Project Title

Combined activity and cognitive intervention to optimize recovery from critical illness in ICU survivors: COMBAT-ICU trial

Study Background

Given the advances in medical innovations and care for critically ill patients in intensive care units (ICUs), most patients today survive.[1,2] It is common for ICU survivors to experience long-term impairments known as post-intensive care syndrome (PICS).[3] A multicenter cohort study of 4,793 ICU survivors (median length of ICU stay = 3 days) revealed over 50% of them suffer from PICS one year after ICU discharge, with physical functioning the most affected domain.[4] Physical impairments often manifest as a loss of muscle mass and function, fatigue, and exercise limitation, often caused by ICU-acquired weakness, a state of diffuse and generalized muscle weakness that develops after the onset of critical illness without another identifiable cause. In addition, depending on the clinical subgroup, up to 100% of ICU survivors suffer from some degree of cognitive impairment at hospital discharge, particularly in the memory, executive function and attention domains, with 50% of them having impairment that persists for years.[5] Finally, ICU survivors also frequently suffer psychological impairments such as anxiety, depression and post-traumatic stress disorder.[6]

Clinical guidelines published by the American College of Critical Care Medicine and the Society of Critical Care Medicine recommend application of the ABCDEF bundle (e.g. breathing trials, delirium monitoring, early mobilization) in the ICU setting to prevent short- and long-term functional insults in critically ill patients by altering the learned non-use mechanism.[7] Yet, effective bundle implementation is challenging because of various patient-, clinician- and ICU-related barriers hinder effective bundle implementation.[8] Although a recent meta-analysis (N = 60) confirmed the short-term effects of early mobilization during ICU admission on improving patients' physical function at hospital discharge, no long-term benefits were seen 6 months after discharge.[9] The lack of long-term effects for early interventions highlights the need to provide ongoing support for ICU survivors after hospital discharge.

PICS can persist for months or even years, which is devastating for patients as it jeopardizes their daily functioning, ability to return to work and quality of life (QoL).[10] Moreover, patients with PICS are associated with increased mortality in the first year after ICU discharge,[11] healthcare utilization and cost.[12] A multicenter cohort study found that acute respiratory distress syndrome survivors with psychological symptoms were associated with increased hospitalizations and those with better physical functioning and QOL were associated with fewer hospitalizations and reduced cost.[12] Furthermore, critical illness is a family crisis that imposes significant psychological distress on family members, a phenomenon identified as PICS-Family.

As PICS is a relatively new syndrome, research is accumulating on different approaches to tackling it, such as nutritional therapy, ICU diaries, psychosocial counselling, cognitive

and physical rehabilitation, with the latter receiving the most attention to date. A systematic review of 6 studies on exercise rehabilitation for ICU survivors who had been mechanically ventilated for at least 24 hours reported mixed findings on functional capacity, and no beneficial effect was documented on health-related QoL (HRQoL).[13] Similar findings were reported by another meta-analysis of 10 studies that synthesized the evidence on physical rehabilitation among ICU survivors and found limited or no change in HRQoL or mortality.[14] A full-scale randomized controlled trial (RCT) tested an 8-week home-based individualized and progressive multicomponent exercise program (N = 195) delivered through 3 home visits and 4 telephone calls.[15] The other RCT (N = 150) tested a physiotherapist-led transitional rehabilitation program covering both the in-patient and out-patient period among patients admitted to ICU for at least 5 days.[16] Compared to usual care with comprehensive in-patient exercise rehabilitation, the additional out-patient exercise training (multicomponent exercise for 8 weeks, 60 minutes/session, twice/week) did not show added benefits on physical function and HRQoL.[16] The high lost to follow-up rate and incompletion rate of out-patient exercise training might explain for its modest effects.[16] The poor treatment compliance raises the concern that even cantered-based or gymnasium-based training can optimize the training with exercise equipment, the travelling demand for ICU survivors may serve as a significant barrier to hamper the adherence. Indeed, ICU survivors have cited travel to training centers and a lack of motivation as the major factors in their poor rehabilitation attendance.[17]

Another limitation of previous studies is that they tested a single strategy, generally an exercise intervention, to manage physical impairment or PICS as a whole. A multimodal rehabilitative approach may be needed for this vulnerable cohort. A study tested a multicomponent rehabilitation program with cognitive and exercise components delivered in separate sessions.[18] Despite the small sample size (N = 21), the program was found to be effective in improving executive function and functional status as compared to usual care. The other was a proof-of-concept 3-arm study randomized ICU patients to usual care, in-patient physical therapy or in-patient combined cognitive and physical therapy. Those in the combined therapy group continued to receive 6-session home-based cognitive therapy using goal management training after discharge. The combined therapy was found to be feasible and safe, but no significant effects on cognitive, functional and HRQoL were detected at the 3-month follow-up.[19] Such findings were likely due to the study's inadequate power and the lack of physical training after discharge.

Indeed, compelling evidence is accumulating to suggest that simultaneously or sequentially combined exercise and cognitive interventions are more efficacious than single-domain training in promoting physical, functional and cognitive performance in both cognitively impaired and healthy older populations.[20] Such a novel combined intervention in a single training session has never been tested among ICU survivors.

Study Objective & Study Design

This mixed-methods study comprising a 3-arm pilot RCT and a qualitative study aims to investigate the preliminary effects and feasibility of a home-based combined activity and cognitive intervention for ICU survivors (COMBAT-ICU). Adopting a 3-arm design with COMBAT-ICU, exercise and attention placebo study arms will enable us to evaluate the added effects, if any, of the novel combined intervention compared with the standard

exercise-only rehabilitation strategy and attention placebo. Data triangulation from quantitative and qualitative aspects can facilitate result interpretation. The study's objectives are:

1. To evaluate the preliminary effects of the COMBAT-ICU intervention for ICU survivors on PICS, physical, mental and cognitive outcomes, HRQoL, unplanned re-hospitalisation rate, and mortality.
2. To explore the feasibility and acceptability of the COMBAT-ICU intervention and ICU survivors' intervention engagement experience.

The hypothesis of the first objective is that upon completion of the COMBAT-ICU intervention, ICU survivors will have reduced PICS, improved physical function, mental health, cognition and HRQoL, and reduced unplanned readmissions and mortality compared with the exercise and attention placebo groups at post-intervention and 3 months thereafter. While the hypothesis of the second objective is that the COMBAT-ICU intervention is feasible and acceptable for ICU survivors.

Subjects

The COMBAT-ICU trial will be conducted in three hospitals in Hong Kong. The eligibility criteria are Chinese adults aged ≥18, admitted to ICU for at least 4 days as patients often develop long-standing PICS when the length of ICU stay is more than 3 days,[4] has been discharged home, able to perform basic activities of daily living before ICU admission, living with family, have an electronic device that can access the internet (patient/family) and able to walk for at least 10 meters (assisted or unassisted). Patients will be excluded if they cannot read Chinese, have musculoskeletal injury precluding exercise training, are receiving structured out-patient pulmonary or cardiac rehabilitation after discharge, or have clinically evident dementia or significant impairment from an acute brain problem (e.g. traumatic brain injury, stroke, subarachnoid hemorrhage or hypoxic brain injury) that precludes following the study protocol. Those with prolonged length of stay (≥28 days) in the step-down wards will also be excluded as their long-term impairments are likely altered during the extended stay and treatments received in the post-ICU setting.

A research assistant will identify potential participants in the ICU, and then conduct eligibility screening and recruit participants on the day before their discharge from hospital and given one day for consideration after explanation of the informed consent. A study implementation protocol is shown in Appendix 1. After obtaining written consent, baseline data will be collected and participants will be randomised to the COMBAT-ICU, exercise or attention placebo groups. Block randomization will be performed and stratified on study sites, this stratification strategy can ensure balance group allocation of patients from different settings, where patients' socio-economic status and clinical practice may differ. Patients will be allocated in a 1:1:1 ratio according to a computer-generated random sequence list for each stratum. Sequentially numbered opaque sealed envelopes will be used to ensure allocation concealment.

Sample Size

For the sample size of the pilot RCT, as no previous study has tested the effects of a similar intervention, we conservatively assume a small effect size (i.e. between 0.1 and <0.3) on the primary outcome (i.e. PICS). According to the method proposed by Whitehead et al.,[21] a sample size of 20 per study group would give the main trial 80% power at a 5% level of significance to detect between-group changes in the outcome at the post-intervention time points. The total sample size is therefore 60. All participants in the COMBAT-ICU group will be invited to participate in the subsequent qualitative study.

Study intervention

COMBAT-ICU group: This is a home-based, combined exercise and cognitive intervention personalized to the physical and cognitive performance of ICU survivors, a clinical cohort characterized by heterogeneity in physical and cognitive performance upon discharge from hospital. The COMBAT-ICU intervention will last for 8 weeks, with 3 sessions per week, 24 sessions in total. A blended training platform with supervised in-person home visits and a real-time supervised online and unsupervised self-practice approach will be used to deliver the intervention, with the platform gradually shifted from home visits to unsupervised self-practice according to participants' physical functioning level. Family caregivers will be involved in the intervention, so that they can facilitate home-based training. Each intervention session will last for 80 minutes and comprise 45 minutes of exercise training, a 5-minute break and 30 minutes of cognitive training.

Exercise training: Weeks 1 and 2 will be the induction phase, all sessions will be supervised with two home visit sessions and one online session in real-time. The aim is to allow participants to familiarize themselves with the intervention protocol and master the skills of various activities. The arrangement will not only boost self-efficacy and motivation to engage in the intervention, but also ensure safety and facilitate rapport-building. For the exercise training, each session will start with a warm-up, followed by core exercise training and a cool-down exercise. A series of flexibility training and stretching exercises will be performed during the warm-up and cool-down phases (10 minutes in total). The core exercise session will comprise exercises tailored to participants' functional performance in 4 domains: mobility, balance, strength and endurance. A standardized protocol (Appendix 2) with simple performance-based tasks will be used to evaluate participants' functional level in the 4 domains, resulting in Levels 1 to 4, to indicate increasing levels of functional performance.[22] The relative time for each domain of exercise training will depend on the results of functional performance, which will be repeated on a weekly basis. For instance, more debilitated participants in Level 1 or 2 will spend more time performing balance and mobility exercises in the core training. Once improvements are observed in these domains, the training focus will shift to endurance exercise in the subsequent weeks. The training for Level 3 and 4 participants with less impairment in mobility and balance will focus primarily on endurance and resistance exercise. The types of exercise for each domain are selected on the basis of practicability in a home setting using simple equipment such as elastic bands and ankle weights. Balance training will involve both static and dynamic exercises, and mobility training will combine balance movements with mobility, for instance, dynamic start and stop, brief episodes of accelerated gait speed, and changing direction while walking. Strength training will focus on large muscle groups over four limbs. The training for more debilitated participants will

mainly utilize their own body weight as resistance, such as guarded stand and seated toe raises and adding assistive light resistance exercises. When they progress to a higher functional level, resistance bands and cuff weights will be used to exert additional resistance. During endurance training, more debilitated participants will focus on repeated bouts of walking at usual speed, with rest breaks as needed. The duration of each bout will gradually lengthen according to participants' tolerance. Chair and stepping exercises will be added for participants with a higher functional level.

The intervener will progressively scale up the exercise intensity according to the individual's progress during the intervention, with exercise intensity and its progression guided by participants' resting heart rate monitored by an activity tracker, rate of perceived exertion (RPE) and symptoms. RPE reflects patients' subjective perception of exercise intensity and ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximum exertion". The initial exercise session will aim at a resting heart rate plus 20-30 beats/minute, whereas RPE will target "somewhat hard" (12 to 14) to achieve a moderate level of intensity. The intervener will observe the home environment, explore participants' daily routine and provide individualized advice on the integration of exercise tasks into their daily activities. Weeks 3 to 6 will be the maintenance phase. For participants with a higher functional performance level (Level 3 or 4), the mode of delivery will change to one home visit and two online training sessions. The intervener will apply the same principle to carry out exercise training and its progression. Weeks 7 and 8 will be the consolidation phase, consisting of two online sessions and one unsupervised self-practice session. Exercise videos will be supplied to guide participants' self-practice. For participants with a lower functional level (i.e. Level 1 or 2), training will be delivered exclusively through home visits throughout the intervention period until their functional performance progresses to a higher level (i.e. Level 3 or 4).

Cognitive training: The cognitive component (30 minutes/session) will be delivered immediately after the exercise training using a readily available computer-based training platform: CogniFit.[23] The intervener will familiarize participants with the user interface and provide verbal instruction during the training if necessary. The training platform/venue will be the same as that in the exercise session. CogniFit is a scientifically validated cognitive training program developed by a team of neurologists, psychologists and scientists.[23] At baseline, participants will be evaluated on 15 tasks to assess a wide range of cognitive abilities in 20 minutes. The training content will be personalized to the level of difficulty that best suits the participant's cognitive function level. Each cognitive training session will include a mix of 4 cross-modality brain stimulating games aimed at training attention, memory, executive function and other cognitive processes and a cognitive assessment task to allow the program to track changes in cognitive function. The types and complexity of the games will be determined automatically by the program in the first 4 weeks. From Week 5 onwards, participants can select games according to their interest once they have mastered the rules of different games.

Exercise group: Participants in the exercise group will receive an 8-week, home-based, exercise intervention. The implementation protocol is the same as that of the exercise component of the COMBAT-ICU intervention, 3 sessions per week, and 45 minutes per session. Weeks 1 and 2 will be the induction phase, all sessions will be supervised with

two home visit sessions and one online session in real-time. Weeks 3 to 6 will be the maintenance phase. For participants with a higher functional performance level (Level 3 or 4), the mode of delivery will change to one home visit and two online training sessions. Weeks 7 and 8 will be the consolidation phase, consisting of two online sessions and one unsupervised self-practice session. They will not receive any structured cognitive training.

Attention placebo group: To reduce the potential bias from greater attention for the COMBAT-ICU and exercise groups, participants in the attention placebo group will receive a telephone call every 2 weeks, 8 weeks in total, with the conversation focused on information provision and brief counselling relating to their health conditions. They will also receive the routine care provided by the healthcare system, including medical follow-ups with the clinical team, without structured out-patient rehabilitation services.

Primary and Secondary Outcomes

The following validated performance-based and patient-reported measures will be used for outcome evaluation at baseline (T0), immediate post-intervention (T1) and 3 months post-intervention (T2):

Primary outcome

Patient-reported PICS: The 18-item Post-Intensive Care Syndrome Questionnaire (PICSQ)[24] will be used to measure the extent of PICS. The PICSQ consists of 3 subscales, physical, cognitive and mental, and is rated on a 4-point Likert scale ranging from 0 to 3. It has good internal consistency (Cronbach's alpha = 0.93). Its criterion validity is evidenced by its strong correlation with frailty and HRQoL measures, and factor analysis confirmed its construct validity.[24]

Secondary outcomes

Performance-based physical function: The 6-Minute Walk Test (6MWT) will be used to evaluate aerobic capacity and endurance. Standard measurement guidelines will be followed, and the distance walked will be recorded. The Time-Up-Go test will be used to measure functional mobility, assessed by the time it takes to stand up, walk a distance of 10 feet, turn, walk back and sit down. Handgrip strength will be assessed by a dynamometer to evaluate muscle strength of upper limbs. The Short Physical Performance Battery will be used to assess functional capacity. It consists of 3 timed tasks: standing balance, walking speed and chair stand tests.

Performance-based cognitive function: The Montreal Cognitive Assessment will be used to assess global cognition, and the Colour Trails Test to measure executive function and attention. The latter test has two parts: part 1 assesses visual-motor processing speed and attention, and part 2 sequencing and mental flexibility in addition to processing speed and attention. The Digit Span test will be used to measure short-term and working memory.

Patient-reported mental health: The Patient Health Questionnaire-9 will be used to measure the frequency of depressive symptoms in the past 14 days. Its 9 items are rated on a 4-point scale ranging from 0 to 3, with higher sum scores indicating more depressive symptoms. The Generalized Anxiety Disorder Scale-7 will be used to measure anxiety levels. Ratings on a 4-point scale (0-3) indicate the frequency of anxiety symptoms in the past 14 days, with higher total scores representing greater anxiety.

HRQoL: The EuroQol Five Dimensions Five Levels (EQ-5D-5L) will be used to measure HRQoL. It consists of two parts: EQ-5D descriptive system and EQ visual analogue scale. The first part uses 5 levels to indicate a participant's health state on 5 dimensions – mobility,

self-care, usual activities, pain/discomfort and anxiety/depression – and the second part is an additional self-rated health item rated on a visual analogue scale ranging from 0-100.
Unplanned hospital readmission and mortality: Hospital utilisation data and mortality will be monitored from T0 to T2 through electronic medical record review.
Feasibility, trialability and acceptability: The recruitment rate, eligibility screening and randomisation procedures, protocol implementation, outcome measurement, blinding, and cost of implementation (equipment, manpower and social cost) will be documented. To assess intervention acceptability, the attendance and retention rates will be recorded. A logbook will be developed to document the dose of supervised and unsupervised self-training. Moreover, all participants in the COMBAT-ICU group will be invited to complete a satisfaction survey and semi-structured qualitative interview upon completion of the COMBAT-ICU intervention. The interview will be conducted through face-to-face format and will last for approximately 1 hour, which will focus on exploring the acceptability and perceived effects from participants' perspective.

Methods of Data Analysis

Descriptive statistics will be used to summarize the recruitment, attendance and retention rates, the cost of implementation, and participant satisfaction. The RCT data will be analyzed according to the intention-to-treat principle. The study groups' baseline characteristics will be compared using the chi-square test, Kruskal-Wallis test or one-way analysis of variance (ANOVA) where appropriate. In line with the findings of a recent meta-analysis,[25] the following variables will be treated as potentially confounding variables: age, sex, previous mental health problems, disease severity (APACHE II score), and negative ICU experience (measured by the Intensive Care Experience Questionnaire). Variables with p-values ≤ 0.10 for between-group differences at baseline will be statistically adjusted in the analysis. Generalized estimating equation modelling will be performed to determine the effects of the COMBAT-ICU intervention by comparing the intervention group with the exercise and attention placebo groups across the study time-points. All statistical analyses will be performed using IBM SPSS 28.0. All statistical tests will be two-sided, and the significance level will be set at 0.05.

For the qualitative data, the audio-recorded interviews will be transcribed verbatim. After checking the accuracy of the transcriptions, content analysis will be performed to code the data on participants' acceptability and perceived effects of the intervention. The technique of joint displays using an informational matrix will be used to integrate quantitative and qualitative data in order to seek for convergence of results. The trustworthiness of the qualitative analysis will be enhanced by audio-recording the interviews, conducting an audit trail, and involving two project team members in coding the data independently and developing the categories, subcategories and themes.

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