49.07±6.82		66.69±6.84

Data expressed as means ± standard deviations.
IKES: isometric knee extension strength
JOA hip score: Japanese Orthopedic Association hip score
a) interaction ($p<0.01$, $F=2.87$), main effect of fracture types ($p<0.001$, $F=30.03$), main effect of assessment timepoint ($p<0.001$, $F=34.73$)
b) interaction ($p<0.01$, $F=2.95$), main effect of fracture types ($p<0.001$, $F=14.66$), main effect of assessment timepoint ($p<0.001$, $F=218.50$)
Significant level: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

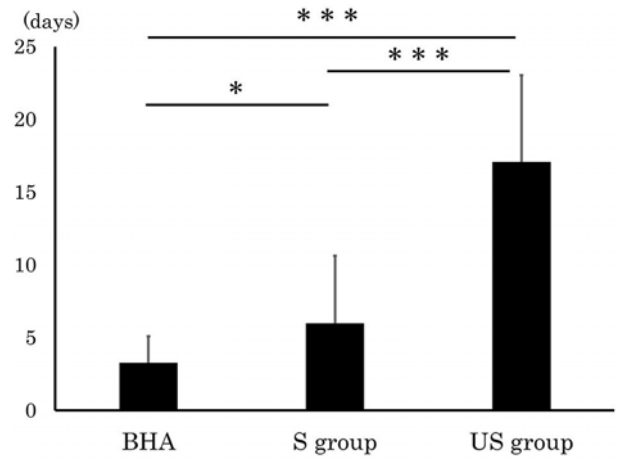

Figure 1. The number of days for SLR to become independent
BHA group was significantly better than S group and US group. S group was significantly better than US group. *Significant level at $p < 0.05$. ***Significant level at $p < 0.001$.

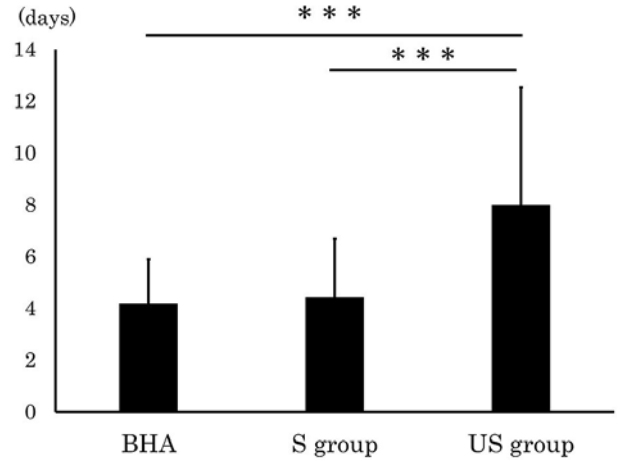

Figure 2. The number of days for transfer to become independent
US group was significantly worse than BHA and S group. There was no difference between BHA group and S group. ***Significant level at $p < 0.001$.

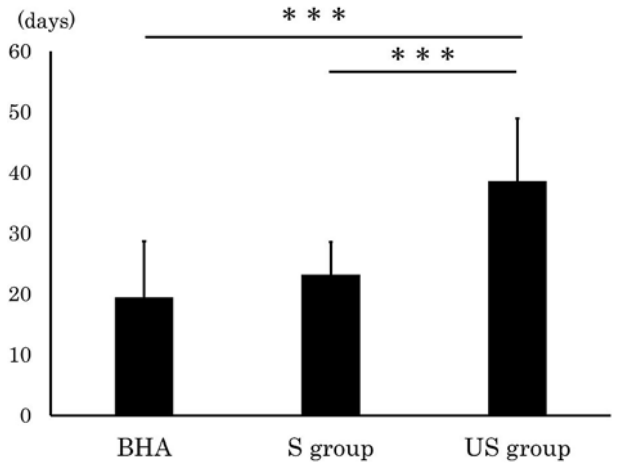

Figure 3. The number of days for T-cane gait to become independent
US group was significantly worse than BHA and S group. There was no difference between BHA group and S group. ***Significant level at $p < 0.001$.

ciated with this muscle weakness. Hence, IKES was significantly higher and the number of days required to develop SLR ability to become independent were significantly lesser in the BHA group than in the S and US groups.

The JOA hip scores of the BHA group was higher than those of the S and US groups. There was no difference between S group and US group. The JOA hip score comprised pain, range of motion (ROM), gait ability, and activities of daily living (ADL) ability. Researchers have previously reported that the trochanteric fracture often caused periosteal pain, especially pain due to weight-bearing in the acute phase[15,16]. Few studies have reported about the postoperative passage for ROM after proximal femoral fractures. There was considerable amount of bleeding after the trochanteric fracture[11,12]. The swelling or edema with bleeding is caused by the loss of soft tissue flexibility, resulting in lower ROM after trochanteric fracture. Considering ADL ability, the number of days required to develop SLR, transfer and gait abilities were significantly lesser in the BHA group than in the S and US groups. SLR ability is associated with getting out of bed. The earlier the patients get out of bed, the earlier they can become independent. In addition, SLR ability is associated with transfer ability. The patients of the US group experienced periosteal pain as well as weight-bearing pain. Therefore, due to pain and SLR inability, the US group required a long time to become independent as compared with the BHA and S groups. Furthermore, the transfer ability of US group was significantly worse than the BHA and S groups. And gait ability after proximal femoral fracture is associated with IKES[18,19]. In addition, the decrease in hip flexion strength after lesser trochanter fracture affected the ability of swing initiation in poorly active patients and reduce their walking stability[20]. Past researchers reported gait ability was most impaired in the US group[9,17]. Therefore, the number of days to develop T-cane-assisted gait abilities to become independent was significantly worse in the US group than in the BHA and S groups. However, there was no differences between BHA and S groups. Therefore, we will assess to evaluate other muscle strength (for example, gluteus medius, gluteus maximus and so on) in the future. For all these reasons, the JOA hip scores of the BHA group was higher than those of the S and US group. However, there was no difference in the JOA hip scores of the S and US groups.

This study had some limitations. First, this study enrolled only 20% of all the patients with proximal femoral fracture because the level of inclusion criteria was high. Second, we did not evaluate the hip muscle strength. SLR ability is associated with iliopsoas muscle strength. The

surgical invasion caused weakness in gluteus medius and maximus, the muscles associated with gait ability. In the future, we will change the inclusion criteria regarding dementia, recruit more patients and examine the other outcomes such as hip muscle strength. In addition, we intend to assess the relationship between the three types of fractures and physical function.

Conclusion

Our study results suggested that physical therapists plan the different rehabilitation program for the patients with proximal femoral fractures who were classified into three types, namely unstable medial femoral neck fracture, stable trochanteric fracture, and unstable trochanteric fracture, instead of two types.

Conflict of Interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Measurement of excitation-contraction coupling time in lower extremities

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ABSTRACT. Objective: The aim of this study was to apply a novel method to measure excitation-contraction coupling time (ECCT) in normal soleus muscles. Methods: We performed simultaneous recordings of soleus compound muscle action potential (CMAP) and foot movement-related potential (MRP), and measured ankle plantar flexion torque in 36 healthy subjects. We calculated ECCT and examined the relations between CMAP, MRP, ECCT and ankle plantar flexion torque. Results: Statistical analyses established reference ranges (mean ± SE) for CMAP (13.4 ± 0.9 mV), MRP (5.3 ± 0.4 m/s^2), ECCT (5.2 ± 0.1 ms), torque (85.9 ± 6.4 Nm) and torque/body weight (1.4 ± 0.1 Nm/kg). The torque showed a positive linear correlation with CMAP (p = 0.041) and a negative linear correlation with ECCT (p = 0.045). Conclusion: Soleus ECCT can be recorded easily, and is useful to assess the impairment of E-C coupling in muscles of the lower extremities.

Key words: excitation-contraction coupling, soleus muscle, plantar flexion, torque, accelerometer

(Phys Ther Res 24: 29-34, 2021)

Excitation-contraction (E-C) coupling in skeletal muscles involves a number of steps. After generation of a muscle action potential, sarcolemmal depolarization spreads transversely to the T tubules. The voltage sensor of the T tubules transmits the electric charge to the ryanodine receptor, resulting in channel opening. This opening leads to Ca^{2+} release from the sarcoplasmic reticulum into the myoplasm. Binding of the released Ca^{2+} to troponin triggers an interaction between actin and myosin filaments. Finally, these filaments slide and muscle fiber length shortens[1-3]. In our previous studies[4-7], we developed a novel method (Imai's method) to estimate the time from muscle depolarization to initiation of muscle contraction. In Imai's method, masseteric compound muscle action potentials (CMAPs) and mandibular movement-related potentials (MRPs) are simultaneously recorded using an accelerometer, after trigeminal nerve stimulation with a needle electrode. The E-C coupling time (ECCT) is obtained from the difference in onset latencies between masseteric CMAP and mandibular MRP. By measuring the bite force using a specialized pressure-sensitive sheet, the correlation between ECCT and bite force can be analyzed. We also applied the principles of this method to intrinsic hand muscles, and recorded ECCTs and MRPs in the hand muscles to estimate the contribution of impairment of E-C coupling to muscle weakness in neuromuscular diseases[8].

Although decreased MRPs and prolonged ECCTs have been demonstrated in the masseter and intrinsic hand muscles in patients with various neuromuscular diseases[7,8], these procedures have not been applied to muscles in the lower extremities. The lower limb muscles are an important target for physical therapy. Applying the technique of ECCT measurement to unconscious patients would allow detection of the onset of E-C coupling impairment even in the absence of any voluntary movement, and facilitate decision on the timing of initiating physical therapy.

In the present study, the soleus muscle was chosen as the lower limb muscle, and the relations between CMAP, MRP, ECCT, and muscle strength (torque) were examined in healthy subjects.

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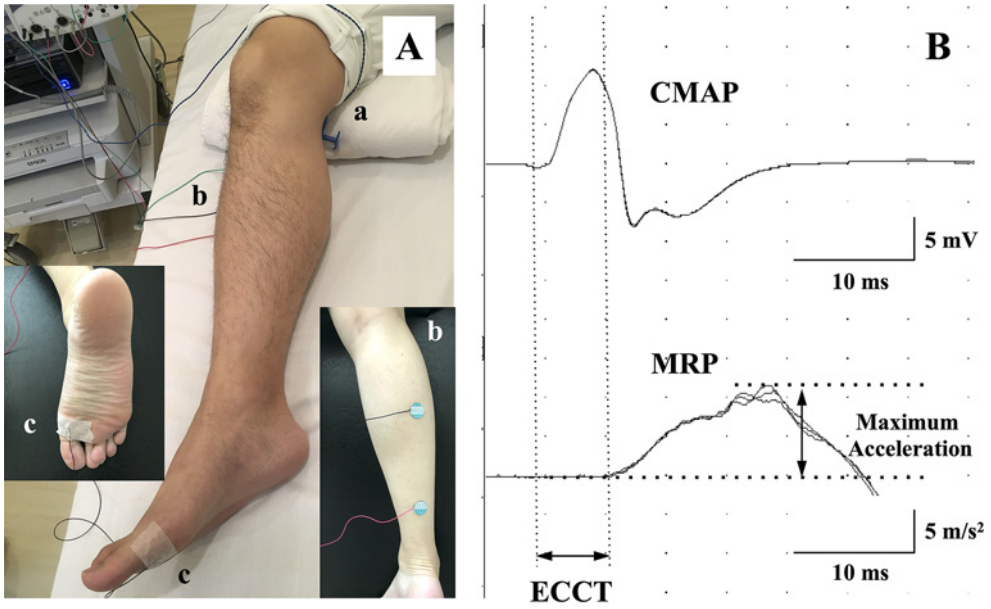

Figure 1. Tibial nerve stimulation with simultaneous recordings of compound muscle action potential (CAMP) and movement-related potential (MRP) from the soleus muscle. (A) Placement of electrodes and accelerometer. The subject resting supine on the bed shows spontaneously flexed ankle joint at 40° (plantar flexion). After tibial nerve stimulation at the popliteal fossa (a), CMAPs are recorded from the soleus muscle using surface disc electrodes in belly-tendon arrangement (b). Simultaneously, MRPs are recorded using an accelerometer taped at the base of hallux (c). (B) Representative waveforms of CMAP and MRP. The amplitude of CMAP is measured from the baseline to the negative peak. Maximum acceleration of foot movement is measured from the initial peak amplitude of MRP. Excitation-contraction coupling time (ECCT) is obtained from the difference of onset latencies between CMAP and MRP.

Methods

1. Subjects

We studied 36 healthy subjects (22 males and 14 females) aged 22 to 82 years (median, 24 years; mean, 40.3 years) at Sapporo Medical University Hospital.

The inclusion criteria and exclusion criteria were as follows:

1) Inclusion criteria

・Person 18 years of age or older

・Person who could maintain supine and prone positions, which are the measurement positions

・Person who could understand the explanations of the assessor and undergo measurements

・Person who gave informed consent to participate in this research

2) Exclusion criteria

・Person with neurological or orthopedic disorders that may affect measurement

・Person who had significant contractures on the joints of the extremities and who had difficulty performing measurements

・People who had inflammation, abrasions, incision, or other wounds on the skin of the body part on which electrical stimulation and electrodes were installed

The median (mean, range) height, weight, body mass index (BMI) and shoe size were 166.0 (166.1, 149.0-181.0) cm, 59.5 (61.8, 46.0-89.0) kg, 22.2 (22.3, 17.3-29.1) and 24.5 (25.0, 23.0-28.5) cm, respectively. A subject was instructed to lie supine on the bed for measurement of range of motion (ROM) and E-C coupling time (Fig. 1), and then lie prone on a custom-made apparatus for torque measurement (Fig. 2). These measurements were performed successively within an hour in our laboratory.

This study was approved by the ethics committee, Sapporo Medical University, Sapporo, Japan (reference number 23-86). All subjects gave informed consent for participation in this study.

2. Measurement of excitation-contraction coupling time

All stimulating and recording procedures were performed using an electromyograph (Nicolet Biomedical, Nicolet Viking Select). Before the electrophysiological assessment, the baseline ankle joint angle was measured using a goniometer (Tokyo University type, 300 mm in length). CMAPs were recorded from the soleus muscle using surface disc electrodes in belly-tendon arrangement, after tibial nerve stimulation at the popliteal fossa. The active elec-

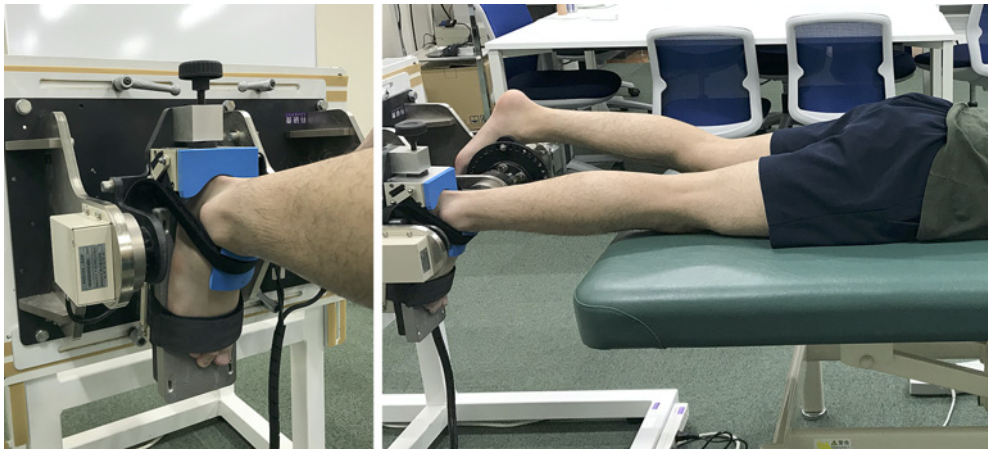

Figure 2. Measurement of torque during isometric ankle plantar flexion using a custom-made ankle joint torque meter. The subject lies prone on the bed. The foot is fixed to the foot plate by a strap, and the ankle joint angle was flexed at 0° for ankle dorsiflexion. The subject is asked to exert force only to execute ankle plantar flexion during isometric contraction.

trode (G1) was placed over the belly of soleus muscle at one-third of the distance from the popliteal crease to the heel, and reference electrode (G2) over the Achilles tendon at one-third of the distance from the heel to the popliteal crease. Simultaneously, MRPs were recorded using an accelerometer (NEC, SV1101) taped at the base of hallux (Fig. 1). The amplitude of CMAP was measured from the baseline to the negative peak using a cursor. The maximal acceleration of foot movement was obtained from the initial peak amplitude of MRP. For stimulation, a 0.2-ms rectangular pulse was delivered to the tibial nerve at the popliteal fossa with gradually increasing intensity to reach a supramaximal response. Once a supramaximal CMAP was obtained, resting CMAP and MRP were recorded successively.

The ECCT was defined as the difference in onset latencies between soleus CMAP and plantar MRP (Fig. 1). We confirmed the reproducibility of the test by repeating a set of several recordings (four times minimum), although our previous study already showed that the latencies of mandibular and thumb MRP were highly reproducible with minimal inter-trial variation[7,8]. The MRP with the shortest latency was used as the representative data for measurements of ECCT and maximal acceleration.

3. Measurement of torque during isometric ankle plantar flexion

The isometric ankle plantar flexion task was performed using a custom-made ankle joint torque meter (Takei Scientific Instruments Co. Ltd.) (Fig. 2). The subject was instructed to lie prone on the bed. The foot was fixed to the foot plate by a strap, the ankle joint angle was flexed at 0° for ankle dorsiflexion. The trunk was not fixed with a belt or other object, and the subject was instructed to grasp the edge of the bed with the upper limbs. During isometric contraction, the subject was asked to exert force to execute only ankle plantar flexion. Each subject performed three trials with $\geq$ 2 min of rest between trials. If the three exerted forces differed by more than 5% between two successive trials, an additional trial was imposed[9]. To record the maximum ankle plantar flexion torque, vigorous encouragement was given to the subject during isometric contraction. After three favorable recordings were completed, the three torques obtained were averaged, and the averaged value was then used as the representative torque during isometric ankle plantar flexion[10]. We also calculated the ratio of torque per body weight (Nm/kg) using the averaged torque and body weight of each subject.

4. Effects of age

The CMAP, MRP, ECCT and ankle plantar flexion torque measured in this study may be affected by age. Therefore, we divided the subjects by the mean age of the group (40.3 years) as the cutoff point into a younger group ($\leq$ 40 years) and an older group (> 40 years), and compared the variables between the two groups.

5. Statistical analysis

Before correlation analysis, Shapiro-Wilk test was conducted to examine if each variable was normally distributed. We used Pearson's correlation coefficient when the variable is normally distributed, and Spearman's rank correlation coefficient when the variable is not normally distributed. Correlation between variables was examined using linear regression analysis. The t-test was used to compare the differences between groups for each variable. The computer software package IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis, and a p-value of below 0.05 was considered as statistically significant.

Results

The median (mean, range) ROM of ankle joint was 17.5 (19.2, 5.0-50.0)° for dorsiflexion and 55.0 (51.4, 30-75)° for plantar flexion. In supine position for ECCT measurement (Fig. 1), the baseline angle of the ankle joint (mean ± SD) was 38.3 ± 7.2° (plantar flexion). Table 1 shows the average values of electrical and mechanical parameters in 36 normal subjects. We confirmed that all these variables were normally distributed using Shapiro-Wilk test before conducting correlation analysis. The values (mean, SE) of CMAP, MRP, ECCT, ankle plantar flexion torque and torque/body weight were 13.4 ± 0.9 mV, 5.3 ± 0.4 m/s^2, 5.2 ± 0.1 ms, 85.9 ± 6.4 Nm and 1.4 ± 0.1 Nm/kg, respectively.

Table 2 showed Pearson's correlation coefficients for the relations between CMAP, MRP, ECCT, ankle plantar flexion torque and torque/body weight. A significant correlation was observed between CMAP and MRP ($p = 0.031$), CMAP and torque ($p = 0.041$), and ECCT and torque ($p = 0.045$). The plantar flexion ROM correlated significantly with mechanical parameters such as plantar flexion torque ($p = 0.015$) and torque/body weight ($p = 0.004$), but did not correlate with electrophysiological parameters of CMAP, MRP and ECCT. In addition, the shoe size and the measured angle of the ankle joint, which were expected to affect MRP, did not correlate with MRP ($r = 0.052$; $p = 0.764$, $r = 0.158$; $p = 0.359$).

CMAP and MRP increased while ECCT decreased as ankle plantar flexion torque increased (Fig. 3). The torque of plantar flexion showed a positive linear correlation with CMAP amplitude ($R^2 = 0.116$, $p = 0.041$; regression equation: CMAP [mV] = 0.047 × plantar flexion torque [Nm] + 9.368) and a negative linear correlation with ECCT ($R^2 = 0.113$, $p = 0.045$; regression equation: ECCT [mV] = -0.008 × plantar flexion torque [Nm] + 5.824). The relation between torque and MRP did not reach statistical significance ($R^2 = 0.0142$, $p = 0.178$; regression equation: [mV]= 0.0142 × plantar flexion torque [Nm] + 4.042).

The variables for each group are presented as mean ± SE. Since each variable had a normal distribution, Student's t-test was performed and the results are shown in Fig. 4. The CMAP was significantly lower in the older group (10.5 ± 1.1 mV) than in the younger group (15.0 ± 1.1 mV) ($t = 2.722$; $df = 34$; $p = 0.010$). Similarly, MRP was significantly lower in the older group (4.3 ± 0.4 m/s^2) than in the younger group (5.8 ± 0.6 m/s^2) ($t = 2.122$; $df = 33.788$; $p = 0.041$). On the other hand, ECCT was not significantly different between the younger (5.3 ± 0.2 ms) and the older groups (5.0 ± 0.3 ms) ($t = 0.751$; $df = 34$; $p = 0.458$). The ankle plantar flexion torque was significantly lower in the older group (53.0 ± 5.0 Nm) than in the younger group (104.5 ± 7.1 Nm) ($t = 5.926$; $df = 33.905$; $p < 0.0005$). These results show that CMAP amplitude, MRP, and ankle plantar flexion torque are affected by age, whereas ECCT is not affected.

Table 1. Average values of electrical and mechanical parameters in normal subjects (n=36)

CMAP amplitude	13.4 ± 0.9 mV
MRP	5.3 ± 0.4 m/s^2
ECCT	5.2 ± 0.1 ms
Torque	85.9 ± 6.4 Nm
Torque/body weight	1.4 ± 0.1 Nm/kg

Data are expressed as mean ± standard error. Torque denotes ankle plantar flexion torque.
CMAP, compound muscle action potential; MRP, movement-related potential; ECCT, excitation-contraction coupling time

Discussion

The present results showed a significant correlation between soleus CMAP and MRP amplitude, and between

Table 2. Pearson's correlation coefficients of electrical and mechanical parameters

	MRP	ECCT	Torque	Torque/body weight	ROM
CMAP amplitude	0.361*	0.003	0.343*	0.477**	0.135
MRP		-0.137	0.230	0.270	0.119
ECCT			-0.336*	-0.185	0.198
Torque				0.926**	0.402*
Torque/body weight					0.470**

*$p < 0.05$, **$p < 0.01$, significant correlation between 2 parameters
Torque and ROM indicate ankle plantar flexion torque and range of motion of ankle plantar flexion, respectively.
CMAP, compound muscle action potential; MRP, movement-related potential; ECCT, excitation-contraction coupling time

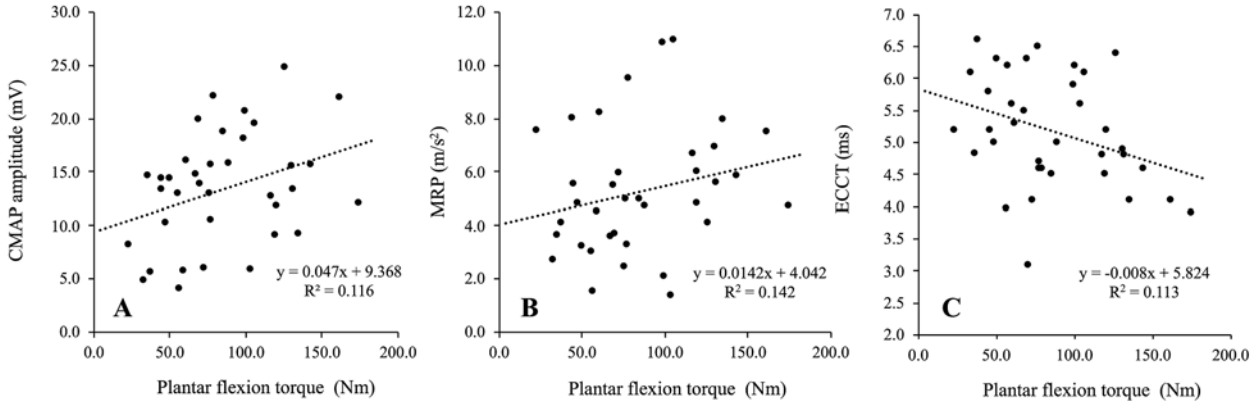

Figure 3. Correlation between torque of plantar flexion and CMAP (A), MRP (B) or ECCT (C). Linear regression analyses show a significant positive correlation between torque and CMAP (p = 0.041) and a negative correlation between torque and ECCT (p = 0.045), but no significant correlation between torque and MRP (p = 0.178). CAMP, compound muscle action potential; MRP, movement-related potential; ECCT, excitation-contraction coupling time.

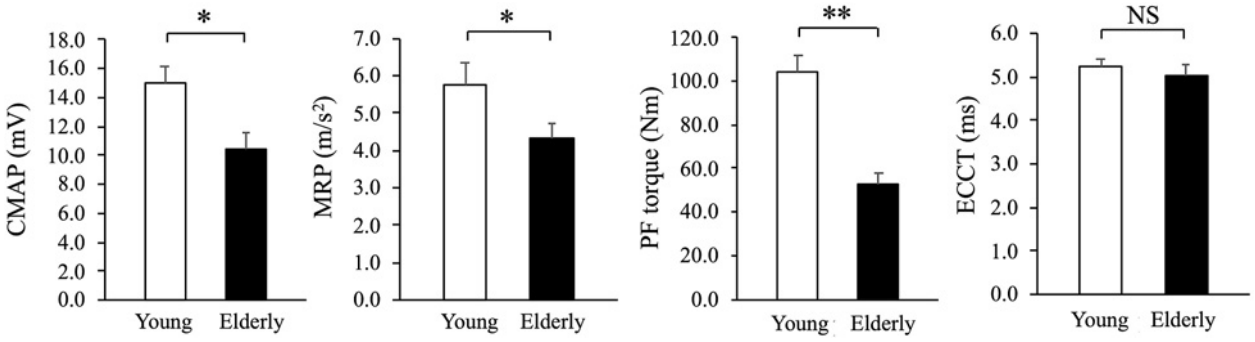

Figure 4. Comparison of CMAP, MRP, ankle plantar flexion torque and ECCT in young (open column) and elderly (closed column) groups. The column and bar indicate mean and SE in each group. CAMP, compound muscle action potential; MRP, movement-related potential; PF, plantar flexion; ECCT, excitation-contraction coupling time. *: p<0.05, **: p<0.01, NS: not significant, by Student's t-test

soleus CMAP and torque of ankle plantar flexion. In addition, soleus MRP was higher as torque increased, although the relationship did not reach statistical significance for linear correlation. These results indicate that soleus CMAP and muscle strength of ankle plantar flexion could be estimated using soleus MRP. Furthermore, a significant correlation was found between soleus ECCT and muscle strength, similar to the significant correlation between masseteric ECCT and bite force[7]. A change in bite force should represent a change in strength of the masseter muscle, because a significant correlation between the magnitude of bite force and masseter morphology has been reported[11,12]. On the other hand, the torque of ankle plantar flexion may include activities of muscles other than the soleus muscle, such as posterior tibial muscle and toe flexor muscles[13]. Therefore, it should be noted that our results may not indicate a direct correlation between soleus muscle strength and soleus CMAP, MRP or ECCT.

The present method can be applied to assess the impairment of E-C coupling associated with neuromuscular disorders even in unconscious patients. For example, intensive care unit-acquired weakness (ICUAW) may be a major target for clinical application of this method. Studies have indicated that ICUAW may be caused by inactivation of muscle membrane derived from sodium channel dysfunction and selective loss of myosin in the skeletal muscle fibers[14,15]. In addition, an experimental study revealed impaired calcium ion release from the sarcoplasmic reticulum, which may in turn cause impairment of E-C coupling in a rat model of ICUAW[16]. Currently, there is no useful technique for assessment of the onset of ICUAW in unconscious patients. The present technique would allow detection of the development of ICUAW even in the absence of any voluntary movement, and facilitate clinical decision of the prescription of physical therapy as soon as ICUAW occurs.

Previous publications have reported the effects of aging on joint ROM as reflected by plastic changes of the muscle-tendon complex and age-related deterioration in flexibility[17,18]. However, our results show no significant cor-

relation between ankle ROM and electrophysiological parameters including CMAP, MRP and ECCT. These results indicate an additional advantage of our technique in allowing robust measurement without being affected by ankle ROM. On the other hand, aging may affect the distribution of skeletal muscle fiber type and sarcoplasmic function[19-21]. Age-related increase of slow twitch fibers may induce slowing of muscle contraction and decrease of phasic muscle power. Also, functional decline of sarcoplasmic reticulum may induce decrease of calcium ion release in the muscle fiber, which may result in impairment of E-C coupling. Further studies in healthy subjects aged over 60 are required to elucidate the possible relationship between aging and the electrophysiological parameters measured using our technique[22], and to establish the precise age-matched normal ranges of these parameters.

Conclusions

In this study, the normal values of CMAP, MRP, ECCT, and muscle strength of the triceps surae muscles were established, and the relationships of these parameters were demonstrated in healthy subjects. The present method is useful for assessing E-C coupling impairment in the lower limb muscles.

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Conflict of Interest: None of the authors has any conflict of interest to disclose.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Estimation of minimal clinically important difference for quadriceps and inspiratory muscle strength in older outpatients with chronic obstructive pulmonary disease: a prospective cohort study

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ABSTRACT. Objective: To estimate the minimal clinically important difference (MCID) of quadriceps and inspiratory muscle strength after a home-based pulmonary rehabilitation program (PRP) in chronic obstructive pulmonary disease (COPD). Method: Eighty-five COPD patients were included. Quadriceps maximal voluntary contraction (QMVC) was measured. We measured maximal inspiratory mouth pressure (PImax), the 6-minute walk distance (6MWD), the chronic respiratory questionnaire (CRQ) and the modified Medical Research Council dyspnoea score (mMRC). All measurements were conducted at baseline and at the end of the PRP. The MCID was calculated using anchor-based (using 6MWD, CRQ, and mMRC as possible anchor variables) and distribution-based (half standard deviation and 1.96 standard error of measurement) approaches. Changes in the five variables were compared in patients with and without changes in QMVC or PImax >MCID for each variable. Results: Sixty-nine COPD patients (age 75±6 years) were analysed. QMVC improved by 2.4 (95% CI 1.1-3.7) kgf, PImax by 5.8 (2.7-8.8) cmH_2O, 6MWD by 21 (11-32) meters and CRQ by 3.9 (1.6-6.3) points. The MCID of QMVC and PImax was 3.3-7.5 kgf and 17.2-17.6 cmH_2O, respectively. The MCID of QMVC (3.3 kgf) could differentiate individuals with significant improvement in 6MWD and PImax from those without. Conclusion: The MCID of QMVC (3.3 kgf) can identify a meaningful change in quadriceps muscle strength after a PRP. The MCID of PImax (17.2 cmH_2O) should be used with careful consideration, because the value is estimated using distributionbased method.

Key words: minimal clinically important difference, muscle strength, chronic obstructive, quadriceps muscle, respiratory muscles

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Weakness of the quadriceps[1)] and respiratory muscle[2)] is an important extrapulmonary manifestation of chronic obstructive pulmonary disease (COPD). Quadriceps muscle weakness contributes to exercise intolerance[3)] and influences survival[1)] in COPD, and respiratory muscle weakness leads to dyspnoea and reduced exercise tolerance in COPD[4)]. Lower limb muscle strength training alone or in combination with endurance training improves quadriceps muscle strength[5,6)], and has inconsistent effects on dyspnoea, exercise capacity and health-related Quality of Life (hQOL) in patients with COPD[5)]. Inspiratory muscle training (IMT) alone or combined with a pulmonary rehabilita-

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tion program (PRP) improves inspiratory muscle strength and endurance, dyspnoea and walking distance in patients with COPD[7,8]. Therefore, lower limb muscle strength training and IMT are the important parts of PRP in individuals with COPD[9]. In consequences of it, a position statement on pulmonary rehabilitation has stated that quadriceps muscle strength should be measured and, if possible, inspiratory muscle strength also should be measured[10].

When interpreting the effects of PRP, the minimal clinically important difference (MCID) is usually used. The MCID of relevant outcomes of PRP have been established, including dyspnoea[11], exercise tolerance[12] and hQOL[13] in stable patients with COPD. There is, however, only one report on the MCID of quadriceps muscle strength after PRP in COPD[14], and the MCID of inspiratory muscle strength remains unestablished. Moreover, the MCID of quadriceps muscle strength has been determined using a distribution-based approach[14]. Although the MCID can be used to evaluate the effect of PRP, it is desirable to determine MCID using an anchor-based approach[15].

If the MCID of quadriceps and inspiratory muscle strength is established, the MCID could help clinicians not only assess whether improvement in muscle strength is clinically meaningful but also interpret how changes in muscle strength contribute to improvement in relevant outcomes (e.g. dyspnoea, exercise capacity, and hQOL) after PRP in COPD. We aimed to estimate the MCID of quadriceps and inspiratory muscle strength after a 3-month PRP in individuals with COPD using anchor-based and distribution-based approaches.

Method

Study design and patients

This study was a prospective cohort study conducted in an acute care hospital. Eighty-five participants of the current study were outpatients with COPD who were referred for a PRP and enrolled in a 3-month PRP from March to September in 2015 to 2017 in our hospital. The inclusion criteria were as follows: age ≥65 years, diagnosis of COPD according to international guidelines[16], no exacerbations of COPD in the previous 3 months and the ability to provide written informed consent. The exclusion criteria were as follows: diagnosis of dementia or other mental disorders, inability to communicate and neurological or musculoskeletal conditions that limit mobility. All measurements were performed at initiation and the end of PRP. This study was performed in conformity with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of Akita City Hospital, 2015 (accepted No.14).

Quadriceps muscle strength

Quadriceps maximal voluntary contraction (QMVC) was measured using the Hydromusculator GT-160 (OG Giken Co., Okayama, Tokyo, Japan) in accordance with the technique described by Seymour et al[17]. Outpatients were positioned in a standard fashion (seated with knees and hips flexed at 90 degrees) and their hip joints and thighs were fixed with belts to ensure that they remained seated. QMVC was defined as the highest mean force that could be sustained for longer than 1 s. Measurements were repeated at least thrice. A rest period of 30 to 60 s was provided between each contraction to allow outpatients to recover from each effort. The highest force was recorded as the patient's QMVC.

Inspiratory muscle strength

Maximal inspiratory mouth pressure (PImax) was measured as respiratory muscle strength using a respiratory dynamometer (VITALOPOWER KH-101, Chest MI, Inc., Tokyo, Japan) following the method recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS)[18]. The inspiratory pressure was maintained for at least 1.5 s, and the maximum pressure sustained for 1 s was recorded as PImax. After careful instructions and practice, measurements were repeated at least thrice, and the highest measurement was used for analysis.

Anchor variables

The modified Medical Research Council dyspnoea score (mMRC)[19], 6-minute walk distance (6MWD) and chronic respiratory questionnaire total score (CRQ)[20,21] were selected as anchor variables for determining MCID for quadriceps and inspiratory muscle strength, because these outcomes are relevant to individuals with COPD and MCID of the three outcomes is established.

The 6MWD test was performed in accordance with the European Respiratory Society (ERS)/American Thoracic Society (ATS) technical standards[22]. The examiners encouraged outpatients every minute of the test using two phrases: "You are doing well" or "Keep up the good work". Outpatients were allowed to stop and rest during the test, but were instructed to resume walking as soon as they could. Outpatients did not practice the 6MWT and underwent a single test.

Pulmonary rehabilitation program

The 3-month PRP was a multidisciplinary home-based program including supervised breathing and exercise training ones every two weeks, education ones a month at our hospital, and unsupervised home-based training every day except days with supervised sessions at their home[23]. Exercise training included upper and lower limb exercises including COPD sitting exercise[24], respiratory muscle stretching, level walking, and inspiratory muscle training (IMT). COPD sitting exercise was performed 1 to 2 sets according to their tolerance. Intensity of level walking was set at 3 to 4 on modified Borg dyspnoea scale. Outpatients were in-

structed to walk at least 15 min and increase the duration of walking up to 60 min. IMT was performed using an inspiratory muscle trainer set at a training intensity of 30%-40% of the PImax. Outpatients were instructed to perform 30-breath twice. The intensity of exercise was reset based on the patient's condition at supervised sessions. The outpatients also underwent a monthly 45-min education program including lectures about equipment use, nutrition, stress management, relaxation techniques, home exercises and the benefits of PRP. Outpatients were asked to practice the same program at their home. Outpatients were instructed to record in an exercise diary each time they completed home-based training. The diary included a checkbox to indicate which of the 4 prescribed exercises were completed. We checked their records at supervised session. Completion of PRP was defined when the completion rate of PRP was more than 60%.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, NY, USA). The assumption of normality was assessed graphically and using the Shapiro-Wilk test. P-values <0.05 were considered statistically significant. To check attrition bias, we compared baseline characteristics of outpatients with COPD who completed RPR (completer) to those not (non-completer).

Paired t-tests were used to determine changes in QMVC, PImax, 6MWD and CRQ before and after PRP. Wilcoxon's signed rank test was used for mMRC. Pearson's or Spearman's rank correlations were performed to assess correlations between changes in anchors and muscle strength.

For estimating MCID of muscle strength, we used anchor-based[14] and distribution-based[25,26] methods in accordance with previous studies. In the current study, a change of 1 point in mMRC[11], 30 metres on the 6MWD test[12] and 10 points on the CRQ[13] were considered as clinically significant changes. The anchor was used to calculate MCID for QMVC and PImax if the anchors fulfilled the following criteria: anchors changed significantly after PRP, and the correlation between changes in QMVC and PImax and changes in anchors was more than 0.3. The MCID of the QMVC and PImax was estimated by calculating the mean change in QMVC and PImax in those achieving the MCID for the mMRC (> 1 point improvement), 6MWD (> 30 meters improvement), or CRQ (> 10 points improvement). For distribution-based methods, we calculated half the standard deviation (SD) (0.5 SD)[14] and 1.96 standard error of measurement (SEM)[25,26].

After estimating MCID, we divided the outpatients into two groups according to whether their QMVC or PImax had improved more than the lower limit of MCID of QMVC or PImax. We then compared changes in mMRC, 6MWD, CRQ, QMVC and PImax. An independent samples t-test was used for continuous variables and the Mann-Whitney U-test for nonparametric.

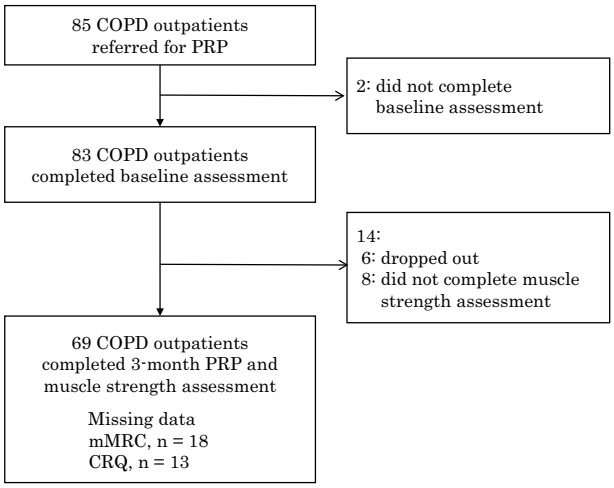

Figure 1. Study flow chart

COPD, chronic obstructive pulmonary disease; PRP, pulmonary rehabilitation program; mMRC, modified Medical Research Council dyspnoea score; CRQ, chronic respiratory questionnaire.

Sample size was estimated with the program G*Power 3.1 for paired t-test with an α of 0.05, power of 0.80, two tails and expected effect size of 0.34 which was derived from the lower limit of effect size of PRP on QOL and exercise capacity in patients with COPD[27]. The calculated sample size was 70, and considering a possible 15% drop-out and missing data rate, the final sample size was determined to be 81.

Results

The study flow chart is shown in Figure 1. Eighty-three out of 85 outpatients with COPD underwent baseline assessment and enrolled in the PRP. Finally, 69 outpatients were included in analysis. There were 18 missing data for mMRC and 13 for CRQ, respectively. Baseline characteristics of the completer and non-completer are displayed in Table 1.

Changes in anchors and muscle strength after PRP are shown in Table 2. The 6MWD improved more than 30 metres in 26 out of 69 outpatients, and the CRQ total increased by more than 10 points in ten out of 56 outpatients.

Figure 2 shows the results of the correlation analyses. There was a correlation (r_s >0.3) between changes in quadriceps muscle strength and 6MWD. Therefore, 6MWD was used as an anchor to calculate the MCID of QMVC. Table 3 shows the MCID of QMVC and PImax.

Table 4, 5 show the differences in changes in mMRC, 6MWD, CRQ, QMVC and PImax between the outpatients with minimal clinically important changes in QMVC (>3.3

Table 1. Baseline characteristics of the completer and non-completer

Variables	Completer	Non-completer	P value	95%CI (lower～upper)
n	69	14	N.A.	N.A.
Age, years	75 (6)	73 (6)	0.200	-1～6
Sex(m:f), n	65:4	14:0	N.A.	N.A.
Height, cm	162.2 (6.7)	167.6 (4.5)	0.006	-9.1～-1.6
Weight, kg	54.6 (10.3)	59.6 (7.6)	0.094	-10.7～0.9
BMI, kg/m^2	20.7 (3.4)	21.2 (2.4)	0.620	-2.4～1.4
FFM, kg	42.1 (7.7)	49.9 (5.6)	0.001	-12.1～-3.5
FFMI, kg/m^2	15.9 (2.3)	17.8 (1.6)	0.005	-3.1～-0.6
FEV_1, L	1.34 (0.63)	1.35 (0.67)	0.992	-0.37～0.37
FEV_1, %pred	57 (26)	56 (27)	0.432	-17～7
GOLD stage, I/II/III/IV	12/27/21/9	1/7/4/2	0.684	N.A.
mMRC	2 (1, 3)	2 (1, 3)	0.025	0～1
6MWD, m	401 (156)	443 (198)	0.378	-138～53
CRQ, point	104.8 (22.7)	104.1 (17.7)	0.918	-12.3～13.7
QMVC, kg	31.5 (10.6)	42.8 (11.5)	0.001	-17.5～-5.0
QMVC-BW	0.58 (0.17)	0.70 (0.17)	0.011	-0.23～-0.03
PImax, cmH_2O	69.0 (34.4)	112.5 (35.7)	< 0.001	-63.6～-23.3

SD, standard deviation; N.A., not applicable; m, male; f, female; BMI, body mass index; FFM, fat free mass; FFMI, fat free mass index; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease classification of severity of airflow obstruction; mMRC, modified medical research council dyspnea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction. Data are presented as mean (SD) or median (25th, 75th percentile).

Table 2. Changes in outcome measures before and after 3 months pulmonary rehabilitation program

Variables	Baseline	at 3 months	Mean difference	P value	95%CI (lower～upper)
mMRC (n = 51)	2 (1, 3)	2 (1.5, 3)	N.A.	0.881	N.A.
6MWD, m (n = 69)	401 (156)	422 (156)	21 (43)	< 0.001	11～32
CRQ, point (n = 56)	104.8 (22.7)	108.7 (22.2)	4.0 (8.7)	< 0.001	1.6～6.3
QMVC, kg (n = 69)	31.5 (10.6)	33.9 (11.2)	2.4 (5.4)	< 0.001	1.1～3.7
QMVC-BW (n = 69)	0.58 (0.17)	0.61 (0.16)	0.04 (0.10)	0.008	0.01～0.06
PImax, cmH_2O (n = 69)	69.0 (34.4)	74.8 (33.2)	5.8 (12.7)	< 0.001	2.7～8.8

N.A., not applicable; mMRC, modified medical research council dyspnea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction. Data are presented as mean (SD) or median (25th, 75th percentile).

kgf) or PImax (>17.2 cmH_2O) (responder-QMVC and responder-PImax, respectively) and those without (non-responder-QMVC and non-responder-PImax, respectively). Changes in 6MWD and PImax were significantly greater in responder-QMVC outpatients compared to non-responder-QMVC outpatients. In contrast, only changes in PImax were significantly different between responder-PImax and non-responder-PImax outpatients.

Discussion

To the best of our knowledge, this is the first study to report the MCIDs of QMVC and PImax using anchor-based and distribution-based methods in outpatients with COPD who underwent a PRP. These MCID values can be used to evaluate whether the changes in quadriceps and inspiratory muscle strength are clinically important after PRP in outpatients with COPD.

MCID of quadriceps muscle strength

To date, there have been no reports on the MCID of QMVC calculated using the anchor-based method, so the values may enable clinicians to evaluate whether the changes in quadriceps muscle strength is clinically meaningful. MCID of 3.3 kgf is 10.5% of the mean of baseline QMVC (3.3 to 31.5 kgf). The value is reported to be within and near the lower limit of the mean changes in isometric quadriceps muscle strength (10 - 21%) in patients with

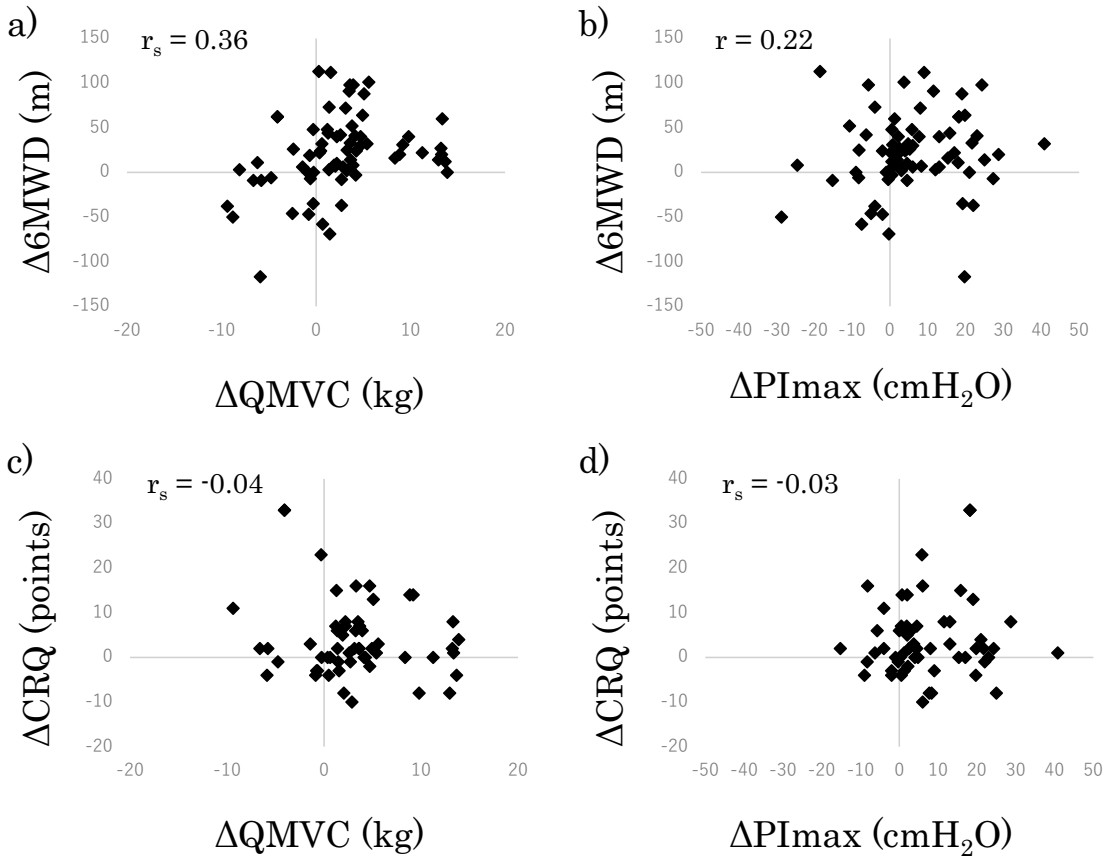

Figure 2. Correlation between changes in QMVC and PImax and changes in 6MWD and CRQ
Δ, changes in each outcome; QMVC, quadriceps isometric maximum voluntary contraction; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; r_s, Spearman's rank correlation coefficients; r, Pearson's correlation coefficients.

Table 3. Minimal clinically important differences of muscle strength

	Anchor-based	Distribution-based	
	Anchor: 6MWD	0.5 SD	1.96 SEM
QMVC, kg	3.3	5.3	7.5
PImax, cmH_2O	N.A.	17.2	17.6

6MWD, six-minute walk distance; SD, standard deviation; SEM, standard error of measurement; QMVC, quadriceps isometric maximum voluntary contraction; PImax, maximum inspiratory pressure; N.A., not applicable.
The SEM of QMVC and PImax is 3.8 kgf and 9.0 cmH_2O, respectively.

COPD who completed a muscle strength training program[6]. Therefore, the MCID value of 3.3 kgf is acceptable. Although the MCID of QMVC estimated using a distribution-based approach was higher than the MCID estimated using an anchor-based approach, we recommend using 3.3 kgf as the MCID of QMVC. The first reason for this is that the MCID derived from a distribution-based approach may be clinically significant, but not minimal[15]. Another reason is because a distribution-based approach is anchor-free, and an MCID estimated using a distribution-based approach could be meaning-free[15]. Moreover, changes in 6MWD and PImax were significantly higher in responder-QMVC outpatients compared to non-responder-QMVC outpatients. Therefore, the MCID of QMVC (3.3 kgf) derived from the anchor-based approach should be used. When using this value, measurement error of QMVC should be considered, because the SEM[25] of QMVC (3.8 kgf) was slightly higher than 3.3 kgf. For example, if the change in QMVC falls within 3.3 to 3.8 kgf, it is unclear whether the change is training-related or due to a measurement error. In contrast, if the change in QMVC exceeds 3.8 kgf, clinicians could be confident that the improvement in QMVC is not due to measurement error and may contribute to at least improvement in exercise capacity and respiratory muscle strength.

MCID of inspiratory muscle strength

This is the first study to investigate the MCID of PImax (17.2 - 17.6 cmH_2O) in outpatients with COPD using a distribution-based approach. The value was similar to overall changes in PImax (13.0 cmH_2O) that was calculated by meta-analysis after IMT in patients with COPD[7]. Previous clinical trial experience, including a systematic review and meta-analysis of clinical trial literature, could be used to de-

Table 4. Changes in outcomes in patients with clinically minimal changes in QMVC

Variables	ΔQMVC, kgf		P value	95%CI
	>3.3 (n=27)	3.3≦ (n=42)		
ΔMRC	0 (0, 0)	0 (0, 0)	0.980	0 ～ 0
Δ6MWD, m	31.0 (16.0, 60.0)*	6.5 (-9.0, 40.0)	0.002	10.0 ～ 48.0
ΔCRQ, point	2.0 (0, 7.5)	2.0 (-2.0, 7.0)	0.703	-3.0 ～ 4.0
ΔQMVC, kg	5.1 (3.9, 11.2)*	0.35 (-2.50, 1.90)	< 0.001	4.9 ～ 10.2
ΔPImax, cmH_2O	9.6 (13.8)*	3.3 (11.5)	0.044	0.2 ～ 12.4

Δ, changes in each outcome; QMVC, quadriceps isometric maximum voluntary contraction; mMRC, modified Medical Research Council dyspnoea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; PImax, maximum inspiratory pressure.
* $p < 0.05$.
Data are presented as mean (SD) or median (25th, 75th percentile).

Table 5. Changes in outcomes in patients with clinically minimal changes in PImax

Variables	ΔPImax, cmH_2O		P value	95%CI
	>17.2 (n=16)	17.2≦ (n=53)		
ΔMRC	0 (0, 0)	0 (0, 0)	0.788	0 ～ 0
Δ6MWD, m	20.6 (53.7)	21.3 (40.4)	0.956	-25.6 ～ 24.2
ΔCRQ, point	2.0 (0, 8)	2.0 (-1.0, 7.0)	0.640	-4.0 ～ 6.0
ΔQMVC, kg	3.6 (-2.4, 5.3)	2.0 (-0.3, 3.9)	0.486	-2.9 ～ 3.6
ΔQMVC-BW	0.05 (-0.06, 0.10)	0.03 (0.00, 0.06)	0.594	-0.05 ～ 0.06
ΔPImax, cmH_2O	21.4 (19.1, 24.7)*	1.3 (-4.0, 5.8)	< 0.001	17.5 ～ 24.8

Δ, changes in each outcome; PImax, maximum inspiratory pressure; mMRC, modified Medical Research Council dyspnoea score; 6MWD, six-minute walk distance; CRQ, Chronic Respiratory Questionnaire; QMVC, quadriceps isometric maximum voluntary contraction.
* $p < 0.05$.
Data are presented as mean (SD) or median (25th, 75th percentile).

termine clinically significant changes in an outcome[15]. Therefore, the MCID of PImax in the current study was acceptable. The value enables clinicians to evaluate the changes in PImax is clinically significant in terms of inspiratory muscle strength. We note that the MCID of PImax is anchor-free, so it is unclear whether improvement in PImax by more than MCID contributes to improvement in other relevant outcomes. Indeed, no significant difference in changes in the anchors was found in responder-PImax compared to non-responder-PImax outpatients in the current study. These results suggest that PImax may not always be a relevant outcome in stable outpatients with COPD undergoing PRP. In other words, PImax should be chosen as an outcome in stable COPD outpatients with reduced inspiratory muscle strength and persistent activity-related dysponea[28].

Relationships between muscle strength and anchor variables

In the current study, we chose the mMRC, 6MWD and CRQ as possible anchors due to their known MCID and relevance in individuals with COPD undergoing PRP. mMRC failed to improve after PRP and could not be used as an anchor. A possible explanation of it is that mMRC is a 5 grades scale and was not responsive to assess the effect of PRP. This is in line with previous study[29]. Correlations between changes in PImax and 6MWD were very weak, so 6MWD could not be used as an anchor for PImax. A possible explanation for the weak relationships is that many other variables, including pulmonary function, body composition and psychological factors, contribute to 6MWD in patients with COPD[30,31]. Therefore, correlations between changes in PImax and 6MWD were very weak. Correlations between changes in muscle strength and hQOL were very weak, so CRQ could not be used as an anchor for QMVC and PImax. A possible explanation for the weak relationships is that variability in the correlation between physical performance and hQOL has previously been shown[32], which is consistent with our nonsignificant and very weak correlations between changes in muscle strength

and CRQ. Therefore, correlations between changes in QMVC and PImax and changes in CRQ were very weak in this study.

Limitations

There were several limitations to this study. First, this study was a single-centre study, so the possibility of selection bias cannot be ignored. Second, attrition bias should be carefully considered, because quadriceps muscle strength at baseline was significantly lower in completer than non-completer. Copay et al. reported that the change in patient-reported outcomes depends on the baseline status of the patient[33]. Therefore, patient characteristics should be carefully considered when using the MCID values estimated in the current study. Third, our PRP was a multidisciplinary home-based program. Thus, it was unclear whether the MCID of QMVC and PImax in this study could be used in individuals with COPD undergoing supervised PRP. Forth, effects of PRP were relatively smaller in our study comparing with a previous systematic review[27]. This could affect the MCID of QMVC estimated by anchor-based method in the current study, as the number of outpatients used to calculate MCID is relatively small (n = 26). Fifth, only 6 MWD was used as an anchor to calculate MCID of QMVC due to the weak correlations of changes in QMVC and PImax to changes in anchor variables. It is recommended that multiple anchors be used to estimate MCID of an outcome when using anchor-based method[15]. Finally, the MCID of the QMVC was estimated only by calculating the mean change in QMVC in those achieving the MCID for the 6 MWD (> 30 meters improvement). This method had potential risk for overestimation of MCID of QMVC, because outpatients with large improvement in 6MWD were included to calculate MCID of QMVC. These two limitations could also affect the value of MCID of QMVC.

Conclusions

The MCID of QMVC and PImax was estimated in outpatients with COPD who underwent a PRP. A gain of at least 3.3 kgf and 17.2 cmH_2O represented a clinically meaningful improvement in quadriceps and inspiratory muscle strength after the PRP, and these values can be used to evaluate the outcomes of PRP.

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Conflict of Interest: The authors have no competing interests to declare.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Effects of physical activity on quality of life and physical function in postoperative patients with gastrointestinal cancer

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ABSTRACT. Objectives: This study was to clarify changes in physical function and quality of life (QOL) for postoperative, and to examine the influence of the amount of physical activity on these variables. Methods: This study included 29 patients who underwent gastrointestinal cancer surgery. The QOL measurement was used to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for preoperative and 2nd and 4th postoperative weeks. Physical function measured knee extension strength, 4 m walk time, 5 times sit-to-stand test, and 6-minute walk for preoperative and 1st and 2nd postoperative weeks. The amount of physical activity score was based on METs-hours, which is estimated from cumulative physical activity. As basic characteristics were investigated cancer stage, comorbidities and complications, and operative. Statistical analysis was repeated measures analysis of variance was performed to observe postoperative changes in physical function and QOL. Furthermore, stepwise multiple regression analysis was used to the parameters of physical function and QOL affected by the physical activity score were investigated. Results: Physical function decreased postoperatively and generally improved 2nd postoperative week. Though scores on the QOL functional scales improved, some items did not improve sufficiently. Multiple regression analysis showed that physical activity score had an effect on constipation and emotion functioning. Conclusions: Improvement in symptom scales is not sufficient in a short period of time, and they need to be followed up by increasing the amount of physical activity and promoting instantaneous exercise.
Key words: Postoperative, Physical activity, Quality of Life, Gastrointestinal cancer

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Surgical resection, an important treatment for gastrointestinal cancers, involves the use of general anesthesia. Controlled ventilation during surgery affects postoperative respiratory function[1,2)]. Postoperative pain, analgesia, and immobility also contribute to respiratory function deterioration[3)]. Further, in the case of patients who have undergone gastric cancer surgery, weight loss[4)] and decrease in muscle mass contribute to poor prognosis[5)].

In the Enhanced Recovery After Surgery protocols[6)] (ERAS), perioperative rehabilitation aims to promote early mobilization and increase physical activity. It is generally reported that early mobilization contributes to the prevention of pulmonary complications and improvement of respiratory function[3,7,8)]. Major abdominal surgery is associated with a reduction in functional capacity with regard to physical function, activities of daily living (ADL), and quality of life (QOL)[9)]. It has been reported that improvement of postoperative physical function takes 6 months to achieve[9)]. However, while one study indicated improvements in the 4th and 8th postoperative weeks[10)], another mentioned only the 4th postoperative week[11)]. Thus, it is evident that the postoperative recovery period is multidimensional and not constant. To improve postoperative physical function, several comparative trials on perioperative rehabilitation protocols[6,12-14)] have been conducted, but with inconsistent results.

In terms of physical function and QOL after cancer surgery, older adults have not shown sufficient ADL[15)]. Additionally, there are indications that in the postoperative stage, patients with gastric cancer present with various long-term symptoms[16)] and chronic pain even up to 6

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Table 1. Postoperative rehabilitation protocol used during the study

◯ Time schedule	
Postoperative 1st day;	Early mobilization encouraged
2nd - 5th day;	Encouragement to continue and prolong out-of-bed activities
	Walking (walking distance 400m)
	Light resistance training, respiratory exercise
6th - 9th day;	Resistance training, bicycling
	Activity of Dairy Living exercise
Continue until descharge (postoperative 10th - 14th day)	
◯ Exercise	
Aerobic exercise	
Type; Bicycling	
Strength; Set target heart rate for karvonen formula within borg scale 13	
Time; 20 - 40 minites	
Resistance training	
Type; Weight and weight load training	
Strength; About 15 repetition maximum	
Part; Lower extremity; Knee extention / Hip flexion / Hip abduction	
Hip extention / Calf raise / Squat	
Upper extremity; Elbow flexion / Shoulder abduction / Shoulder elevation	
Trunka; Abdominal exercise / Bridging	

months later[17]. A systematic review of post and perioperative rehabilitation programs has shown that exercise improves health-related QOL[18]. However, these positive results must be interpreted cautiously[18]. Owing to the heterogeneity in exercise programs and measures used to assess health-related QOL, there is a risk of bias in many trials[18]. Thus, as studies of postoperative recovery have not presented consistent results, it is important to examine the recovery of physical function and QOL in the as an example of Japan. In addition, while physical activity appears necessary to improve physical function and QOL, the specifics of exercise programs and the optimal amount of exercise they should encompass remain unclear[18].

The objective of this study was to clarify changes in physical function and QOL after a program and to examine the influence of the amount of physical activity on these variables. We hope that the results can facilitate improvements in perioperative rehabilitation programs, leading to more effective treatment.

Methods

Participants

The participants were patients who were hospitalized at the institution to which the authors are affiliated and underwent surgery for gastrointestinal cancers between June 2016 and August 2018. To be included in the study, patients had to be able to: 1) undergo physical function assessment and take a written preoperative survey; 2) undergo physical function assessments during the follow-up period; and 3) take a written survey at and after discharge. Exclusion criteria were patients' conditions that hindered physical function assessment and an inability to take a written survey.

Of the 409 patients who underwent surgery during the study period, only 32 could be investigated preoperatively. Of these, 3 patients were unable to undergo the preoperative follow-up investigation. Thus, this study included 29 patients.

Rehabilitation was performed according to the postoperative rehabilitation protocol (Table 1), which was implemented regardless of the operative procedure or the level of invasiveness. However, therapists adjusted the postoperative rehabilitation program and load according to the patient's condition. In other words, individual activities were adjusted in accordance with patients' pain levels, vital sign status, and cardiopulmonary function. The exercises were selected from criteria the criteria, like walking exercise, the aerobic program, and resistance training.

Only physical assessments considered necessary for standard therapy were performed; experimental interventions were excluded. The study complied with the Declaration of Helsinki, and written informed consent was obtained from all participants after explaining the nature of the study to them. This study was approved by the ethics committee of Kanmon Medical Center (approval number: 2016-015). This observational study was conducted according to the STROBE checklist.

Data collection

We investigated disease-specific QOL, physical function, and physical activity. Basic characteristics were obtained from medical records. Disease-specific QOL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[19]. The QLQ-C30 was administered thrice: preoperatively, in the 2nd postoperative week (at discharge), and in the 4th postoperative week. Physical function was measured using isometric knee extension strength, 4 m walk time, the 5 times sit-to-stand test, and a 6-minute walk. The knee extension strength, 4 m walk time, and 5 times sit-to-stand test measurements were taken preoperatively and in the 1st and 2nd postoperative weeks. The 6-minute walk was conducted in the 1st and 2nd postoperative weeks. Physical activity score was measured on an average of 3 days from 1st to 2nd postoperative week. Basic characteristics were collected from medical records after discharge.

Physical function measurements

Knee extension strength was measured using a handheld dynamometer (Mobie MT-100W, Sakai Medical Co., Ltd., Tokyo, Japan) based on the method introduced by Kato et al.[20]. A fixing band was used at the distal lower leg when the lower leg was hanging in the sitting position. The measurement was performed only on the right lower limb, and the average value of 2 measurements was used for analysis. The 4 m walk time measurement and 5 times sit-to-stand test were conducted according to the Short Physical Performance Battery[21] protocol. The 6-minute walk was measured according to the American Society of Thoracic Surgeons protocol[22]. If the patient took a long time to complete the 4 m walk and 5 times sit-to-stand test, the conclusion was that movement was delayed, and the patient's state was poor. If the 6-minute walk was extended, it was interpreted that the patient was in a good condition.

Disease-specific QOL measurement

The QLQ-C30 is a disease-specific QOL survey for patients with cancer that has proven valid and reliable[19]. The Japanese version of the survey used in the present study has also been reported to be accurate and reliable[23]. This patient-based assessment tool comprises the global health status to measure overall QOL, 5 functional scales to measure activity, and 9 symptom scales that measure physical symptoms. The 5 functional scales are physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The symptom scales include fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The tool includes 30 questions scored on a 4-point scale from "Not at all" to "Very much," with each category scored from 0 to 100. For categories corresponding to global health status and the functional scales, a higher score (close to 100) indicates a better condition. However, for the categories corresponding to the symptom scales, a higher score indicates a more severe condition.

Measurement of physical activity score

Physical activity score was calculated from exercise in rehabilitation and self exercises. We did not include ADL other than exercise during hospitalization. The method of calculation was based on the content of exercise and time spent doing it. Time spent doing rehabilitation was counted as actual time, and self exercises were interviewed. METs values were estimated from the surveyed exercises using Ainsworth et al.'s[24] summary of physical activity and a conversion table by the Ministry of Health, Labour and Welfare[25]. One METs is considered a resting metabolic rate obtained during sitting at rest. Defined by how much more of the subjected activity is against it[24,25]. METs-hours were calculated by multiplying the METs value of the exercise content by the time performed. The estimation of METs-hours in physical activity questions has been used in many studies[26-29], with proven reliability[30-32]. METs-hour was studied in the three days prior to discharge, approximately the 2nd postoperative week, and the mean value of three days was determined for METs-hour/day. Some study[33] of the postoperative physical activity were of short duration and used METs-hours/day. The calculation of this study was performed by the author alone. The importance of physical activity for cancer patients has been reported[26-29], and self-report measures have been the most common method of surveying the amount of physical activity[34]. From those results, estimates of METs and METs-hours were calculated. They were mainly performed on patients living at home, and the self-report measures covered all aspects of life. This study investigated only for exercise and these self-report measures were not applicable.

Investigation of basic characteristics

Basic characteristics (patient Attributes, laboratory findings, and treatment data) were investigated. A physician established cancer staging according to the TNM classification recommended by the Union for International Cancer Control[35]. Comorbidities included cancer, hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular diseases, orthopedic diseases, and medical diseases. Participants with exercise habits were those who performed exercises more than 3 METs at least thrice a week. In terms of blood laboratory findings, albumin and C-reactive protein levels were investigated preoperatively and at discharge. Respiratory function was defined as the percent vital capacity and forced expiratory volume in 1 second/forced vital capacity preoperatively.

Statistical analysis

The report was prepared according to the STROBE checklist. QLQ-C30 scores and physical function decreased significantly immediately after the surgery, with potential for subsequent improvement. We consider it necessary to know the degree of improvement in each aspect to gain a comprehensive understanding. Therefore, the mixed-effects model for repeated measures was used to elucidate postoperative changes in QLQ-C30 scores and physical function evaluation results. Multiple comparisons were performed using the Bonferroni method for items that showed significant differences in the paired t-test.

The comprehensive effect of rehabilitation after gastrointestinal surgery is undetermined[6,12-14]. Therefore, we analyzed the influence of physical activity score, including rehabilitation, on QOL and physical function. To analyze the effects of postoperative exercise on QLQ-C30 score and physical function evaluation, stepwise multiple regression analysis was performed. The dependent variable was the physical activity score, while the independent variables were the QLQ-C30 score from the 4th postoperative week and the physical function evaluation from the 2nd postoperative week.

SPSS version 25.0 for Mac (IBM Corporation, Armonk, NY, USA) and R2.8.1 (CRAN, freeware) were used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Participants' basic characteristics

The participant's descriptive statistics are shown in Table 2. Some participants had comorbidities without any serious effects on physical activity. The mean postoperative hospital stay was 15.8 ± 6.4 days. Postoperative rehabilitation was initiated on the first day after surgery and covered the entire postoperative hospital stay. Postoperative complications were found in 5 patients, including anastomotic stricture in 3 cases and anastomotic leakage in 2 cases. Patients with postoperative complications were hospitalized for an average of 26 days, which tended to prolong the overall hospitalization period. However, they had no restriction on activity.

Changes in physical function measurements and QOL from the preoperative to the postoperative period

The results of the physical function measurements and QLQ-C30 scores taken preoperatively and postoperatively, as well as the mixed-effects model for repeated measures analysis results, are shown in Table 3.

In terms of physical function measurement results (Table 3), knee extension strength decreased in the 1st postoperative week but tended to increase in the 2nd postoperative week. On the contrary, 4 m walk time and the 5 times sit-to-stand test increased in the 1st postoperative week but tended to decrease in the 2nd postoperative week. Knee ex-

Table 2. Descriptive statistics for Basic characteristics (basic data, laboratory findings, and treatment data)

Characteristic	Measurements	
Age (y)	68.2 ± 10.0	
Sex (n)	Men	19
	Women	10
Body mass index (kg/m^2)	22.7 ± 3.1	
Cancer site (n)	Liver	1
	Stomach	20
	Colon	7
	Pancreas	1
Cancer stage (n)	I	14
	II	6
	III	7
	IV	2
Preoperative chemotherapy (n)	Yes	2
	No	27
Comorbidity		
Cancer (n)	Yes	3
	No	26
Hypertension / Hyperlipidemia/ Diabetes mellitus (n)	Yes	15
	No	14
Cerebrovascular disease (n)	Yes	2
	No	27
Orthopedic disease (n)	Yes	6
	No	23
Medical disease (n)	Yes	8
	No	21
Preoperative %VC (%)	104.1 ± 17.3	
Preoperative FEV_1/FVC (%)	74.4 ± 7.8	
Preoperative albumin (g/dl)	4.1 ± 0.5	
Postoperative albumin (g/dl)	3.3 ± 0.6	
Preoperative CRP (mg/dl)	0.8 ± 2.9	
Postoperative CRP (mg/dl)	2.1 ± 2.1	
Exercise habits (n)	Yes	7
	No	22
working (n)	Yes	11
	No	18
Operative procedure (n)	Laparoscopic	17
	Laparotomy	12
Operation time (minutes)	238.5 ± 83.70	
Blood loss (ml)	147.2 ± 204.2	
Postoperative complication (n)	Yes	5
	No	24
Length of stay (day)	15.8 ± 6.4	

Units in parentheses. Results are presented as mean ± SD or number of participants.

%VC: Percent vital capacity

FEV_1/FVC: Forced expiratory volume in 1 second/ forced vital capacity

CRP: C-reactive protein

Table 3. Preoperative and postoperative changes over time in physical function measurements and EORTC QLQ-C30

		preoperative (pre)	1st postoperative week (po1w)	2nd postoperative week (po2w)	MMRM P value		
					pre vs po1w	pre vs po2w	po1w vs po2w
Physical function measurement	Knee extension strength (Nm/kg)	1.11 ± 0.45	0.94 ± 0.45	1.13 ± 0.56	N.S.	N.S.	0.030
	4 m walk time (sec)	3.33 ± 1.53	4.17 ± 1.94	3.76 ± 2.73	0.001	N.S.	N.S.
	5 times sit-to-stand test (sec)	9.57 ± 5.49	13.47 ± 6.92	11.21 ± 5.50	0.000	0.049	0.004
	6-minute walk (m)	–	336.8 ± 113.7	390.6 ± 110.4	–	–	0.000
		preoperative (pre)	2nd postoperative week (po2w)	4th postoperative week (po4w)	MMRM P value		
					pre vs po2w	pre vs po4w	po2w vs po4w
EORTC QLQ-C30	Global scales						
	Global health status	58.62 ± 25.54	53.45 ± 20.95	54.89 ± 20.84	N.S.	N.S.	N.S.
	Functional scales	81.69 ± 12.84	75.79 ± 13.84	78.93 ± 14.12	N.S.	N.S.	N.S.
	Symptom scales	14.24 ± 11.00	27.06 ± 14.48	24.14 ± 14.05	0.000	0.001	N.S.
	Functional scales						
	Physical functioning	87.36 ± 15.36	77.93 ± 18.09	80.92 ± 12.31	0.010	N.S.	N.S.
	Role functioning	85.63 ± 20.76	58.05 ± 30.09	68.97 ± 19.27	0.000	0.009	N.S.
	Emotional functioning	72.70 ± 23.13	80.75 ± 16.68	79.02 ± 23.53	N.S.	N.S.	N.S.
	Cognitive functioning	86.78 ± 15.67	81.61 ± 17.45	86.21 ± 18.4	N.S.	N.S.	N.S.
	Social functioning	76.44 ± 31.03	72.41 ± 28.27	76.44 ± 19.17	N.S.	N.S.	N.S.
	Symptom scales						
	Fatigue	20.69 ± 17.50	37.16 ± 23.62	36.40 ± 16.51	0.001	0.001	N.S.
	Nausea and vomiting	4.60 ± 14.01	5.75 ± 11.16	9.20 ± 16.42	N.S.	N.S.	N.S.
	Pain	11.49 ± 18.42	32.76 ± 25.39	26.44 ± 19.68	0.001	0.027	N.S.
	Dyspnea	11.49 ± 20.46	22.99 ± 22.01	20.69 ± 22.56	N.S.	N.S.	N.S.
	Insomnia	16.09 ± 27.63	39.08 ± 32.21	19.54 ± 26.00	0.000	N.S.	0.002
	Appetite loss	12.64 ± 22.56	34.48 ± 32.71	29.89 ± 27.23	0.002	0.019	N.S.
	Constipation	18.39 ± 28.99	29.89 ± 27.23	25.29 ± 24.65	0.025	N.S.	N.S.
	Diarrhoea	8.05 ± 14.52	18.39 ± 21.06	19.54 ± 18.93	N.S.	0.038	N.S.
	Financial difficulties	24.14 ± 34.38	18.39 ± 26.10	18.39 ± 26.10	N.S.	N.S.	N.S.

Units or details in parentheses. Results are presented as mean ± SD N.S. are Not Significant MMRM: Mixed-effects model for repeated measures

tension strength increased significantly between the 1st and 2nd postoperative weeks. The 4 m walk time increased significantly from the preoperative period to the 1st postoperative week. Performance on the 5 times sit-to-stand test increased from the preoperative period to the 1st postoperative week, decreased significantly between the 1st and 2nd postoperative weeks, and overall showed a significant increase from the preoperative period to the 2nd postoperative week. The 6-minute walk also increased significantly between the 1st and 2nd postoperative weeks.

In terms of QLQ-C30 results (Table 3), global health status and functional scale scores decreased in the 2nd postoperative week and somewhat increased in the 4th postoperative week, but the differences were not significant. Symptom scale scores increased significantly in the 2nd postoperative week. In terms of functional scale subscale items, physical and role functioning scores decreased substantially in the 2nd postoperative week. Furthermore, role functioning scores substantially reduced in the 4th postoperative week as compared to the preoperative period. Symptom scale subscale items—fatigue, pain, insomnia, appetite loss, and constipation—significantly worsened from the preoperative period to the 2nd postoperative week. Fatigue, pain, appetite loss, and diarrhea also worsened significantly between the preoperative period and the 4th postoperative week. However, insomnia decreased considerably between the 2nd and 4th postoperative weeks.

Relationship between postoperative physical activity score and postoperative physical function and QLQ-C30 score

The results of postoperative physical activity score are shown in Table 4. The main exercise items were walking, bicycling and resistance training. These activities were converted into METs and averaged over three days, resulting in 2.1 ± 0.7. According to the results of multiple regression analysis (Table 5), constipation and the emotional functioning score of the QLQ-C30 in the 4th postoperative week affected the amount of postoperative exercise. ANOVA re-

Table 4. Postoperative measurement of physical activity score (average of 3 days before discharge)

Physical activity score (METs-hour/day)	02.1 ± 0.7

Units in parentheses. Results are presented as mean ± SD
METs: Metabolic equivalents
Main activities:
[3.0METs] Walking; 2.5mph, level, firm surface
[3.5METs] Walking; 2.8 to 3.2 mph, level, moderate pace, firm surface
[3.5METs] Conditioning exercise; bicycling, stationary, 30-50 watts
[4.8METs] Conditioning exercise; bicycling, stationary, 51-89 watts
[3.5METs] Conditioning exercise; resistance (weight) training

Table 5. Stepwise multiple regression analysis results; 2nd postoperative week physical function and 4th postoperative week QLQ-C30 that affect postoperative physical activity

	Partial regression coefficient	Standard partial regression coefficient	Significant probability	95% Confidence interval	
				Lower	Upper
Constipation	-0.02	-0.69	0.00	-0.03	-0.01
Emotional functioning	-0.01	-0.50	0.02	-0.03	-0.01
Constant	-3.75		0.00	-2.61	-4.89

$R^2 = 0.33$, ANOVA $p < 0.01$, Durbin-Watson ratio = 1.69

sults were significant, but the R^2 was 0.33, indicating a low goodness of fit. The test for normality of residuals was significant.

Discussion

The purpose of this study was to examine the impact of physical activity score on postoperative physical function and QOL. Regarding physical function in the 2nd postoperative week and QOL in the 4th postoperative week, there were some items that showed significant improvements, but they were not enough. Although there are many reports[9,10,11,36] on postoperative functional recovery, there is no consensus, and we will present the interpretation of the results of this study. Few reports have examined which parts of the postoperative physical function measurements and QOL subscale are affected by the amount of physical activity. In this study, constipation symptoms tended to decrease with increased physical activity scores. The following is a discussion of changes in physical activity scores and QOL scores, and the effects of the amount of physical activity.

Open and laparoscopic surgeries for gastrointestinal cancer are highly invasive procedures, resulting in increased postoperative protein catabolism[37]. Protein catabolism degrades the muscle and reduces physical activity[37]. In addition, suppression of activity because of postoperative pain contributes to a decrease in overall physical activity[38]. The results of this study also showed reduced activity in the 1st postoperative week compared to preoperative activity levels. Performance on the 5 times sit-to-stand test in the 2 nd postoperative week did not improve back to preoperative levels. Post-operative recovery was reported that activity levels were still low at the 4th postoperative week[10]. In addition, it was reported to the time for recovery as the physical function was 6 weeks, while ADL took 6 weeks to 3 months to recover[9]. Thus, postoperative recovery requires a medium to long term period of time. In our hospital, most patients are discharged after approximately 2 weeks and return to work and social activities. We believe that this is done in the context of inadequate post-operative recovery. The 5 times sit-to-stand test and 4 m walk time are measured as an examination of the instantaneous element. There have been no reports measuring and examining these as a postoperative assessment of gastrointestinal surgery. Many post-operative exercise programs include aerobics exercise and other[11,12], resulting in an improvement in the 6-minute walk[39]. The lack of improvement in the 5 times sit-to-stand test in this study indicates that the instantaneous component is slow to improve. The 5 times sit-to-stand test is requiring more of lower limb speed and/or power[40]. Not only that, it is multidimensional, including variables such as sensory-motor, balance, and psychological parameters[40]. We think this is why the improvement differs from knee extension strength, which we consider to be a strong component of the same strength. We think that in the post-operative period, even though muscle power can be exerted, it is difficult to control overall muscular activity and balance, and that agitation due to post-operative anxiety and other emotions can affect performance on the 5 times sit-to-stand test.

The 5 times sit-to-stand test is more relevant to the IADLs, which require more complex skills than the ADLs[41]. Therefore, improving performance on the 5 times sit-to-stand test, which was inadequately improved at 2 weeks postoperatively, would improve quality of life more. Incorporating spur-of-the-moment activities into the exercise may also lead to that improvement.

In terms of the QLQ-C30, physical and role domain scores decreased in the 2nd postoperative week compared to preoperative scores. Role functioning scores in the 4th postoperative week were still lower than those before surgery; thus, the improvement was not sufficient. Many symptom scale items worsened in the 2nd postoperative week. There were also many symptoms that did not improve in the 4th postoperative week. Antonescu et al.[36] reported that QOL after gastrointestinal surgery decreased in the 1st postoperative month but returned to preoperative levels at 2 months after surgery. Therefore, the fact that a certain degree of recovery was achieved at the 4th postoperative week is a satisfactory result and an effect of accelerated activity. Matsushita et al.[42] stated that global QOL, physical scale, and appetite scores worsened before discharge, with recovery at 6 months postoperatively. However, they reported that improvements in the physical and cognitive domains and pain are not sufficient for recovery. The social domain, insomnia, and financial difficulties were reported to have improved after discharge. In the present study, the physical domain generally improved at 2nd postoperative week, but the role domain showed a lack of improvement, contrary to Matsushita et al.'s report[42]. On the contrary, in the symptom scale items, there is a general agreement in terms of insufficient improvement. The role functioning represents the performance of work, daily activities, and leisure time activities[43]. It is said to indicate the severity of the disease. However, it is also considered important to activate behaviors[43], including those that may be beneficial in promoting activities. With respect to symptom scale items, and greater residual fatigue is reported after gastric cancer surgery[44]. We think that the susceptibility to fatigue affects the role functioning and also affects emotional functioning. Although residual fatigue is strongly a result of disease characteristics, it is the exercise therapy that could improve it. Pain, appetite loss and diarrhea on the symptom scale were also not sufficiently improved, but these were more strongly influenced by treatment. These are poorly improved at 4th postoperative week, but they do improve over time[36,42,43]. There are no reports of benefit from exercise therapy, and more detailed studies are needed. This may require an instantaneous exercise component, which was not sufficiently improved in this study.

Factors related to the amount of postoperative exercise were constipation and the emotional functioning of the QLQ-C30. In our view, higher physical activity leads to a decrease in constipation and remaining instability in the emotional functioning. In their meta-analysis, Nakano et al.[45] concluded that exercise is not effective at reducing constipation in patients with cancer. However, in their systematic review, Albrecht et al.[46] found improvements in constipation. In the present study, exercise had a positive effect on constipation. After gastrointestinal surgery, peristalsis is reduced from the effects of anesthesia[47]. Postoperative ileus occurs in many cases and is believed to resolve spontaneously[48]. However, there are also cases of paralytic ileus, which may last twice as long[6]. Most of the time, medication is the mainstay of treatment, and testing the efficacy of exercise alone is difficult. However, the results of this study suggest that increased physical activity may lead to the suppression of constipation symptoms. In the future, we would like to further examine the importance and effectiveness of physical activity by adjusting for confounding factors. Activity had a positive effect on constipation, while the emotional functioning was rated lower. In the context of mental factors after gastrointestinal surgery, Schag et al.[49] reported that employed patients have a lower overall QOL; in other words, the more active they are, the lower their QOL. An association between depressive symptoms, QOL, and pain has also been reported in patients with cancer[50]. We believe that patients who are more active are also more likely to have higher goals and experience mental health problems, including anxiety about social activities. Thus, follow-up in the context of rehabilitation as well as self-activity may help mitigate psychological problems. Owing to the nature of cancer, we believe that the association between postoperative activity, exercise, and mental factors should continue to be investigated.

After gastrointestinal surgery, not only does physical function generally deteriorate but also various symptoms of the digestive system remain. Besides, as nutrition intake is challenging, patients often experience a lack of vitality and mental health problems. In this study, various factors related to postoperative physical symptoms were clarified, and we believe that they will contribute to the improvement of future interventions.

Limitations

This study has several limitations. First is the small sample size. The participants constituted only approximately 7% of surgical patients during the study period. Second, cases that meet the inclusion criteria are often cooperative, positive, and active. Therefore, the possibility of selection bias cannot be ruled out. Third, there is a possibility of measurement bias in the measurement of physical activity. In recent years, accelerometers and wearable devices have been increasingly used to measure physical activity and are considered more reliable than self-reported measures. In this study, these terminals could not be used due to cost issues and the possibility of inconvenience in wearing the devices. Fourth, there are limitations related to the analysis.

Gastrointestinal cancers can exist at multiple sites, such as the stomach and colon, which may have lowered the study's analytical accuracy. In addition, in the multivariate analysis, only QOL and physical function were used, and other confounding factors were not included. Therefore, it is necessary to adjust for confounding factors as the number of cases increases. For these limitations, the comparative trials are required, and future studies should apply appropriate methodologies to investigate the benefits of rehabilitation.

Conclusions

In this study, changes in physical function and QOL during postoperative rehabilitation were revealed. It is also important to examine whether the amount of physical activity affects physical functioning and QOL, and therefore, how the amount of physical activity affects physical function and QOL. Although physical function and QOL improved after surgery, instantaneous factors and physical symptoms were not seen for the 2nd postoperative or 4th postoperative week was not enough improvement in a short period of time. The amount of physical activity affects constipation and mental health, and we recommend increasing patients' physical activity levels. There is also a need to follow up with rehabilitation. In addition, consideration should be given to incorporating instantaneous programs.

Relevance to clinical practice

There are few reports examining the significance of rehabilitation during hospitalization in patients undergoing surgery for gastrointestinal cancers. In this study, we obtained an interesting result: a greater amount of postoperative exercise resulted in reduced constipation. The opportunity to exercise after gastrointestinal cancer surgery is not limited to rehabilitation. However, in rehabilitation, it is important to develop assessments and protocols and promote exercise in daily care.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Minimum standards of clinical practice for physical therapists working in intensive care units in Japan

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ABSTRACT. Objective: Early mobilization and rehabilitation has become common and expectations for physical therapists working in intensive care units have increased in Japan. The objective of this study was to establish consensus-based minimum clinical practice standards for physical therapists working in intensive care units in Japan. It also aimed to make an international comparison of minimum clinical practice standards in this area. Methods: In total, 54 experienced physical therapists gave informed consent and participated in this study. A modified Delphi method with questionnaires was used over three rounds. Participants rated 272 items as "essential/unknown/non-essential". Consensus was considered to be reached on items that over 70% of physical therapists rated as "essential" to clinical practice in the intensive care unit. Results: Of the 272 items in the first round, 188 were deemed essential. In round 2, 11 of the 62 items that failed to reach consensus in round 1 were additionally deemed essential. No item was added to the "essential" consensus in round 3. In total, 199 items were therefore deemed essential as a minimum standard of clinical practice. Participants agreed that 42 items were not essential and failed to reach agreement on 31 others. Identified 199 items were different from those in the UK and Australia due to national laws, cultural and historical backgrounds. Conclusions: This is the first study to develop a consensus-based minimum clinical practice standard for physical therapists working in intensive care units in Japan.
Key words: Intensive care units, Physiotherapy, Minimum standards, Education

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Early mobilization and rehabilitation in intensive care units (ICU) requires a multi-disciplinary team of doctors, nurses, and physical therapists. Physical therapists must have a minimum level of knowledge, task-related skills, and suitable attitude towards intensive care to work functionally as a member of the ICU multidisciplinary team.

In 2016, Skinner and colleagues explored consensus-

based minimum standards of clinical practice for physiotherapists working in critical care settings in Australia and New Zealand[1]. Using a modified Delphi technique, senior or specialist critical care physiotherapists and appropriate academic staff who met defined eligibility criteria completed three rounds of questionnaires to establish a framework of minimum standards. More recently, Twose and colleagues published minimum standards of clinical practice for physiotherapists working in critical care settings in the United Kingdom[2]. They followed Skinner and colleagues' research methods and used the same modified Delphi approach. These papers are useful in providing an occupational description for physical therapists working in ICU. However, the activities, scope and role of physical therapists depends on the laws, culture and history of the country. It is therefore necessary to know the minimum standards of clinical practice along with the role of physical therapy when citing and referring to overseas scientific research papers from countries with different laws and cultures relating to physical therapy.

Early mobilization and rehabilitation were not actively carried out in ICU in Japan until quite recently[1] despite Level 1 evidence of the benefit of physical therapy intervention in Western countries[2]. The Japan Society of Intensive Care Medicine (JSICM) organized the Intensive Care Early Rehabilitation Committee (ICERC) in 2014, aiming to establish a suitable system of early rehabilitation in ICU in Japan. The committee planned to develop an evidence-based expert consensus for early rehabilitation in ICU, and this was published in February 2017[3]. In financial year 2018, this led to the introduction of an additional fee for early mobilization and rehabilitation (5,000 yen/patient/day, 14 days upper limit) for ICU. Since then, early mobilization and rehabilitation in Japan has made considerable progress and is now being performed in many institutions. However, it is possible that the knowledge and abilities of physical therapists may have not been fully understood by other medical professions in Japan. Providing documentation of minimum standards of clinical practice for physical therapists will therefore increase understanding of physical therapy and help the critical care team to develop. Establishment of minimum standards of clinical practice for Japanese physical therapists working in ICU is important for core competency development of physical therapists and will show why physical therapists are needed in acute care hospitals. These standards may also be used as a critical care competency list for clinical physical therapists, leading to the provision of entry-level course materials.

The ICERC of the JSICM decided to create minimum standards of clinical practice for physical therapists working in ICU in Japan. The aim of this investigation was to establish a framework for these minimum standards. It also aimed to make an international comparison of minimum standards of clinical practice for physical therapists working in ICU.

Method

Design

This study followed the modified Delphi method used previously[1]. The Delphi technique is a method of bringing together expert opinion through a series of iterative questionnaires. The process aims to reach a group consensus. Relying on just one expert to determine minimum standards can lead to bias. Delphi techniques are particularly useful when there is no single 'right' answer, such as decision-making, policy, or long-term prediction.

Participants

Potential participants were recruited from among current members of the JSICM. The Japanese Physical Therapy Association, the professional organization of Japanese physical therapists, has no special interest group for acute care and has no certification system for intensive care practice or competence. Therefore, this survey was conducted among current physical therapist members registered with the JSICM. All were qualified physical therapists with at least five years of experience working in hospitals with ICU.

The inclusion criteria were being (1) a certified respiratory physiotherapist, certified cardiac physiotherapist, or certified physiotherapy specialist in visceral impairment, with certification by the Japanese Physical Therapy Association, or (2) respiratory therapists certified by the joint committee of the three scientific societies (Japanese Association for Thoracic Surgery, The Japanese Respiratory Society and Japanese Society of Anesthesiology) or a Senior instructor certified by the Japanese Association for Cardiac Rehabilitation. The exclusion criteria were having less than five years of work experience in acute care hospitals, less than two years of intensive care experience, or no experience of teaching young physical therapists in ICU and/or not agreeing to participate.

Questionnaire development

The questionnaire used within this study was based on the Australasian questionnaire used by Skinner et al[1]. The JSICM-ICERC has established an exploratory working group of competency for physical therapists working in ICU. This working group consisted of intensivists, physicians, nurses, physical therapists, occupational therapists, and speech therapists with experience in ICU. First, this working group translated 224 questionnaire items from Skinner's study into Japanese. The translated items were verified by mutual review within the committee to confirm the accuracy of the translation. This working group added 48 more items that were considered potentially necessary for the understanding of healthcare professionals involved

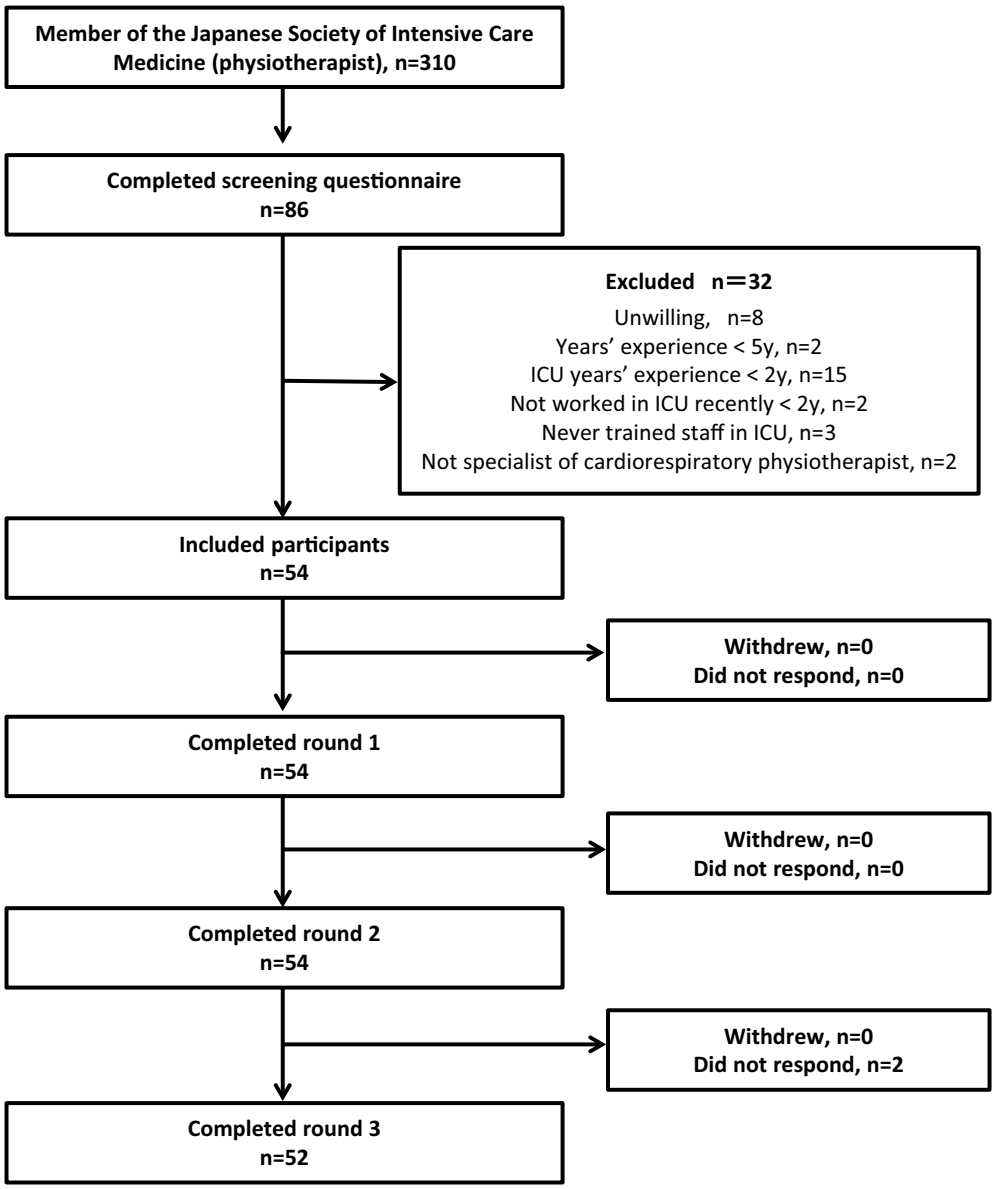

Figure 1. Participants selection and completion rate
ICU, intensive care unit.

in early rehabilitation in Japan. The final version of the questionnaire contained 272 items.

Preparation

The Human Research Ethics Committees of Tokoha University (013013F) approved the study. Written informed consent was obtained in advance by giving potential participants an information sheet with the main purpose, content, and handling of the findings.

First, an e-mail was sent to all physiotherapist members of the JSICM (n=310) to ask if they wished to participate in this study. Those who were willing to participate were given access to a specific website to answer the questionnaire. All questionnaires including consent forms were distributed electronically via Google Forms (Google, United States). In total, 86 physical therapists (27.7%) expressed their intention to participate and answered questions about the inclusion and exclusion criteria. This process gave 54 physical therapists out of these eligible, who provided informed consent and were registered as the study participants, giving a recruitment success of 17.4% (of 310 invited) (Figure 1).

In line with previous studies, the participants were asked to assess whether each of the 272 items were "Essential" or "Not Essential" as a minimum standard for physical therapists working in ICU. They could also answer that they were "Unsure". Although we did not specify an upper or lower limit for the number of "Essential" or "Not Essential", the questionnaire emphasized that participants should:

1) Be accurate and careful when answering;
2) Not give the same answer for all items; and
3) Consider which activities were necessary for physi-

Table 1. Participants' characteristics

		Invited	Completed round 1	Completed round 2	Completed round 3
		(n=54)	(n=54)	(n=54)	(n=52)
Clinical experience,	Median (IQR)	14 (11-18)	14 (11-18)	14 (11-18)	13.5 (11-17)
Years	Range	5-31	5-31	5-31	5-31
ICU clinical experience,	Median (IQR)	9 (6-12)	9 (6-12)	9 (6-12)	9 (6-12)
Years	Range	5-20	5-20	5-20	5-20
ICU experience in senior role, n (%)		100 (100)	100 (100)	100 (100)	100 (100)
Cardiopulmonary physiotherapy manuscript Publication, n (%)	0	28 (52)	28 (52)	28 (52)	27 (52)
	1-4	17 (31)	17 (31)	17 (31)	17 (32)
	≧5	9 (17)	9 (17)	9 (17)	8 (16)
ICU physiotherapy manuscript Publication,	0	36 (67)	36 (67)	36 (67)	35 (67)
n (%)	1-4	14 (26)	14 (26)	14 (26)	13 (25)
	≧5	4 (7)	4 (7)	4 (7)	4 (8)
Specialist physical therapist (Cardiovascular, respiratory and metabolic disorder) *		10 (19%)		10 (19%)	10 (19%)
Certified physical therapist (respiratory) *		19 (35%)		19 (35%)	19 (35%)
Certified physiotherapist (cardiovascular) *		15 (28%)		15 (28%)	15 (28%)
Certified respiratory therapist**		46 (85%)		46 (85%)	46 (85%)
Certified cardiac rehabilitation instructor***n (%)		27 (50%)		27 (50%)	27 (50%)

IQR: interquartile range, ICU: intensive care unit

*Japanese Physical Therapy Association,

** Japanese Association for Thoracic Surgery, Japanese Respiratory Society and Japanese Society of Anesthesiologists

*** Japanese Association of Cardiac Rehabilitation

cal therapists in the current legal and medical system in Japan.

The first Delphi round began on October 19, 2019 with a response period of three weeks. The response period for the second and third rounds was set at two weeks, with the third round ending on December 21. 2019. Reminders to the responses were sent by email one week and three days before the end of each Delphi round.

In the first round, items that were considered essential by more than 70% of the participants were adopted as minimum standards. Items that were deemed "Not Essential" by more than 70% of participants were excluded from the minimum standards to be consistent with previous studies[1,2]. Items were also excluded from subsequent rounds if fewer than 30% of participants thought they were essential for clinical practice for physical therapists working in ICU. Items that were considered essential by fewer than 70% of participants were sent to the second round. In the second and third rounds, the same process was used. In all three rounds, items that were considered essential by at least 70% of participants were included in the "Minimum standards of clinical practice for physical therapists working in ICU in Japan" as in previous studies[1,2].

The basic attributes and responses of the participants were aggregated in Microsoft® Excel® for Office 365 MSO, the average ± standard deviation of the normal distribution was used, and if not suitable, the median (24th, 75th percentile) was shown.

Results

Of the 86 physical therapists who expressed their willingness to participate in the study, 54 physical therapists (62.8%) were eventually participated in the study according to the inclusion and exclusion criteria (Figure 1). Table 1 shows the characteristics of the 54 participants. All participants had at least five years of clinical experience in the ICU as a physical therapist, with 100% being specialist physical therapists (as defined by the Japanese Physical Therapy Association). The average length of clinical experience as a physical therapist for participants was 14 years (11-18 years), and the average length of service in ICUs was 9 years (6-12 years). The participants included three academic faculty members. All these three academic faculty members concurrently work at their related hospitals, so the data for this survey came from total 54 hospitals.

The highest number (%) and lowest number (%) of items selected as "essential" per participant in Round 1 were 260 (95%) and 164 (60%), respectively. Figure 2 shows the three rounds of the Delphi process. Of the 272 items in the first round, 188 were deemed essential. In round 2, 11 of the 62 items that failed to reach consensus in

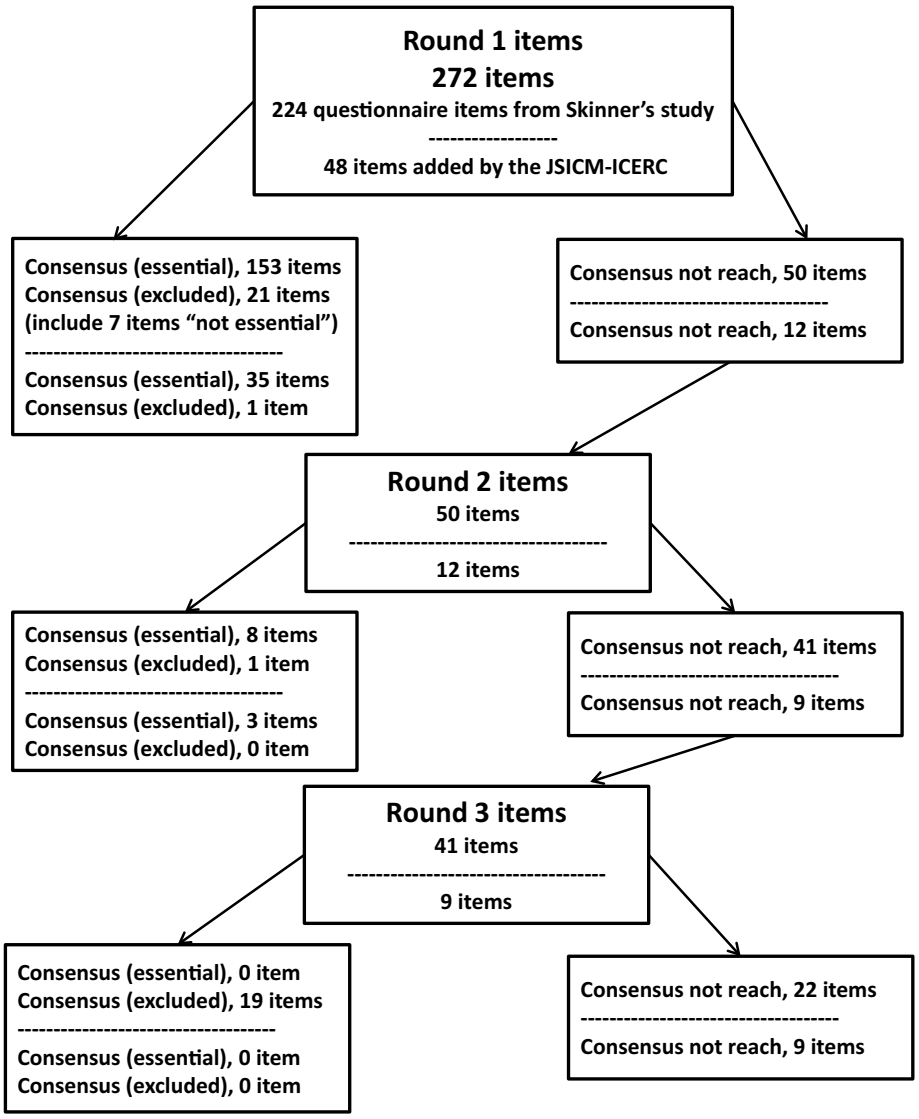

Figure 2. Flow of items through the Delphi rounds.
JSICM, the Japanese Society of Intensive Care Medicine; ICERC, the Intensive Care Early Rehabilitation Committee.

round 1 were also deemed essential. No items were classified as not essential in round 2. In round 3, none of the 50 items that failed to reach consensus in round 2 were deemed essential. There were 31 items on which participants failed to reach agreement.

In this study, participants took three Delphi rounds to reach a consensus that 161 of the 224 questionnaire items from Skinner's study[1] were essential. Table 2 shows the 161 items that were agreed to be essential, and during which round this agreement was reached. Table 2-4 also show comparisons with prior studies in Australia and New Zealand[1] and United Kingdom[2]. Items that were considered essential in this survey but not in the UK and Australia included some cardiovascular items such as knowledge of calcium channel blockers, cardiac output measurements, pulmonary arterial catheter measurements, intra-aortic balloon pump and advanced electrocardiograms. Our survey also confirmed that it is essential for physical therapists to be able to accurately and independently evaluate and interpret the findings from imaging investigations including computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography. Only Japanese physical therapists considered that it was essential for them to be able to interpret and assess nutritional status including food administration, volume and type. Similarly, there was a greater interest in delirium, sedation and analgesia in Japan than in the UK and Australia.

Table 3 shows the 41 items that were excluded because less than 30% of participants thought they were essential across the three Delphi rounds. These 41 items included seven items that more than 70% of the participants deemed not essential. Many of these items were also excluded in the UK and Australian surveys, but the following items were considered essential in the UK and Australia:

Table 2. Items agreed to be essential (> 70% of participants said they were "essential")

item	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
A physiotherapist is aware or has knowledge of					
Key literature that guides evidence-based physiotherapy practice in critical care settings					
Key literature that guides evidence-based physiotherapy practice in critical care settings	100	—	—	*	NRC
The actions and implications for physiotherapy of the following medications					
Analgesia	93	—	—	*	N/A
Anti-arrhythmics (e.g. amiodarone, digoxin)	96	—	—	*	*
Anti-hypertensives (e.g. beta-blockers, hydralazine)	98	—	—	*	*
Bronchodilators	89	—	—	*	*
Calcium channel blockers	87	—	—	NRC	NE
Sedation and neuromuscular paralyzing agents	100	—	—	*	*
Vasopressors/inotropes (e.g. dobutamine, milrinone, adrenaline, dopamine, noradrenaline)	100	—	—	*	*
Methods for advanced hemodynamic monitoring, can interpret the measurements and understands the implications for physiotherapy of					
Implanted or external pacemakers, and determine the presence of pacing on ECG	96	—	—	*	NRC
PiCCO measurements (e.g. CO, CI, SVV, SVRI etc.)	83	—	—	NE	NE
Pulmonary arterial catheter measurements (e.g. CO, CI, SVRI, PAP, etc.)	85	—	—	NE	NE
A physiotherapist can understand					
Equipment (including recognition of equipment), can use/safely apply or handle equipment, understands the implications for physiotherapy of					
Arterial lines	100	—	—	*	*
Central venous catheters	98	—	—	*	*
ECMO	74	—	—	NE	NE
Endotracheal tubes and tracheostomy	100	—	—	*	*
Indwelling urinary catheters	91	—	—	*	*
Intercostal catheters	100	—	—	*	*
Intra-aortic balloon pump	89	—	—	NRC	NE
Intracranial pressure (ICP) monitors and extra-ventricular drains (EVD)	91	—	—	*	NE
Nasogastric tubes	98	—	—	*	*
Oxygen therapy devices	100	—	—	*	*
Vascath/hemodialysis/continuous veno-venous hemodiafiltration	94	—	—	*	*
Wound drains	100	—	—	*	*
The key principles of providing the following differing modes of mechanical/assisted ventilation including					
Airway Pressure Release Ventilation (APRV)	76	—	—	NE	NE
Assist-control	98	—	—	*	NRC
BiLevel	83	—	—	*	*
CPAP	98	—	—	*	*
PEEP/EPAP	100	—	—	*	*
Pressure-regulated Volume Control (PRVC)	81	—	—	*	N/A
PS/IPAP	100	—	—	*	*
SIMV (Volume) / (Pressure)	93	—	—	*	*
Weaning protocols	96	—	—	*	NRC

Table 2. Items agreed to be essential (> 70% of participants said they were "essential") (continued)

item	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
Pathophysiology and presenting features, likely medical management and implications for physiotherapy for a range of conditions including					
Acute coronary syndrome (e.g. angina, STEMI, NSTEMI)	100	—	—	*	*
Acute lung injury/acute respiratory distress syndrome (ARDS)	98	—	—	*	*
Burns (cutaneous/inhalational)	81	—	—	NRC	NE
Chest trauma	93	—	—	*	*
Community acquired/nosocomial/hospital-acquired pneumonia (including VAP)	100	—	—	*	*
Guillain-Barre Syndrome	76	—	—	*	*
Heart failure	100	—	—	*	*
Hepatitis	72	—	—	NRC	NE
ICU-acquired weakness (ICU-AW)	100	—	—	*	*
Immunocompromise	65	85	—	*	*
Intracerebral hemorrhage/Subarachnoid hemorrhage	100	—	—	*	*
Metabolic/electrolyte disturbances	98	—	—	*	NRC
Multi-organ failure/MODS	94	—	—	*	*
Multi-trauma	93	—	—	*	NRC
Obstructive respiratory disease (e.g. asthma, COPD)	100	—	—	*	*
Pancreatitis	76	—	—	*	NRC
Pleural effusion	98	—	—	*	*
Post-abdominal surgery	98	—	—	*	*
Post-cardiac surgery	94	—	—	*	NRC
Post-surgery other (e.g. orthopaedic, vascular)	94	—	—	*	N/A
Post-thoracic surgery	100	—	—	*	NRC
Renal failure (acute and chronic)	100	—	—	*	*
Respiratory failure (Type I and II)	100	—	—	*	*
Restrictive respiratory disease (e.g. pulmonary fibrosis, kyphoscoliosis)	98	—	—	*	*
Shock (cardiogenic)	98	—	—	*	*
Shock (septic)	94	—	—	*	*
Spinal cord injury	96	—	—	*	*
Suppurative lung disease (e.g. cystic fibrosis, bronchiectasis)	74	—	—	*	*
Systemic inflammatory response syndrome (SIRS)	89	—	—	*	*
Thromboembolic disease (e.g. deep vein thrombosis, pulmonary embolus)	100	—	—	*	*
Thrombotic cerebrovascular accident	96	—	—	*	N/A
Traumatic brain injury	94	—	—	*	*
A physiotherapist can accurately/independently (assess and) interpret					
Readings from clinical monitoring including					
Advanced ECGs (i.e. conduction block, 12-lead ECG)	80	—	—	NE	NRC
Basic ECGs (i.e. sinus rhythm/tachycardia/bradycardia, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, asystole, PVCs)	98	—	—	*	*
Blood pressure (systolic, diastolic, and mean arterial blood pressure)	100	—	—	*	*
Body temperature	100	—	—	*	*
Central venous pressure	94	—	—	*	NRC
End tidal carbon dioxide	83	—	—	*	*
Fluid intake and output	96	—	—	*	*
Heart rate	100	—	—	*	*

Table 2. Items agreed to be essential (> 70% of participants said they were "essential") (continued)

item	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
Nutritional status including feed administration, volume and type	85	—	—	NE	NE
SpO2/Pulse oximetry	100	—	—	*	*
Findings from laboratory investigations including					
Albumin	94	—	—	NE	NE
Blood glucose levels	96	—	—	*	*
C-reactive protein (CRP)	100	—	—	NRC	*
Creatinine kinase (CK)	98	—	—	NRC	NE
Hematocrit	83	—	—	NE	NE
Hemoglobin	100	—	—	*	*
Liver function tests (e.g. ALT, LDH, Bilirubin)	93	—	—	NE	NE
Neutrophil counts	80	—	—	NRC	NE
Platelets, APTT (activated partial thromboplastin time), INR (international normalized ratio)	87	—	—	*	*
Renal function tests (e.g. urea, creatinine)	93	—	—	*	NRC
Respiratory function tests (e.g. FEV1, FVC etc.)	98	—	—	*	NRC
Troponin	76	—	—	*	*
White cell count (WCC)	98	—	—	*	*
Findings from imaging investigations (excluding the imaging report) including					
Chest radiographs (CXR)	94	—	—	*	*
CT - Brain imaging	74	—	—	NE	NE
CT - Chest imaging	81	—	—	NE	NE
MRI - Brain	74	—	—	NE	NE
Skeletal X-rays	81	—	—	NRC	NE
Ultrasound - Chest	74	—	—	NE	NE
Results from neurological equipment/examinations and functional tests including					
Ability to interpret a delirium assessment (e.g. the CAM-ICU)	96	—	—	NRC	N/A
Ability to perform a delirium assessment (e.g. the CAM-ICU)	83	—	—	NE	NE
An ability to interpret a Glasgow Coma Score (GCS)	100	—	—	*	*
An ability to interpret an assessment of cranial nerve function	93	—	—	NRC	NE
An ability to interpret an assessment of sedation levels (e.g. Ramsey Sedation Scale, Richmond Agitation-Sedation Scale)	100	—	—	*	NRC
An ability to perform a Glasgow Coma Score (GCS)	93	—	—	NRC	NE
An ability to perform a neurological examination of motor and sensory functions (e.g. light touch, pain, ASIA score)	98	—	—	*	NRC
An ability to perform an assessment of cranial nerve function	93	—	—	NE	NE
An ability to perform an assessment of sedation levels	98	—	—	NE	NE
Intra-cranial pressure (ICP) monitors (intra-parenchymal, intra-ventricular) and cerebral perfusion pressure (CPP)	52	74	—	*	NRC
Indices from blood gas measurement including					
A-a gradient	81	—	—	NE	NE
Base excess	76	—	—	*	*
HCO3	91	—	—	*	*
Lactate	87	—	—	NE	NRC
PaCO2	100	—	—	*	*
PaO2, SpO2, SaO2	100	—	—	*	*

Table 2. Items agreed to be essential (> 70% of participants said they were "essential") (continued)

item	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
PaO2/FiO2 ratio	100	—	—	*	NE
pH	98	—	—	*	*
Venous blood gas interpretation (including SvO2)	74	—	—	NRC	NE
(assess and interpret) Mechanical ventilation settings/measurements including					
Breath types (spontaneous, mandatory, assisted)	100	—	—	*	*
Maximum inspiratory pressure (MIP) measurements	63	72	—	NE	NE
Peak inspiratory pressure	93	—	—	*	*
Respiratory rate	100	—	—	*	*
Static and/or dynamic lung compliance measures	61	72	—	NE	NE
The level of FiO2	100	—	—	*	*
The level of PEEP	100	—	—	*	*
The level of PS	98	—	—	*	*
Tidal volume	100	—	—	*	*
A physiotherapist can					
Perform and accurately interpret the results of common respiratory examinations including					
Auscultation	100	—	—	*	*
Observation of respiratory rate	100	—	—	*	*
Palpate the chest wall	94	—	—	*	*
Patterns of breathing	100	—	—	*	*
Assess					
The effectiveness/quality of a patient's cough (on or off mechanical ventilation)	96	—	—	*	*
Provide the following techniques, including an understanding of indications, contraindications, evidence for the technique, and progressions					
ACBT [breathing control, thoracic expansion and FET]	83			*	*
Assisted coughing - chest wall	85	—	—	*	*
Assisted coughing - subcostal thrusts for spinal cord injuries	54	74	—	*	NRC
Bed exercises (e.g. passive - active - resisted range of motion exercises)	100	—	—	*	*
Braces	74	—	—	NE	NE
Directed coughing/instructing the patient to cough effectively	96	—	—	*	*
Electrical stimulation (e.g. for isolated muscle activation to prevent muscle wasting, such as neuromuscular/functional electrical stimulation)	78	—	—	NE	NE
Humidification	76	—	—	*	*
Inexsufflator (Cough Assist)	65	70	—	NE	*
Inspiratory muscle training	78	—	—	NE	NE
Mobilization of non-ventilated patient (e.g. sitting on edge of bed, stand, hoist or slide transfer to chair, march on spot, walk, use of gait aids)	100	—	—	*	*
Mobilization of ventilated patient (e.g. sitting on edge of bed, stand, hoist or slide transfer to chair, march on spot, walk, use of gait aids)	98	—	—	*	*
NIV/BiPAP - for use during exercise or mobilization including initiation and titration of	69	70	—	NRC	NE
Patient positioning for prevention of pressure ulcers, management of tone, maintenance of musculoskeletal function	100	—	—	*	*
Patient positioning for respiratory care - including use of side lie, sitting upright, postural drainage (modified or head down tilt)	100	—	—	*	*

Table 2. Items agreed to be essential (> 70% of participants said they were "essential") (continued)

item	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
Patient prone positioning in severe respiratory failure/acute lung injury	87	—	—	NRC	NRC
Pursed lip breathing	98	—	—	*	N/A
Suction via a tracheal tube (Endotracheal tube, tracheostomy, minitracheostomy)	67	72	—	*	*
Supported coughing	98	—	—	*	*
Treadmill, cycle ergometry (e.g. Motomed) or stationary bike	87	—	—	NRC	NE
A physiotherapist can					
Complete musculoskeletal and/or functional assessments including					
Ability to assess tone (e.g. utilizing a Modified Ashworth Scale) and reflexes	100	—	—	*	NRC
Deep vein thrombosis screening (i.e. color, temperature, touch, swelling, Homan's test)	93	—	—	*	*
Dynamometry	81	—	—	NRC	NE
Manual muscle testing (e.g. MRC scale)	98	—	—	*	*
Objective measures of cardiopulmonary exercise tolerance (e.g. 6-minute walk test; incremental shuttle walk test)	87	—	—	NRC	NE
Objective measures of physical function [e.g. the Physical Function ICU Test (PFIT), Timed Up and Go Test (TUG), 6MWT, De-Morton Mobility Index (DEMMI)]	93	—	—	*	NE
Objective measures of quality of life (e.g. Short Form 36, EQ-5D, AQoL)	72	—	—	NE	NE
Peripheral edema	96	—	—	*	*
Range of motion	100	—	—	*	*
Appropriately					
Be aware of inotropes and implications for physiotherapy treatment	100	—	—	*	N/A
Be aware of sedation and implications for physiotherapy treatment	98	—	—	*	N/A
Liaise with medical/nursing staff to increase/decrease inotropes to achieve physiotherapy goals	85	—	—	*	N/A
Liaise with medical/nursing staff to increase/decrease sedation to achieve physiotherapy goals	94	—	—	*	N/A
A physiotherapist can					
Assess and interpret ventilator waveforms	89	—	—	NE	N/A
Determine the appropriateness of a patient for extubation	83	—	—	NRC	NRC

AUS-NZ: Australia and New Zealand, UK: the United Kingdom, *: Essential, NRC: did not reach consensus, NE: not essential, N/A: not available

ECG: electrocardiogram, PiCCO: pulse contour cardiac output, CO: cardiac output, CI: cardiac index, SVV: stroke volume variation, SVRI: systemic vascular resistance index, PAP: pulmonary artery pressure, ECMO: extracorporeal membrane oxygenation, CPAP: continuous positive airway pressure, PEEP: positive end expiratory pressure, EPAP: expiratory positive airway pressure, PS: pressure support, IPAP: Inspiratory Positive Airway Pressure, SIMV: synchronised intermittent mandatory ventilation, STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, VAP: ventilator-associated pneumonia, MODS: multiple organ dysfunction syndrome, COPD: chronic obstructive pulmonary disease, PVC: premature ventricular contraction, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, CAM-ICU: confusion assessment method for the intensive care unit, CT: computed tomography, MRI: magnetic resonance imaging, ASIA: American Spinal Cord Injury Association, HCO3: bicarbonate, PaCO2: partial pressure of arterial carbon dioxide,

PaO2: partial pressure of arterial oxygen, SPO2: peripheral capillary oxygen saturation, SaO2: arterial oxygen saturation, pH: potential of hydrogen, SvO2: mixed venous oxygen saturation, FiO2: fraction of inspired oxygen

ACBT: active cycle of breathing technique, FET: forced expiratory technique, MRC: Medical Research Council, 6MWT: 6-minute walk test, EQ-5D: EuroQol 5 Dimension, AQoL: Assessment of Quality of Life

Table 3. Items that participants agreed to exclude

	Round 1 %	Round 2 %	Round 3 %		AUS-NZ	UK
The actions and implications for physiotherapy of the following medications						
Prostacyclin	35	22	—		NE	NE
A physiotherapist can understand						
Equipment (including recognition of equipment), can use/safely apply or handle equipment, understands the implications for physiotherapy of						
Sengstaken-Blakemore/Minnesota tubes	13	—	—		NE	NE
Pathophysiology and presenting features, likely medical management and implications for physiotherapy for a range of conditions including						
Brain death and organ procurement	19	—	—		NRC	NRC
Results from neurological equipment/examinations and functional tests including						
Electroencephalograms (EEG)	11	—	—		NE	NE
Extra-ventricular drain (EVD)	48	50	29		*	N/A
Indices from blood gas measurement including						
P50	13	—	—		NE	NE
A physiotherapist can						
Perform						
a cuff volume and/or pressure test on an endotracheal tube (or tracheostomy)	35	39	23		NRC	NRC
Swallow assessment	30	43	22		NE	NE
Provide the following techniques, including an understanding of indications, contraindications, evidence for the technique, and progressions						
Additional rehabilitation techniques (e.g. hydrotherapy, Wii)	22	—	—		NE	NE
Assisting bronchoscopy via delivery of secretion mobilization techniques (e.g. vibrations, assisted coughing) during the procedure	54	61	28		NE	NE
Bronchial lavage (i.e. up to 120 ml in one treatment session administered by bronchoscopy for sputum/organism retrieval for diagnostic purposes)	13	—	—	#	NE	NE
Buteyko breathing	4	—	—		NE	N/A
Cough stimulation - oropharyngeal catheter stimulation	19	—	—		*	*
Cough stimulation - tracheal rub	15	—	—		*	NE
Feldenkreis	2	—	—		NE	NE
Glottal stacking (frog breathing)	26	—	—		NE	NE
Inspiratory hold/sustained maximal inspiration	50	57	27		*	N/A
Instillation of normal saline into the endotracheal tube (i.e. < 20 ml in one treatment session aimed at increasing sputum yield by diluting and loosening thick secretions)	9	—	—	#	NRC	*
Intermittent positive pressure breathing (IPPB, The Bird)	31	33	18		NE	*
Manual airway clearance techniques - percussion, vibration, chest shaking	41	50	27		*	*
Manual hyperinflation (MHI)	39	37	23		*	*
Nasopharyngeal airway suctioning including insertion of NP airway	39	33	12		*	*
NIV/BiPAP - for Type I or Type II respiratory failure, initiation and titration of e.g. COPD exacerbation with hypercapnia	39	33	22		NE	NRC

Table 3. Items that participants agreed to exclude (continued)

	Round 1 %	Round 2 %	Round 3 %		AUS-NZ	UK
NIV/BiPAP - intermittent, short term applications during physiotherapy to assist secretion mobilization techniques or lung recruitment including initiation and titration of	65	65	27		NRC	NRC
Oropharyngeal airway suctioning including insertion of OP airway	37	37	14		*	*
Other breathing techniques (e. g., Buteyko)	13	—	—		NE	NE
Performing bronchoscopy independently	4	—	—	#	NE	NE
Periodic/intermittent CPAP (non-invasive via mask) including initiation and titration of	35	48	22		NRC	NRC
Positive pressure devices for airway clearance (e.g. AstraPEP, PariPEP, TheraPEP or oscillating expiratory pressure devices like Acapella, Flutter)	44	56	25		*	NRC
Splinting and/or casting for the upper and lower limbs	43	44	19		NE	NE
Ventilator hyperinflation (VHI) via an endotracheal tube or tracheostomy	20	—	—		NRC	NRC
Complete musculoskeletal and/or functional assessments including						
Bioimpedance testing of body composition	43	50	24		NE	NE
Appropriately request/coordinate the following						
Titration of analgesia to achieve physiotherapy goals	67	69	27		*	*
A physiotherapist can						
Decannulate a tracheostomy	9	—	—	#	NE	NE
Determine the appropriateness of tracheostomy decannulation	50	35	16		NRC	NRC
Extubate a patient	4	—	—	#	NE	NE
Intubate a patient	2	—	—	#	NE	NE
Lead the co-ordination of cuff deflation trials	19	—	—		NE	NE
Lead the co-ordination of speaking valve trials	28	—	—		NE	NE
Lead the co-ordination of weaning protocols	43	43	20		NE	NE
Tracheostomy exchange	2	—	—	#	NE	NE

AUS-NZ: Australia and New Zealand, UK: the United Kingdom, *: Essential, NRC: did not reach a consensus, NE: not essential, N/A: not available

#: Items determined as not essential (consensus >70% "not essential")

NP airway: nasopharyngeal airway, OP airway: oropharyngeal airway, NIV/BiPAP: non-invasive ventilation/ biphasic positive airway pressure, COPD: chronic obstructive pulmonary disease, PEP: positive expiratory pressure.

cough stimulation-tracheal rub, manual airway clearance techniques, manual hyperinflation, suctioning, titration of analgesia to achieve physiotherapy goals.

Table 4 shows the 22 items where participants failed to reach a consensus, and the percentage of participants who felt these items were essential. Of the 22 items for which no consensus was reached, 20 items were also determined to be not essential or not reach a consensus in the UK and Australia excluding the knowledge of the actions and implications for physiotherapy of mucolytics and oxygen therapy including initiation and titration.

Finally, Table 5 shows the results for the 48 items added by the JSICM-ICERC. Of these 48 items, 38 items were considered essential, and nine failed to reach consensus.

Discussion

Consensus was reached in three Delphi rounds that 161 (71.9%) of the 224 questionnaire items from Skinner's study[1)] were essential. Items ranged from pathophysiology and clinical signs and symptoms related to physical therapy, to physical therapy practice. Skinner et al. reported that 132 (58.0%) items of knowledge and skill were deemed essential as a minimum standard of clinical practice in critical care in Australia and New Zealand[1)]. Twose et al. reported that 107 (47.7%) items were considered essential in the UK[2)]. There are several possible reasons why Japa-

Table 4. Items on which consensus was not reached in any round

	Round 1 %	Round 2 %	Round 3 %	AUS-NZ	UK
A physiotherapist is aware or has knowledge of					
The actions and implications for physiotherapy of the following medications					
Mucolytics	52	39	50	*	*
Nitric oxide	56	50	43	NRC	NE
The key principles of providing the following differing modes of mechanical/ assisted ventilation including					
High frequency oscillatory ventilation (HFOV)	50	54	38	NE	NE
Pathophysiology and presenting features, likely medical management and implications for physiotherapy for a range of conditions including					
Fat embolism	63	69	44	*	NRC
Organ transplantation	37	48	37	NE	NE
Findings from laboratory investigations including					
Procalcitonin	56	61	44	NE	NE
Sputum cultures	44	52	45	*	NRC
Findings from imaging investigations (excluding the imaging report) including					
CT - Spine imaging	65	63	45	NE	NE
MRI - Chest	57	57	43	NE	NE
MRI - Spine	59	63	48	NE	NE
Indices from blood gas measurement including					
Anion gap	54	65	46	NE	NE
Oxygen content (CaO2)	61	59	41	NE	NE
(assess and interpret) Mechanical ventilation settings/measurements including					
Maximum expiratory pressure (MEP) measurements	52	67	37	NE	NE
Upper and lower inflection points of P-V curves	52	46	30	NE	NE
A physiotherapist can					
Perform and accurately interpret the results of common respiratory examinations including					
Interpret the rapid shallow breathing index (RSBI)	59	61	43	NE	NE
Measure peak cough flow on or off mechanical ventilation	50	59	40	NE	NE
Perform					
Respiratory function tests (e.g. for measurement of FEV1, FVC, PEF)	61	67	46	*	NE
Spontaneous breathing trial	56	57	32	NE	NE
Provide the following techniques, including an understanding of indications, contra-indications, evidence for the technique, and progressions					
Autogenic drainage	50	59	31	NE	NE
Collars	69	63	35	NRC	NE
Oxygen therapy including initiation and titration of oxygen therapy	63	63	35	*	*
Recruitment maneuvers	63	59	31	NE	NE

AUS-NZ: Australia and New Zealand, UK: the United Kingdom, *: Essential, NRC: did not reach a consensus, NE: not essential
CT: computed tomography, MRI: magnetic resonance imaging, P-V: pressure-volume, FEV1: forced expiratory volume in one second, FVC: Forced vital capacity, PEF: peak expiratory flow

nese physical therapists included more items as essential than experienced physical therapists in other Western countries. Physiotherapy in ICU in Japan has developed rapidly since 2017. As multi-disciplinary teams have developed with other critical care health professions, physical therapists may have felt that they needed a wider range of knowledge and skills to practice patient-centered care. Further research is needed to determine what expertise and skills are sought from physical therapists by physicians and nurses in ICU. Internationally, the role of physical therapists working in ICU has not been clearly defined. Their role in early mobilization and rehabilitation overlaps considerably with that of nurses[3]. It is therefore possible that physical therapists participating in this study thought they should have a broader range of knowledge and skills, comparable to those of nurses. The development of these minimum standards of clinical practice gives clear definition to the role of physical therapists in ICU. This may lead to quality assurance of physiotherapy in critical care and subsequently improve health outcomes for patients[4].

Items that were considered essential in our survey but not in the UK and Australia included many cardiovascular

Table 5. Items added by the JSICM-ICERC

	Round 1 %	Round 2 %	Round 3 %	
A physiotherapist is aware or has knowledge of				
The actions and implications for physiotherapy of the following medications				
Steroids	94	—	—	*
Sodium bicarbonate (meiron, etc.)	63	57	51	NRC
A physiotherapist can understand				
Equipment (including recognition of equipment), can use/safely apply or handle equipment, understands the implications for physiotherapy of				
Pump catheter for auxiliary circulation (IMPELLA)	52	48	41	NRC
Epidural catheter	89	—	—	*
The key principles of providing the following differing modes of mechanical/assisted ventilation including				
NIV (Non-Invasive Ventilation)	98	—	—	*
Brain Monitor (BIS Monitor)	48	61	51	NRC
Indirect calorimeter	31	44	37	NRC
Peripheral insertion center venous catheter (PICC catheter)	80	—	—	*
Pathophysiology and presenting features, likely medical management and implications for physiotherapy for a range of conditions including				
Hemorrhagic shock	93	—	—	*
Anaphylactic shock	59	78	—	*
Sepsis	96	—	—	*
Post-Intensive Care syndrome (PICS)	96	—	—	*
Disseminated intravascular coagulation syndrome (DIC)	87	—	—	*
Mediastinitis	91	—	—	*
Post-resuscitation encephalopathy	67	80	—	*
Postcardiac Syndrome (PCAS)	78	—	—	*
Myasthenia gravis (MG)	76	—	—	*
Parkinson's disease	81	—	—	*
Abandoned syndrome	96	—	—	*
A physiotherapist can accurately/independently (assess and) interpret				
Readings from clinical monitoring including				
Transdermal carbon dioxide fractional pressure (PtcCO2)	52	70	—	*
Findings from laboratory investigations including				
Fibrinolytic inspection (FDP, D-dimer)	94	—	—	*
Cerebral natriuretic peptide (BNP)	94	—	—	*
Electrolytes (sodium, potassium, calcium, magnesium, phosphorus)	94	—	—	*
Findings from imaging investigations (excluding the imaging report) including				
Abdominal X-rays (free air, ascites, ileus, etc.)	57	65	47	NRC
Aortic contrast examination	46	56	30	NRC
Results from neurological equipment/examinations and functional tests including				
Ability to assess pain (NRS, VAS, BPS, CPOT, etc.)	100	—	—	*
Ability to practice pain assessment (NRS, VAS, BPS, CPOT, etc.)	98	—	—	*
Objective evaluation of the spirit (e.g. HADS, IES-R)	48	56	45	NRC
Objective evaluation of cognitive function	78	—	—	*
Indices from blood gas measurement including				
Venous blood mixing ratio (shunt rate)	57	50	32	NRC
Dead cavity ventilation rate	59	63	38	NRC
(assess and interpret) Mechanical ventilation settings/measurements including				
inspiratory time (Ti)	70	—	—	*
I/E ratio	80	—	—	*

Table 5. Items added by the JSICM-ICERC (continued)

	Round 1 %	Round 2 %	Round 3 %	
A physiotherapist can				
Perform				
Kahlek test	24	30	14	NE
Provide the following techniques, including an understanding of indications, contraindications, evidence for the technique, and progressions				
Deep inspiratory and respiratory aids for increased lung capacity under spontaneous breathing	94	—	—	*
Preoperative non-smoking guidance	85	—	—	*
Complete musculoskeletal and/or functional assessments including				
ADL rating	98	—	—	*
A physiotherapist can				
Safety management (prevention of fall and route removal)	100	—	—	*
Infection prevention	96	—	—	*
Communication within the team (appropriate reporting and consultation, participation in implementation plan, proposals for cooperation and role sharing)	98	—	—	*
Check the fixation of tubes and lines	96	—	—	*
Communication with patients with ventilators	100	—	—	*
Proper release and mounting of physical restraints	78	—	—	*
Communication with patient families	98	—	—	*
Patient and Family Engagement/Empowerment	93	—	—	*
Conducted multi-job collaboration and multi-job conferences	100	—	—	*
ABCDEF Bundle	98	—	—	*
Improvement of the environment before and after, during rehabilitation	100	—	—	*

JSICM-ICERC: The Japan Society of Intensive Care Medicine, the Intensive Care Early Rehabilitation Committee

*: Essential, NRC: did not reach a consensus, NE: not essential

BIS: bispectral, PICC: peripherally inserted central catheter, NRS: numerical rating scale, VAS: visual analogue scale, BPS: Behavioral Pain Scale, CPOT: Critical-Care Pain. Observation Tool, HADS: Hospital Anxiety and Depression Scale, IES-R: Impact of Event Scale-Revised, I/E ratio: inspiratory/expiratory ratio, ADL: activities of daily living

items such as knowledge of calcium channel blockers, cardiac output measurements, pulmonary arterial catheter measurements, intra-aortic balloon pump and advanced electrocardiograms. In Japan, the Dohi-Anderson Criteria[5,6] and the Guidelines for the Safety Management and Promotion of Rehabilitation Medicine of the Japanese Association of Rehabilitation Medicine[7] have been traditionally used as risk management standards in the clinical setting. These include many cardiovascular-related indices, and the importance of cardiovascular indices has long been recognized as a risk management standard for rehabilitation. In addition, the evidence-based expert consensus for early rehabilitation in ICU published by the JSICM includes many cardiovascular items in the inception and cessation criterion for early mobilization and rehabilitation[8,9]. This may have caused Japanese physical therapists to consider that many cardiovascular items were essential.

Our survey also confirmed that it is essential for physical therapists to be able to accurately and independently evaluate and interpret the findings from imaging investigations including CT, magnetic resonance imaging MRI, and echocardiography. This was different from the surveys in the UK and Australia. One of the reasons for this is that Japanese hospitals have much higher rates of CT and MRI usage than in the UK and Australia. Physical therapists in Japan therefore have easier access to a variety of imaging test results. Japan has 111.49 CTs per million people (2017), which is very high compared to 9.46 in the UK (2014) and 67.2 in Australia (2018)[10].

Only Japanese physical therapists considered that it was essential for them to be able to interpret and assess nutritional status including food administration, volume and type. The JSICM has recently published the Japanese Guidelines for Nutrition Support Therapy in the Adult and Pediatric Critically Ill Patients[11,12]. The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN)[13], and The European Society for Clinical Nutrition and Metabolism (ESPEN)[14] have also published the guideline on clinical nutrition in the ICU. These guidelines strongly recommend nutritional management for severely ill patients according to their condition and stage. In severe sepsis, extensive burns, and severe trauma, the immune response from various hormones (e.g. cortisol, glucagon, and catecholamine) and proinflammatory cytokines that increase catabolism as a biological defense response leads to a rapid development

of metabolic reactions and a hyper-catabolic state, leading to severe nutritional disorders[15,16]. The development of nutritional disorders (hyper-catabolism) worsens the prognosis, including infectious complications, increased mortality, and prolonged hospital stay[17]. One systematic review found that the rate of malnutrition in acutely ill patients was 38-78%, and malnutrition was an independent predictor of ICU length of stay, ICU readmission, infection incidence, and in-hospital mortality[18]. The decrease in skeletal muscle associated with poor nutritional status has a significant impact on prognosis[19]. It is therefore recommended that patients who are at high nutritional risk because of failure of oral intake or other reasons should be screened for nutrition early on during their stay in ICU and started on enteral or parenteral nutrition within 24-48 hours[20]. In Japan, from April 2020, a new reimbursement will be added for nutritional management, such as enteral nutrition, during the early stages of a stay in ICU, as a way to promote early discharge and return home. The rapid spread of understanding of the importance of nutritional management in intensive care in Japan may therefore have influenced the results of this study. In addition, the dietitians as part of the critical care team has become a regular feature of the critical care team, and there is a clear division of roles within the critical care team for each health professional in Australia and the UK. The presence of dietitians in critical care teams is still not that common although there is a strong interest in nutrition management in critical care in Japan. That might explain some of the difference.

Similarly, there was a greater interest in delirium, sedation and analgesia in Japan than in the UK and Australia. This may be partly because the JSICM recently translated "Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU (2018)"[21] in addition to "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU (2013)"[22], so there was heightened interest in this area by Japanese physical therapists during this Delphi process.

A further 48 items that JSICM-ICERC considered necessary for physical therapists in Japan were added to the survey. Japanese physical therapists considered recent concerns such as post-intensive care syndrome (PICS), pain assessment, and cognitive function assessment to be essential. They also believed that they should learn the basics of team medicine, including infection prevention, safety management, and communication within the team, including family members. Consideration of tubes, lines, restraining bands, conferences, bundles, and environmental maintenance were also important common items for the ICU team to promote early withdrawal and rehabilitation, and are characteristic of the minimum standards for physical therapy in Japan.

There were considerably more items considered essential by Japanese physical therapists than their counterparts in the UK and Australia. However, there were also some items that were not considered essential in Japan but were in the UK and Australia. For example, "Instillation of normal saline into the endotracheal tube (i.e. $<$20 ml in one treatment session aimed at increasing sputum yield by diluting and loosening thick secretions)" was considered essential in the UK. Oxygen therapy including initiation and titration of oxygen therapy, cough stimulation-oropharyngeal catheter stimulation, manual hyperinflation (MHI) and nasopharyngeal airway suctioning including insertion of nasopharyngeal airway were considered essential in both the UK and Australia. In Japan, physical therapists are not permitted to undertake these invasive interventions. This variation therefore reflects differences in national laws. Explaining the knowledge and skills of physical therapists elsewhere will improve understanding of physiotherapy among other healthcare professionals.

The activities, scope and role of physical therapists vary depending on national laws, culture and history. The results of this study provide views of Japanese physical therapists on the minimum standards of clinical practice for physical therapists working in ICU in Japan. However, intensivists, specialist nurses and certified nurses who work in ICU may have different views on what is required of physical therapists. Studies are currently investigating the knowledge and skills required by Japanese physical therapists working in ICU. Using this information, and the international comparisons here, JSICM-ICERC will be able to determine the minimum standards of clinical practice for physical therapists working in ICU in Japan. This will provide a rationale for developing entry-level educational materials for physical therapists and lead to quality assurance for physical therapists.

Conclusions

This study identified 199 items of knowledge and skills that are considered essential as minimum standards of clinical practice for physical therapists working in ICU in Japan. The findings of this study may help to define content on intensive care in undergraduate and post-graduate education programs in physiotherapy in Japan. The minimum standards of clinical practice for physical therapists working in ICU, as considered by experienced physical therapists in Japan, differed from those in the UK and Australia due to national laws, cultural and historical backgrounds. Further studies are necessary to show the utility of this framework in practice.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Risks of Muscle Atrophy in Patients with Malignant Lymphoma after Autologous Stem Cell Transplantation

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ABSTRACT. Objective: Muscle atrophy is associated with autologous stem cell transplantation (ASCT)-related outcomes in patients with malignant lymphoma (ML). However, the impact of ASCT on muscle mass remains unclear in patients with ML. The aims of this study were to investigate changes in muscle mass and risk profiles for muscle atrophy after ASCT. Method: We enrolled 40 patients with refractory ML (age 58 [20-74] years, female/male 16/24, body mass index (BMI) 21.1 kg/m^2 [17.1-29.6]). Psoas muscle mass was assessed using the psoas muscle index (PMI) before and after ASCT. Statistical analysis used: Independent factors associated with a severe decrease rate of change in PMI were evaluated by decision-tree analysis, respectively. Results: PMI was significantly decreased after ASCT (4.61 vs. 4.55 cm^2/m^2; P=0.0425). According to the decision-tree analysis, the regimen was selected as the initial split. The rates of change in PMI were −5.57% and −3.97% for patients administered MCEC and LEED, respectively. In patients who were administered LEED, the second branching factor was BMI. In patients with BMI < 20.3 kg/m^2, the rate of change in PMI was −7.16%. On the other hand, the rate of change in PMI was 4.05% for patients with BMI ≥ 20.3 kg/m^2. Conclusion: We demonstrated that muscle mass decreased after ASCT in patients with ML. Patients who received MCEC and patients with low BMI were at risk for a decrease in muscle mass.

Key words: muscle atrophy, sarcopenia, skeletal muscle index, hematopoietic stem cell transplantation, hematologic malignancies

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Sarcopenia is a complex syndrome characterized by the progressive and generalized decrease of skeletal muscle mass and strength[1,2)]. The prevalence of sarcopenia ranges from 15% to 50% in patients with cancer, 30% to 45% in patients with liver failure, and 60% to 70% in critically ill intensive care patients[3)]. Sarcopenia is associated with infectious complications, prolonged duration of mechanical ventilation, longer hospitalization, greater need for rehabilitation care after hospital discharge, and the pathogenesis of various diseases[3-5)]. Furthermore, it is a major feature of cancer cachexia, and is also associated with a reduced quality of life (QOL) and survival[6)].

Alongside sarcopenia, muscle atrophy has recently been identified as a poor prognostic factor for survival outcomes in cancer patients[4)]. Muscle atrophy can impair the efficacy of many different therapeutic treatments[7)]. In addition, treatment-related toxicity due to chemotherapy regimen-related toxicity (RRT) and lying in bed associated with cancer-related fatigue (CRF) are related[8)]. CRF is the most commonly reported side effect in cancer patients. This debilitating fatigue often causes skeletal muscle loss with a reduction in overall physical activity, which can lead to a

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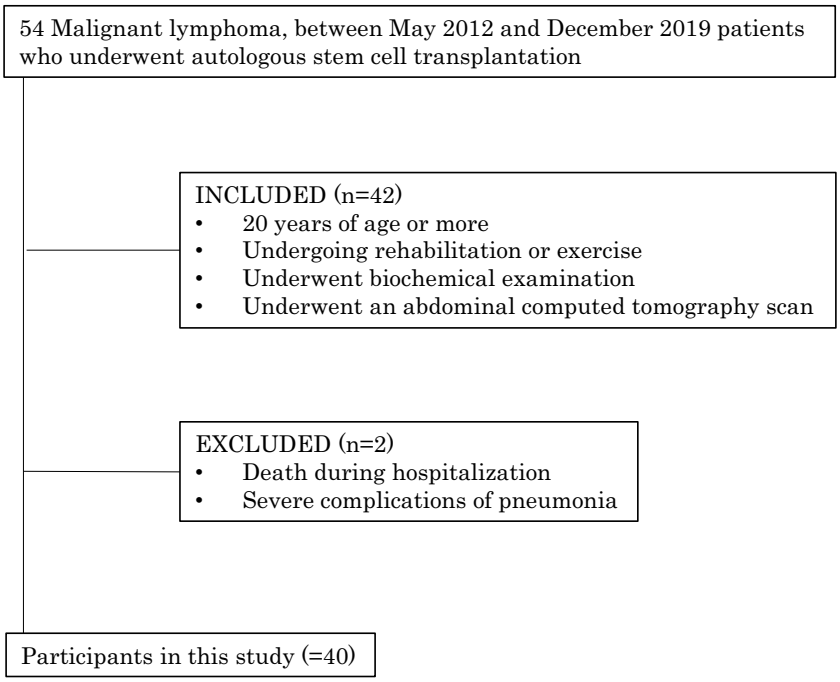

Figure 1. Study flow chart

reduction in physical function[9].

Hematopoietic stem cell transplantation (HSCT) is a breakthrough curative treatment for patients with hematologic malignancies such as multiple myeloma and refractive malignant lymphoma (ML)[10]. However, the direct effects of malignancy, effects of chemotherapy / radiation, drug treatment, and sedentary behavior all likely contribute to increased fatigue after HSCT[11]. In this way, it is the most effective treatment for improving prognosis and QOL. However, HSCT aggravates muscle atrophy as a result of declining physical activity and toxicity due to high-dose chemotherapy[12]; the association between skeletal muscle reduction and clinical outcomes after HSCT have also been suggested[13]. There were several reports with regards to changes in skeletal muscle mass and the effects of exercise therapy after HSCT[14]. The association between skeletal muscle reduction clinical outcomes and prognosis after HSCT has also been suggested in the previous reports[13,15,16]. While patients with hematological malignancies are treated with HSCT, the influence of HSCT on skeletal muscle mass have not been previously described in detail despite the known relationship between auto-HSCT and muscle atrophy.

Therefore, the aims of this study were to investigate changes in skeletal muscle mass after HSCT. Also, we investigated the risk profile associated with decreased skeletal muscle mass.

Materials and Methods

Study Design

This observational study aimed to investigate changes in skeletal muscle mass and its risk factors in patients with in-hospital ML after HSCT.

Ethics

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in the prior approval given by the institutional review board of Kurume University (Approval number:18018). An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection. None of the patients were institutionalized.

Subjects

We identified 54 ML patients who, between May 2012 and December 2019, underwent autologous stem cell transplantation (ASCT) in Kurume University Hospital. Of these patients, 42 consecutive patients who underwent (1) 20 years of age or more, (2) undergoing rehabilitation or exercise, and (3) who underwent biochemical examination and an abdominal computed tomography (CT) scan including the third lumbar vertebrae level (L3) before and after ASCT were enrolled in this study. Two patients who (1) death during hospitalization and (2) severe complications of pneumonia were excluded from this study. After applying inclusion and exclusion criteria, 40 patients were enrolled (Figure 1).

Evaluation of Skeletal Muscle Mass

Skeletal muscle mass was measured by diagnostic CT scans at L3, as previously described[16]. The CT scans used for analysis were carried out as part of the ML assessment. The CT scans were obtained and evaluated for body com-

position data by two government-certified physical therapists who were blinded to the patients' information under the guidance of a diagnostic radiologist. Skeletal muscle mass was evaluated by the psoas muscle index (PMI) index, and PMI was calculated by normalizing the L3 psoas muscle areas by the square of the height (m^2)[16]. This analysis was performed using the diagnostic software ImageJ[17]. Muscle atrophy was defined as a PMI < 6.36 cm^2/m^2 for male or < 3.92 cm^2/m^2 for female, according to a previous report in Asian adults[18].

Evaluation of Visceral Fat Area (VFA) and Subcutaneous Fat Area (SFA)

VFA and SFA were measured as previously described[19]. Briefly, the VFA and SFA were measured by diagnostic CT scanning at the umbilical crossing line[19]. CT scan images had already been performed for the assessment of ML. Similarly, the VFA and SFA were measured using the diagnostic software ImageJ[17].

Conditioning Regimen Administered Before ASCT

Patients began treatment with upfront high-dose chemotherapy followed by ASCT after induction and consolidation chemotherapy. The pre-transplant conditioning regimen administered before ASCT was the LEED regimen, consisting of cyclophosphamide (60 mg/kg on days before ASCT 4 and 3), etoposide (250 mg/m^2 twice daily from days before ASCT 4 to 2), melphalan (130 mg/m^2 on the day before ASCT 1), and dexamethasone (40 mg/body from days before ASCT 4 to 1)[20] and the MCEC regimen consisting of ranimustine (200 mg/m^2 on days before ASCT 8 and 3), carboplatin (300 mg/m^2 from days before ASCT 7 to 4), etoposide (500 mg/m^2 from days before ASCT 6 to 4), and cyclophosphamide (50 mg/kg on days before ASCT 3 and 2)[20-22].

Rate of Change in PMI

To investigate changes in PMI before and after ASCT, the rate of change in PMI after ASCT relative to before ASCT was calculated.

ASCT Rehabilitation Protocol

To maintain physical ability during the hospitalization for ML treatment, enrolled patients were treated with equivalents/40 minutes/day of therapeutic exercise instructed by physical therapists certified for the rehabilitation of ML patients. The therapeutic exercise was developed according to the guidelines of the American College of Sports Medicine and our hospital cancer rehabilitation protocol[23,24]. These therapeutic exercise protocols were performed in a clean room and consisted of the four types of exercise below:

1) Stretching

At the beginning of therapeutic exercise, patients performed a series of stretching exercises for 3 minutes, which targeted the quadriceps femoris muscles, hamstrings, and gastrocnemius. Static stretching was held for 10-20 seconds until the point of feeling tightness or slight discomfort[23,24].

2) Strength training

Patients participated in strength training targeting the lower limb muscles. Squat and standing calf raise were performed 20 times each.

3) Balance training

Patients practiced tandem stand or one-legged stand for 4 minutes.

4) Endurance training.

Finally, patients were trained with bicycle ergometers or walking for 10 minutes. The intensity of exercise was adjusted by 11-13 points on the Borg scale, a subjective rating of perceived exertion[24].

Statistical Analysis

Data are expressed as median (interquartile range [IQR]), range, or number. Changes in PMI before and after ASCT were evaluated by Wilcoxon signed-rank tests. Rate of change in skeletal muscle mass VFA and SFA were evaluated by the difference in PMI, VFA, and SFA between before and after ASCT. Besides, independent factors and a cutoff value of revealed risk factors associated with the rate of change in PMI were analyzed by using decision-tree analysis, as previously described[23,25]. Decision tree analysis, the objective variable is the rate of change of PMI. Explanatory variables were selected from the following variables: age, sex, BMI, colonization of resistant bacteria, conditioning regimen, grip strength, rehabilitation implementation rate, VFA, SFA, levels of hemoglobin, albumin, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). We examined the rate of change in PMI of each factor derived from the decision tree analysis using ANOVA analysis of variance followed by Tukey's multiple comparison test[26]. All analyses were performed using JMP Pro® 13 (SAS Institute Inc., Cary, North Carolina, USA). The level of statistical significance was set at $P < 0.05$.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. The median age was 58 years, and the ratio of females to males was 1:1.5 (16/24). The median body mass index was 21.1 kg/m^2. The majority of patients had a performance status (PS) of 0 or 1 (PS0 = 42.5%; PS1 = 30.0%). Colonization of resistant bacterial infections occurred in 25% (10/40) of the enrolled patients. Patients began treatment with upfront high-dose chemotherapy followed by ASCT after induction and consolidation chemotherapy. The conditioning regimen administered before ASCT was 37.5% and 62.5% for LEED and MCEC, respectively. The median level of PMI

Table 1. Patient characteristics

	Reference Value	Median (IQR)	Range (min–max)
Number		40	
Age (years)		58 (52–67)	20–74
Sex (female/male)		16/24	
BMI (kg/m^2)	18.5-24.9	21.1 (19.8–23.2)	17.1–29.6
Performance Status (0/1/2/3/4)		42.5%/30.0%/22.5%/5.0% (17/12/9/2)	
PMI (female) (cm^2/m^2)	≥ 3.92	3.75 (3.35–4.43)	2.19–4.92
PMI (male) (cm^2/m^2)	≥ 6.36	5.82 (4.65–6.77)	3.02–9.00
PMI (low/normal)		24/16	
Colonization of resistant bacteria (yes/no)		10/30	
Regimen (LEED/MCEC)		15/25	
Bathel index		100 (100–100)	85–100
Hospitalization (days)		24 (21–35)	17–126
Period to engagement (days)		11 (10–11)	10–25
Rehabilitation implementation rate (%)		72.5 (58.2–81.5)	12.5–100

Abbreviations: IQR, interquartile range; BMI, body mass index; PMI, psoas muscle index.

before ASCT was 3.75 cm^2/m^2 in female patients and 5.82 cm^2/m^2 in male patients (Table 1).

Differences in Variables Before and After ASCT

The median period of hospitalization was 24 days (range: 17-126 days). During this period, all patients underwent cancer rehabilitation and a significant decrease was observed in PMI (Figure 2). Table 2 shows a summary of differences in body composition, and biochemical examinations before and after ASCT. During hospitalization, BMI, VFA, SFA, and grip strength decreased significantly (Table 2), along with red blood cell count and platelet count. Additionally, serum albumin and total protein levels significantly decreased during hospitalization. However, no change was seen in BUN, creatinine, and eGFR levels during hospitalization (Table 2).

Decision Tree Analysis for Rate of Change in PMI

To clarify the clinical profile of the reduction in PMI, a decision-tree analysis was created using two divergence variables to classify three groups of patients (Figure 3). According to the decision-tree analysis, the regimen was selected as the initial split. In patients administered MCEC, the median rate of change in PMI was −5.57%. In patients administered LEED, the median rate of change in PMI was −3.97% and the second branching factor was BMI. In patients with BMI < 20.3 kg/m^2, skeletal muscle decrease was observed and the median rate of change in PMI was −7.16%. Conversely, Patients with BMI ≥ 20.3 kg/m^2 had increased PMI, with the median rate of change of 4.05% (Figure 3).

Difference in Rate of Change in PMI for Factors Derived from the Decision Tree Analysis

In Table 3, we clarified the rate of change in PMI patients with MCEC (Group 1), LEED/BMI<20.3 kg/m^2 (Group 2), and LEED/BMI≥20.3 kg/m^2 (Group 3) derived from the decision tree analysis (Table 3). The ANOVA analysis of the rate of change in PMI was found to be significant (Table 3). Concerning the rate of change for PMI in Tukey's multiple comparison test, Group 1 was significantly lower than Group 3. There was no significant difference between Groups 1 and 2. Also, no significant difference was seen in Groups 2 and 3 (Table 3).

Discussion

In this study, we demonstrated that skeletal muscle mass after ASCT was significantly decreased compared to that before ASCT in ML patients. Besides, we revealed that regimen and BMI before ASCT, but not age and sex, were factors associated with PMI. Thus, ML patients with "administered MCEC regimen" and "administered LEED regimens with BMI < 21.3 kg/m^2" were at risk for decreased skeletal muscle mass after ASCT.

PMI significantly decreased after ASCT. Patients who undergo HSCT frequently experience considerable deterioration of their health status as a result of high-dose chemotherapy, resulting in reduced physical activity[12]. Physical inactivity is sufficient to cause prolonged, physical dysfunction, muscle atrophy, and weakness. In addition, muscle atrophy that occurs frequently during ASCT hospitalization has been suggested to be related to nutritional intake[27]. Similarly, serum albumin levels also decreased significantly in enrolled patients. A decrease in serum albumin level also occurs after ASCT, similar to a previous re-

Table 2. Differences in body composition, muscle mass, and biochemical examinations before and after ASCT

	Before ASCT		After ASCT		
	Median (IQR)	Range (min–max)	Median (IQR)	Range (min–max)	P-value
BMI (kg/m^2)	21.1 (19.8–23.2)	17.1–29.6	19.9 (18.4–22.3)	15.9–27.4	<.0001
VFA (cm^2)	54.0 (27.2–85.9)	7.3–200.2	50.3 (19.4–85.1)	4.85–189.4	0.0318
SFA (cm^2)	92.2 (55.0–143.3)	15.0–296.7	84.3 (51.3–130.0)	19.0–270.3	0.0035
Grip strength (female) (Kg)	18.9 (16.3–23.5)	7.1–30.2	16.4 (13.0–20.3)	9.4–28.3	0.0117
Grip strength (male) (Kg)	31.5 (28.8–38.5)	22.4–45.5	29.1 (26.7–34.1)	13.7–41.8	0.0151
Red blood cell count (×10^4/μL)	307 (280–345)	230–473	288 (258–316)	217–392	0.007
Hemoglobin (g/dL)	9.9 (8.6–10.9)	7.2–14.1	9.0 (8.2–10.0)	6.8–12.2	0.148
White blood cell count (/μL)	4000 (2625–4875)	1500–20500	4400 (3200–5100)	1100–12000	0.8144
Lymphocytes (%)	21.5 (15.3–29.9)	4.0–50.0	30.4 (11.8–42.1)	4.0–66.0	0.2058
Platelet count (×10^3/mm^3)	183 (133–247)	20–380	55 (28–100)	8–204	<.0001
AST (IU/L)	25 (19–31)	11–108	30 (22–38)	16–82	0.2912
ALT (IU/L)	23 (14–34)	9–166	26 (15–38)	12–119	0.6869
Lactate dehydrogenase (IU/L)	244 (201–313)	112–613	246 (199–267)	135–1033	0.1588
Total protein (g/dL)	6.4 (6.1–6.9)	5.2–30.3	5.9 (5.2–6.0)	4.0–6.9	<.0001
Albumin (g/dL)	4.0 (3.6–4.3)	2.9–4.9	3.3 (3.1–3.7)	1.4–4.0	<0.001
Prothrombin activity (%)	114 (104–127)	10–140	120 (95–138)	62–140	0.2552
BUN (mg/dL)	13.0 (9.1–14.8)	6.0–27.0	10.4 (7.8–16.0)	4.6–74.1	0.7392
Creatinine (mg/dL)	0.6 (0.4–0.7)	0.3–1.6	0.6 (0.5–0.8)	0.3–1.4	0.5731
eGFR (mL/min/1.73 m^2)	108 (79–126)	22–168	98 (73–128)	41–202	0.7252
Uric acid (mg/dL)	4.6 (3.8–5.4)	0.6–15.8	4.2 (3.3–5.6)	0.4–7.9	0.2561
Sodium (mmol/L)	143 (140–143)	134–148	141 (139–142)	131–147	0.0564
Potassium (mmol/L)	4.1 (3.8–4.3)	3.4–6.2	4.0 (3.6–4.3)	3.4–4.5	0.2507
Chloride (mmol/L)	105 (103–107)	101–110	105 (102–107)	99–114	0.7625

Abbreviations: IQR, interquartile range; ASCT, autologous peripheral blood stem cell transplantation; BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

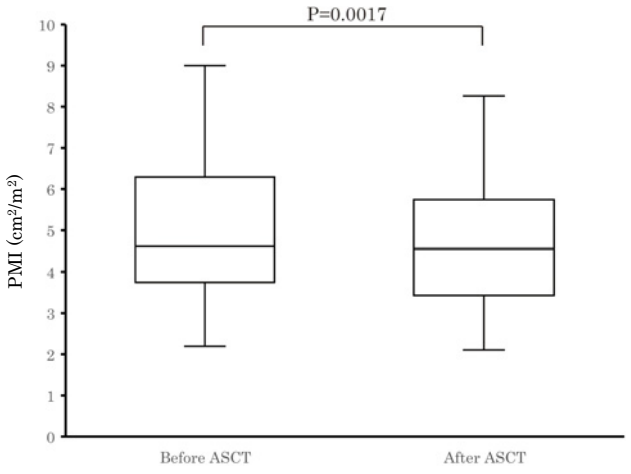

Figure 2. Changes in PMI, before and after ASCT. Abbreviations: PMI, psoas muscle index.

port[27,28]. The serum albumin level is a negative acute-phase protein that decreases in concentration with ongoing systemic inflammation, poor health, and malnutrition. Because these unfavorable conditions lead to decrease in skeletal muscle mass, low albumin concentrations might reflect low muscle mass. The results of the present study are consistent with these findings and indicate that low serum albumin levels may serve as an early warning sign of muscle atrophy[29]. Thus, our data were in good agreement with previous reports and indicate that rapid depletion occurs in patients with ML who have undergone ASCT. Moreover, a decrease in serum albumin levels has been reported to be associated with prognosis[30], and requires further investigation. Thus, in patients who underwent ASCT may experience muscle atrophy alongside reduced physical activity and malnutrition.

In this study, a conditioning regimen was administered before the ASCT was selected as the variable for the initial split for the change rate in PMI. It remains unclear why the rate of change in PMI was significantly lower in patients administered MCEC than in patients administered LEED. Sarcopenia, including skeletal muscle atrophy, is associated with RRT in cancer patients[8]. Factors associated with RRT include the type of chemotherapy and dosage and duration of administration[22]. Administered regimen MCEC has a higher dose and frequency of chemotherapy than Adminis-

Table 3. Rate of change in PMI of "MCEC Group", "LEED/BMI<20.3 kg/m² Group" and "LEED/BMI≥20.3 kg/m² Group" patients with ML

	Group1 MCEC	Group 2 LEED/BMI<20.3 kg/m²	Group 3 LEED/BMI≥20.3 kg/m²	P-value
	Median (IQR)	Median (IQR)	Median (IQR)	
Number	25	5	10	
Rate of change in PMI (%)	-5.57 (-9.46– -1.66)	-7.16 (-15.90– -4.02)	4.05† (-10.4–17.73)	0.0196

†Group 1 vs. Group 3; P<0.05

Abbreviations: IQR, interquartile range; BMI, body mass index; PMI, psoas muscle index.

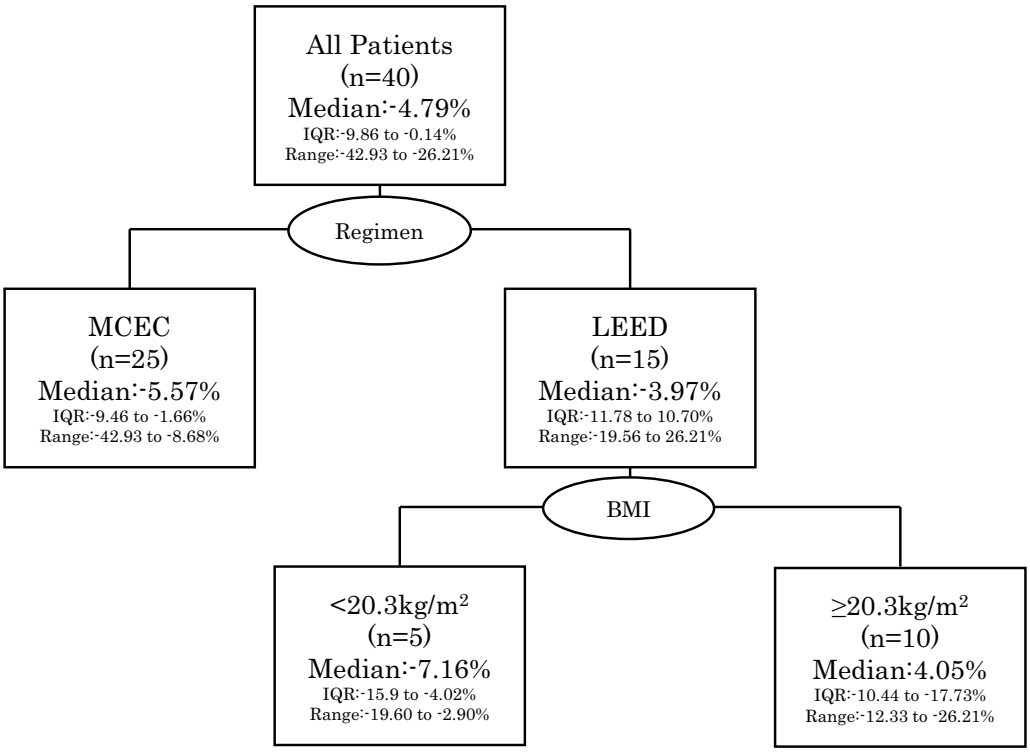

Figure 3. Decision-tree analysis for rate of change in PMI patients with ML underwent ASCT.
Abbreviations: IQR, interquartile range; PMI, psoas muscle index; BMI, body mass index.

tered regimen LEED[20]. Also, nutrition-related adverse events occurring after ASCT are all attributable to pretreatment chemotherapy[22]. Oral mucositis is an unavoidable condition of the oral cavity that accompanies chemotherapy for various malignant cases and can lead to impaired nutritional status[31]. Oral mucositis is a potential side effect of cyclophosphamide, carboplatin, and etoposide, and carboplatin and etoposide[22]. These chemotherapies are constituted the MCEC regimen, on the other hand, In the LEED regimen, cyclophosphamide and etoposide chemotherapies are calibrated but others are not[20]. Furthermore, Carboplatin, a platinum-drugs are widely used in Medical Oncology departments to treat common neoplasms[32]. Carboplatin treatment is highly neurotoxic and contributes to cachexia and skeletal muscle mass loss[33]. Carboplatin is constituent chemotherapy of the MCEC regimen but not the LEED regimen. Furthermore, the MCEC regimen caused considerable non-hematologic toxicities in a previous study[34]. Thus, the difference in RRT, oral mucositis, and neurotoxic may be a possible reason for the decrease in PMI between the conditioning regimen administered before the ASCT.

In patients who received LEED, those with a BMI < 20.3 kg/m² had a low rate of change in PMI. The reasons for this are considered as follows. Tey et al. reported that the average BMI of patients with low skeletal muscle index was 21.97 kg/m², which was significantly lower than that of patients with normal SMI in elderly populations[35]. Besides, patients with low lean body mass may therefore be exposed to higher concentrations of cytotoxic drugs than those with a higher lean body mass in patients with diffuse ML treated with chemotherapy[36]. Moreover, a lower BMI was also as-

sociated with an increased risk of febrile neutropenia. And, febrile neutropenia has been reported to be associated with decreased skeletal muscle mass[36]. Thus, patients with low BMI or frailty may experience skeletal muscle loss after ASCT.

This study has several limitations. First, this was an observational study conducted at a single center. Second, due to the retrospective nature of the study, the CT evaluation date and hospitalization for ASCT were not constant. Third, physical activity in daily living and several nutrition-related factors were not evaluated. Fourth, this study included only a limited number of patients, therefore the risk factors for skeletal muscle atrophy could not be examined by multivariate analysis, and prognostic studies were inadequate. Thus, there is a possibility of selection bias, suggesting that further prospective multicenter validation studies that include physical activity and nutritional assessment are required for patients in various conditions. Moreover, a prognosis study of skeletal muscle loss during the HSCT period is also needed.

Conclusion

In conclusion, we demonstrated that skeletal muscle mass was significantly decreased before and after ASCT in patients with ML. Moreover, we found that BMI and a conditioning regimen administered before the ASCT were both associated with muscle atrophy. Thus, patients who were administered MCEC and patients with low BMI who were administered LEED were at risk of decreased skeletal muscle mass after ASCT. Therefore, cancer prehabilitation, including nutrition therapy, before ASCT would be useful for maintaining skeletal muscle mass in patients with ML preparing for ACST.

Conflict of Interest: There is no conflict of interest to disclose.

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PHYSICAL THERAPY RESEARCH

SCIENTIFIC RESEARCH ARTICLE

Incidence of postoperative complications and non-periprosthetic fractures after total hip arthroplasty: A more than 10-year follow-up retrospective cohort study

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ABSTRACT. Objective: Postoperative complications and non-periprosthetic fractures (NPPFs), which was defined as a fracture existing non- periprosthetic implant, after total hip arthroplasty (THA) have a negative effect on the patients' ability to perform activities of daily living. Thus, investigating these incidences of patients after THA will be valuable as it lead to a more strategic physical therapy interventions and advanced research to prevent these problems. The purpose of this study was to investigate the incidence of postoperative complications related to implants and NPPFs in patients after THA, a more than 10-year follow-up. Methods: This is a retrospective cohort study. A total 892 patients with hip osteoarthritis who underwent primary THA were analyzed (age at surgery was 45-79 years; 805 women; the average follow-up period was 12.4-year). The postoperative complications related to implants and NPPFs were calculated using data from their medical records. Results: The postoperative complications occurred in 37 patients, and NPPFs occurred in 72 patients, who were significantly older, and hip and knee OA diagnosis, compared to patients without NPPFs (p <.05). The most common cause of NPPFs was minor trauma. In patients aged ≧ 65 years, significantly more NPPFs occurred during the first year after surgery(p <.05). Conclusion: More than 10-year after THA, the incidence of NPPFs was higher than that of postoperative complications related to implants. Older patients who had hip and knee OA were a significantly higher risk of developing NPPFs due to falls within the first year after surgery.

Key words: total hip arthroplasty, postoperative complications, non- periprosthetic fractures, fall

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Total hip arthroplasty (THA) is a successful treatment to provide pain relief, improve patients' activities of daily living (ADLs) and quality of life (QOL) for hip osteoarthritis (OA)[1)]. In the majority of developed countries, there has been a significant increase in the utilization of THA in the last 10-year[2)].

However, postoperative complications such as dislocation, loosening due to wear, and periprosthetic femoral frac-

tures (PFFs) increase over time, leading to a decrease in implant survival, ADLs, and QOL[3-5]. In addition, non- periprosthetic fractures (NPPFs), which was defined as a fracture in a bone with an existing non- periprosthetic implant, in patients after joint replacement was a major problem for health care systems that is known to be increased risk of morbidity, post-operative complications required further surgery, and mortality[6]. Previous literature demonstrated the incidence and risk factors of implant-related postoperative complications after THA[3-5]; however, little is known about the incidence of NPPFs in patients long-term after THA.

The number of older patients undergoing THA with osteoporosis and risk of falls are increased due to an aging population, and the incidence of NPPFs may lead to an increase after THA. Thus, it is important to clarify the incidence and predisposing factors for implant-related postoperative complications and NPPFs in order to establish more effective physical therapy interventions. Therefore, the purpose of this study was to examine the incidence of implant-related postoperative complications and NPPFs in patients at a more than 10-year follow-up after THA.

Materials and Methods

Study design

This is a retrospective cohort study.

Patients

We retrospectively reviewed the medical records of 1,586 consecutive patients who underwent primary THA due to hip OA at the authors' hospital between October 2004, and August 2009.

The inclusion criteria were as follows: (1) aged 45-79 years at the time of surgery; and (2) without osteotomy at the time of surgery; (3) had no fracture at the time of surgery; (4) did not have a history of hip surgery; (5) cementless acetabular component; (6) used included metal on polyethylene bearing. The exclusion criteria were as follows: (1) did not visit for regular postoperative medical examination; (2) deceased during the observation period; and (3) severe medical, neurological, or cognitive disease. For patients operated on bilaterally, we counted from the first operated hip.

This study was approved by the Mirai Iryo Research Center (approval number TGE 01339-151).

Surgical procedure and post-operative protocol

All surgeries were performed by the anterolateral approach. In the post-operative protocol, full weight-bearing was allowed on the day of surgery, walk with walker on the day after surgery, and walk with a cane on the second day after surgery. Patients were allowed to discharge the hospital when they could walk with a cane and climb and descend stairs. The length of hospital stay was 7-12 days. Patients were assessed postoperatively at 2-, 6-month, and 1-year, and every 1-2 years thereafter.

At the time of regular medical examinations, patients were given functional evaluations and exercise instruction by a physical therapist for about 20-40 minutes. These exercises were performed mainly open kinetic chain exercises (hip extension, external rotations, and abduction) aimed at improving the range of hip motion, increasing around these hip muscle strength. At the end of each intervention, the physical therapists instructed them to continue appropriate exercise at home.

Evaluations

In this study, we analyzed whether there was a difference in characteristics (age, sex, body mass index (BMI), and hip and knee OA diagnosis or arthroplasty) between patients who had the incidence of postoperative complications or NPPFs and those who did not have these incidences during 10-year after surgery.

The medical records, radiographic evaluation, and self-reported questionnaires were reviewed for age, sex, BMI, hip and knee OA or arthroplasty, postoperative complications, and all fractures. Radiographs of the hip in the anteroposterior and lateral view were assessed at each follow up. Postoperative complications were evaluated by experienced 7 orthopedic surgeons for dislocation, thromboembolic disease (symptomatic venous thromboembolism (VTE)), PFFs, deep periprosthetic joint infection, osteolysis, implant loosening, and revision[7]. When multiple incidences occurred in the same patient, only the first incidence event was included in this study.

NPPFs were assessed from patients' self-report in the questionnaire, based on previous research[8]. For verification of fractures, fracture site were confirmed by review of radiology reports or medical records. The first patient-reported fracture event was used in this study. When two or more fractures occurred at the same time, it was defined as a multiple fracture. Fracture site was described by its anatomical location. Participants were asked about fractures of the clavicle, vertebra, pelvis, contralateral proximal femur, patella, tibia, proximal humerus, proximal radius/ulna, and distal radius. Any spinal fracture (cervical, thoracic, or lumbar) was documented as a "vertebra" fracture since in some cases it was difficult to distinguish the locations of these fractures based on the responses in the questionnaire. Next, the patients were asked to describe when they had a fracture (< 1 year or $\geqq 1$ year after surgery). With regard to the cause of fracture[5], minor trauma was defined as a fall to the floor at the same level on which the patients had been standing or sitting, whereas major trauma included traffic accidents and any other high-energy trauma. Spontaneous fractures were those occurring without any obvious trauma.

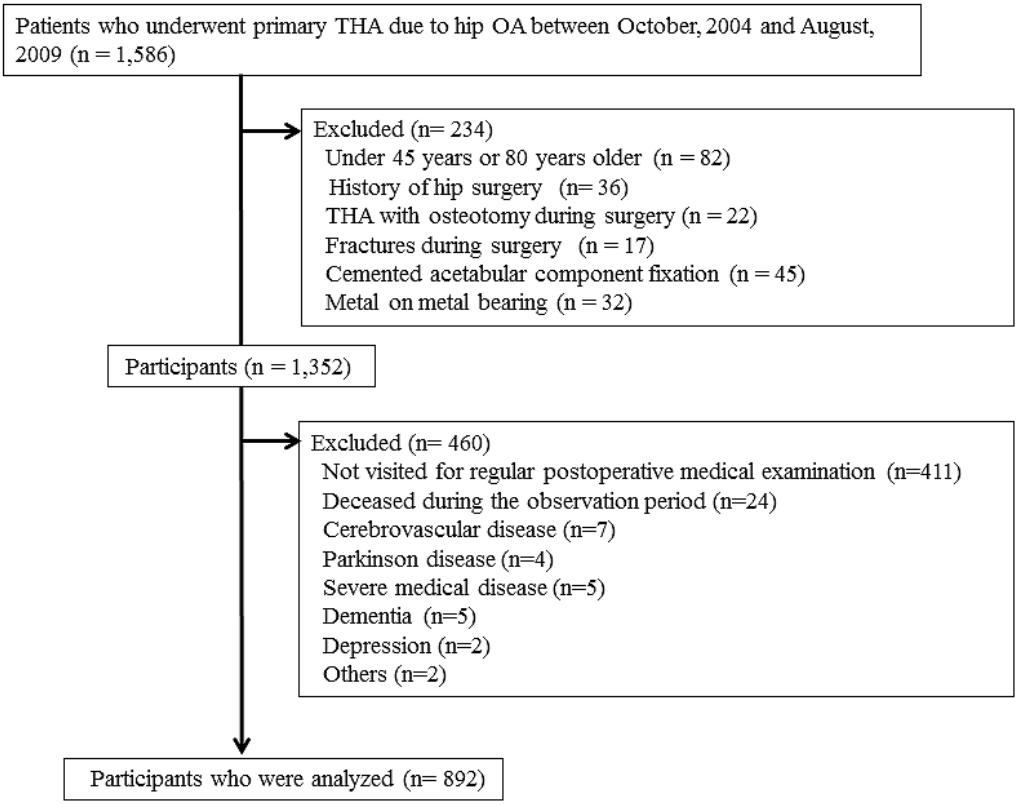

Figure 1. Flow diagram of participant recruitment and follow-up in the present study.

Statistical analysis

Data were organized using descriptive statistics. The mean value and standard deviation of each item in the patient demographics data were calculated. One-way analysis of variance and a chi-square test were used to compare patient backgrounds among the three groups. Bonferroni's post-hoc test was used for each significant difference between the three groups (*P*-values < .017 were considered statistically significant).

As a sub-analysis, we examined the effect of age based on age 65-year[9] on variation in site, fracture type, cause, and the postoperative duration of NPPFs using a chi-square test. Statistical analyses were conducted using IBM SPSS statistics version 24 for Windows (SPSS Inc., an IBM Company, Chicago, IL, USA). *P*-values <.05 were considered statistically significant.

Results

Among the 1,586 possible eligible patients, 1,352 patients were included; of these, 460 patients were excluded due to lost to follow-up, deceased, or other serious neurological, medical, psychosis disease. Finally, a total of 892 patients were followed up at a more than 10-year (10.2-14.8 years) (Fig. 1).

The demographic data are shown in Table 1. The postoperative complications occurred in 37 patients, and NPPFs occurred in 72 patients. The age of patients with postoperative complications were significantly higher compared to patients without postoperative complications. Similarly, patients with NPPFs were also significantly older, and hip and knee OA diagnosis, compared to patients without NPPFs ($p < .05$).

Factors of implant-related postoperative complications were shown in Table 2. The most common implant-related postoperative complication was dislocation. In total, dislocation was observed in 13 patients, 6 and 7 patients developing <1 year and ≧1 year, respectively. Head size of dislocated patient was < 32 mm in 12 patients, and ≧32 mm in 1 patient, respectively. Four patients had recurrent dislocation, and 1 patient required revision surgery. Aseptic loosening of the femoral stems without fracture was observed in 5 patients (2 cemented and 3 non-cemented) and 2 patients in the acetabular cups. PFFs were observed in 5 patients. Two patients were treated with open reduction and internal fixation (ORIF) and two patients received conservative treatment. One patient required revision surgery. Four patients were caused by minor trauma. Deep periprosthetic joint infection was observed in 4 patients. Osteolysis was observed in 4 patients, all of whom had conventional polyethylene. VTE was observed in 1 patient. Three patients had other complications. Among all subjects, 20 patients required revision surgery.

Variation in site, fracture type, cause, and the postop-

Table 1. Patients' demographic data (n=892)

Variable[α]	Postoperative complications (n=37)	NPPFs (n=72)	Without postoperative complications or NPPFs (n=783)	*P*-Value*	Post Hoc Analysis[#]
Age at the time of surgery[β], years	62.7 ± 9.9	65.1 ± 8.8	58.8 ± 7.2	<.001	b, c
Female	34 (91.9)	68 (94.4)	703 (89.8)	0.418	
BMI[β], kg/m^2	22.9 ± 2.3	23.1 ± 3.2	22.8 ± 3.1	0.775	
Hip and knee OA diagnosis or arthroplasty					
OA diagnosed	6 (16.2)	35 (48.6)	129 (16.5)[#]	<.001	
Contrateral hip OA	2 (5.4)	16 (19.4)	49 (6.3)[#]	0.001	
Knee OA	4 (10.8)	19 (26.4)	80 (10.2)[#]	0.002	a, c
Arthroplasty	17 (45.9)	25 (34.7)	337 (43.0)	0.264	a, c
Bilateral THA	15 (40.5)	23 (31.9)	315 (40.2)	0.375	a, c
TKA	2 (5.4)	2 (2.8)	22 (2.8)	0.675	
Implant types					
Femoral component fixation					
Cemented	8 (21.6)	20 (27.8)	62 (7.9)		
DCM-J	4 (10.8)	14 (19.4)	37 (4.7)		
VerSys Heritage	4 (10.8)	6 (8.3)	25 (3.2)		
Cementless	29 (78.4)	52 (72.2)	721 (92.1)		
VerSys HA/TCP fiber metal	27 (73.0)	47 (65.3)	635 (81.1)		
Alloclassic	2 (5.4)	5 (6.9)	59 (7.5)		
APS Natural-Hip	0 (0)	0 (0)	20 (2.6)		
VerSys Beaded full coat	0 (0)	0 (0)	7 (0.9)		
PE					
XLPE	32 (86.4)	66 (91.7)	681 (87.0)		
CPE	5 (13.5)	6 (8.3)	102 (13.0)		
Femoral head size					
< 32 mm	32 (86.4)	67 (93.1)	719 (91.8)		
≧32 mm	5 (13.5)	5 (6.9)	64 (8.2)		

[α]Results are presented as number of cases (%) unless otherwise specified.

[β]Data are expressed as mean ± standerd deviation

NPPFs: non-periprosthetic fractures; BMI: body mass index; THA: total hip arthroplasty; TKA: total knee arthroplasty; OA: osteoarthritis; PE: polyethylene; XLPE: cross-linked polyethylene; CPE: conventional polyethylene

*One-way analysis of variance for continuous variables and chi-square test for categorical variables.

[#]A post hoc analysis was performed using the Bonferroni's method.

a) There is a significant difference between postoperative complications and NPPFs

b) There is a significant difference between Postoperative complications and Without postoperative complications or NPPFs

c) There is a significant difference between NPPFs and Without postoperative complications or NPPFs

erative duration of NPPFs by age group were shown in Table 3. The most common site of NPPFs was vertebra, which were significantly higher in patients aged ≧65 years (p <.001). In contrast, patellar and clavicle fractures were significantly higher in patients aged <65 years (p <.05). There was no significant difference in the incidence of multiple fractures between the two groups (p =.525). The most common cause of NPPFs was minor trauma in both age groups, which was no significant difference between the two groups (p =.120). Finally, in patients aged ≧65 years, significantly more NPPFs occurred during the first year after surgery (p <.05).

Discussion

Our results found that, more than 10-year follow-up after THA, the incidence of NPPFs was twice as higher than that of implant-related postoperative complications. Furthermore, our study also showed that THA patients who were older and had hip and knee OA had a significantly increased risk of developing NPPFs. In addition, the risk of vertebra fractures were significantly higher in patients aged ≧65 years. The most common cause of NPPFs was minor trauma in both age groups. Furthermore, in patients aged ≧ 65 years, significantly more NPPFs occurred during the

first year after surgery. There have been few reports on the incidence of NPPFs after THA. The reason for this might be that previous studies have not focused on NPPFs because these are minor injuries and could not be classified due to the presence of a more complex fracture pattern[6]. This is the first large population-based study to investigate the incidence of not only postoperative complications but also NPPFs more than 10-year follow-up after THA.

Our results showed that the incidence of NPPFs was twice as higher than that of implant-related postoperative complications more than 10-year follow-up after THA. One reason for this may be that, in recent years, implant-related postoperative complications such as dislocation and loosening due to wear have been decreased with the development of XLPE[4,10]. However, even 10-year after THA, muscle strength and functional performance were still deficient[11], and these deficits lead to an increased risk of falls[12,13]. Furthermore, older age was a factor in prolonging recovery of muscle strength and physical function after THA[14,15]. Johnson et al.[16] reported that older patients, who were significantly associated with frailty, were at a significantly higher risk of developing adverse events within the first year after surgery. Therefore, surgeons and physical therapists should consider assessing the risk of falls and fall-induced fractures after THA, especially in patients aged ≧ 65 years, as well as improving muscle strength and functional performance. Recently, Fatoye et al.[17] have shown that 2-12 weeks of physiotherapy interventions might lead to improvements in hip muscle strength and functional performance in patients after THA. In addition, several studies

Table 2. Factors of implant-related postoperative complications (n=37)

Variable[α]	
Dislocation	13
Loosening	7
PFFs	5
Deep periprosthetic joint infection	4
Osteolysis	4
VTE	1
Others	3
Revisions	20
Dislocation	1
PFFs	1
Loosening	7
Deep periprosthetic joint infection	4
Osteolysis	4
Others	3

[α]Results presented as number of cases
VTE: venous thromboembolism
PFFs: periprosthetic femoral fractures

Table 3. Variations in sites, fracture type, causes, and postoperative durations for NPPFs

Variable[α]	< 65 years (n=29)	≧65 years (n=43)	*p*-value
Site			0.009
Vertebra	7	29	**
Patella	8	4	*
Contralateral proximal femur	3	6	
Distal radius	4	2	
Clavicle	5	1	*
Proximal radius/ulna	1	4	
Proximal humerus	2	3	
Pelvis	1	1	
Tibia	2	0	
Fracture type			0.525
Single	25	36	
Multiple	4	7	
Cause			0.12
Minor trauma	16	33	
Major trauma	6	3	
Spontaneous event	4	10	
Postoperative duration			0.015
< 1 year	5	19	
≧1 year	24	24	

[α]Results presented as number of cases.
* $p<.05$, ** $p<.001$

reported that 4-10 weeks of home-based exercises showed similar functional improvements to outpatient physiotherapy interventions[18,19]. Thus, physiotherapy interventions and home-based exercises might be an important factor in improving muscle strength and motor function in post-THA patients. However, only a few studies investigated whether long-term (>12 weeks) physiotherapy interventions and home exercises would restore muscle strength and functional performance to the same level as healthy individuals of the same age and prevent age-related functional decline. Future research is needed to determine whether long-term exercise restores motor function to a similar level as healthy individuals of the same age and prevents age-related functional decline.

The present study showed that, in patients aged ≧65 years, the most common site of NPPFs was vertebra, followed by contralateral proximal femur. More research is needed to explain why there is an increased risk of vertebra and contralateral proximal femur fractures in elderly patients undergoing THA. Some studies showed that, in patients after total joint replacement, decrease of postoperative mobility and daily activity levels might have led to lower bone mineral density (BMD) around hip and spine[20-22], which might increase future osteoporosis-related fracture risk[22,23]. Additionally, Toogood et al.[24] demonstrated that older patients had even lower daily activity levels after THA. Thus, these studies suggest that BMD around the hip and spine may decrease in older patients due to decreased mobility and activities of daily living after surgery, which may increase the risk of vertebral and proximal femoral fractures.

From our results, older THA patients with hip and knee OA were at higher risk of developing NPPFs. Several studies have shown that the relationship between lower extremity OA and falls, and fractures[25,26]. Ikutomo et al.[27] demonstrated that knee extensor muscle weakness and limping were strongly risk factors for falls in patients with end-stage hip OA. Thus, THA patients with lower extremity OA might have the insufficient recovery muscle strength, walking ability, thus an increased risk of falls and fall-induced fractures. Therefore, older THA patients with lower extremity OA may particularly need to be assessed for fall risk and to establish strategies that focus on improving knee extension strength and limping.

In our findings, the most common cause for fractures was minor trauma, even in PFF. Recently, it has been suggested that the incidences of PFFs might increase with age in elderly people with osteoporosis[5]. Previous studies have identified minor trauma as the most common risk factor, accounting for approximately 75% of PFFs[28], with results similar to the present study. PFFs after THA were associated with poorer clinical outcomes, a higher incidence of postoperative complications, and loosening of the stem[5]. In our results, two patients required ORIF and one patient required revision surgery. This suggests that prevention of minor trauma, such as falls, is also important for the prevention of PFFs, which is a serious complication after THA.

This study had several limitations. First, 411 patients (30.4%) were lost to follow up, which might have resulted in a selection bias. Second, previous studies reported that factors such as BMD[20-22], muscle mass[29], and physical activity[22,23] also affected the fractures in the elderly, but this study could not evaluate these factors. Third, in this present study, our results might be underestimated because self-reports were included in the fracture result report. Self-reported relevance was 78% for hip fractures and 81% for wrist or forearm fractures, but vertebra fractures might be underestimated at 51% because many people had no symptoms or few symptoms[30]. Fourth, there was a possibility that some of the subjects deceased due to fractures owing to a lack of detailed investigation of the cause of death. Finally, the impact of preoperative contralateral hip and knee OA on the NPPFs was unknown because this study did not include detailed information about other joint due to the retrospective nature of the study. However, few reports have investigated large-scale data on postoperative complications and NPPFs at a more than 10-year after THA. The findings of our study were important when considering strategies and advanced research on these issues.

Conclusion

Our study demonstrated that, more than 10-year follow up after THA, the incidence of NPPFs was twice as higher than that of postoperative complications related to implants. In addition, the occurrence of NPPFs in patients after THA was significantly associated with older age and hip and knee OA. Older patients who had hip and knee OA were a significantly higher risk of developing NPPFs due to falls within the first year after surgery.

Conflict of Interest: The authors declare no conflict of interest.

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