Exercise interventions are delayed in critically ill patients: a historical cohort study in an Australian tertiary intensive care unit

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Acknowledgements

We would like to thank the dedicated staff of the Princess Alexandra Hospital Physiotherapy Department and Intensive Care Unit for supporting this study. We also would like to thank Rod Hurford, Jim Cloherty and the Metro South Decision Support Team for their assistance to extract patient outcomes and physiological data from electronic medical records.

We would like to acknowledge the support for this work from the Metro South Research Support Scheme (Postgraduate Scholarship), Centre for Functioning and Health Research, Metro South Health, and the Institute of Health and Biomedical Innovation and School of Public Health & Social Work, Queensland University of Technology.

Authors' contributions
MRN, LJC, SMM, LMA, JW contributed to study conception, design, analysis plan, data management, appraisal and editing. AGB contributed to study analysis plan, appraisal and editing. All authors read and approved the final manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

Word Count: 3000 words (excluding structured abstract 248 words, keywords, acknowledgments, tables and 40 references)

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Abstract:

Objectives: This study aims to (i) describe the time to exercise commencement (sitting and upright activities) relative to ICU admission and relative to achievement of initial neurological, respiratory and cardiovascular stability; (ii) examine factors associated with whether sitting and upright activities occurred in ICU; and (iii) examine factors associated with time taken to commence these activities after stability has been achieved.

Design: Five-year historical cohort study.

Setting: An Australian tertiary mixed medical, surgical, trauma ICU.

Participants: The cohort (n=3222, mean(SD) age 54(18) years, 67% male) included consecutive ICU patients with length of stay over 48 hours admitted to a tertiary ICU who achieved stability.

Main outcome measures: Time from stability to patients first completed sitting and upright activities was calculated. Logistic regression (and Cox proportional hazard models) examined whether sitting and upright activities in ICU occurred (and time to these events).

Interventions: None.

Results: For patients who completed exercise interventions (n=1845/3222, 57%), this commenced a median (IQR) 2.3(1.3 to 4.4) days after stability for upright activities and 2.7(1.5 to 5.7) days for sitting. A large proportion of patients did not complete exercise interventions despite achieving stability (n=1377/3222, 43%). Elective surgical admissions, lower illness severity and older age were associated with completion (and earlier completion) of sitting and upright activity ($p<0.01$).

Conclusions: Many stable patients did not commence sitting or upright activity in ICU despite known benefits, or commencement was somewhat delayed. Opportunities may exist to improve patient outcomes through timely implementation of exercise-based interventions.

Keywords: Critical illness; Intensive care units; Rehabilitation; Physical therapy (specialty); Cohort studies; Early ambulation

Background:

Survival rates for patients who have been admitted to intensive care units (ICUs) are improving[1, 2]. However, the number of patients surviving with persistent physical, cognitive and mental health deficits is increasing[1, 3]. Additionally, survivors' health-related quality of life is adversely affected[1, 4] and 60% remain unemployed at 6 months after ICU admission due to poor health[5].

Acute muscle loss is likely to be associated with persistent poor functional outcomes and health-related quality of life. Muscle atrophy is rapid and pronounced in patients with multi-organ failure[6]. Active exercise leads to greater muscle strength at ICU discharge, greater probability of walking without assistance at hospital discharge and improved survival at 6 months post ICU admission[7]. Early exercise is safe and feasible with adverse events (typically minor) reported in less than three percent of interventions[8]

The proportion of critically ill patients admitted to an ICU for over 48 hours that participate in exercise interventions whilst in the ICU is often low, with point prevalence studies reporting 24–50% completing any form of exercise[9-12].

The duration that critically ill patients remain in bed prior to commencing exercise is inconsistent. Intervention studies have reported the median time to sitting out of bed (SOOB) to range between 1.7 and 8.5 days[13-16].There is also inconsistency in the literature regarding the proportion of patients who participate in active out of bed exercise in ICU settings, which has ranged from 40% to 73%[17, 18]. The duration of bed rest in the ICU has been the only risk factor reported to have consistently been associated with persistent muscle weakness[4]. Consequently, longer duration of bed rest in ICU settings may adversely affect survivors' ability to function, maintain employment and their health-related quality of life after their critical illness.

Previous studies examining exercise practices have been limited to point prevalence studies with limited study days examined, interventional studies that are likely to report a greater incidence of activity compared to usual practice, or observational studies with relatively small sample sizes. No studies have yet considered the time to commence activity in ICU relative to the time when a patient could safely commence activity. The present study sought to address these issues by examining a large historical cohort of consecutively admitted critically ill patients who required more than 48 hours length of stay within a tertiary ICU. The aims of this study were to:

(i) describe the time to exercise commencement (sitting and upright activities) relative to ICU admission;

(ii) describe the time to exercise commencement relative to achievement of initial neurological, respiratory and cardiovascular stability;

(iii) examine factors associated with whether sitting and upright activities occurred in ICU; and

(iv) examine factors associated with time taken to commence these activities after neurological, respiratory and cardiovascular stability had been achieved.

Methods

Study Setting

An historical observational cohort study was conducted at a 25-bed adult mixed medical, surgical, trauma ICU in an Australian metropolitan tertiary hospital. The ICU has approximately 2200 admissions per year including 1200 elective surgical, 300 emergency surgical and 700 medical patients. Adult patients from all specialities including liver transplant and spinal cord injury, but excluding maternity and burns are admitted. Cardiology patients are cared for in a separate Coronary Care Unit, unless there is a requirement for invasive ventilation.

Usual practice

There is typically a 1:1 nurse: patient ratio and equivalent to 3.5 physiotherapists for the ICU Monday to Friday and 2 physiotherapists on weekends, an additional physiotherapist is available on-call if respiratory interventions are required overnight. Physiotherapists lead the daily assessment of a patients' ability to participant in an exercise intervention. Other clinicians are consulted regarding concerns or planned procedures that may affect the treatment plan. A pre-specified mobilisation protocol has not been implemented at the study site. Unless contraindications exist, there is an expectation that elective surgery patients are mobilised within ICU prior to discharge to the ward.

Ventilated patients rarely complete upright activities, but occasionally perform sitting activities such as sitting on the edge of the bed or passive slide transfer to sit out of bed.

Ethics

Ethical approval for the study was obtained from the Metro South Human Research Ethics Committee (HREC/12/QPAH/009) and from the Queensland University of Technology University Human Research Ethics Committee (1400000587). These ethical approvals included approval of a waiver of individual consent as this study used routinely recorded information and there was no undue risk to patients' rights or welfare. Public Health Act approval (RD005370) was obtained for the release of Confidential Information for the purposes of research under the provision of Section 280 of the state Public Health Act 2005 for the jurisdiction where the research was conducted.

Clinical Data

Data pertaining to all patients admitted over a 5-year period for more than 48 hours to the study ICU was retrieved by the ICU Computer Information Systems (CIS) Administrator (RH) using Structured Query Language (SQL) queries from an intensive care electronic medical records database (Phillips Medical Systems, IntelliVue Clinical Information Portfolio; ICIP Release D.03.03, Eindhoven, The Netherlands). Regular manual checks of individual cases were conducted (by comparing query output with a manual review of clinical records) were conducted during the development of the SQL queries by the lead investigator (MN) and ICU CIS Administrator (RH) to ensure the accuracy of the queries. Patients' characteristics recorded included gender, age, admission classification (medical, elective surgical and emergency surgical), admission diagnosis, and APACHE III scores. Data pertaining to neurological and physiological parameters, ventilation times, ICU and hospital length of stay, discharge destination, and death in ICU or hospital were also recorded.

The time taken for patients to achieve neurological, respiratory and cardiovascular stability whilst in ICU was calculated. Patients were deemed to have achieved stability at the first time point since admission to ICU when their observations were recorded to be within the ranges specified in Table 1. These definitions were based on safety criteria for active mobilisation of critically ill adults[19] and were defined at study inception, prior to data extraction. These definitions are consistent with published expert consensus recommendations for the mobilisation of mechanically ventilated adults[20].

ICU electronic medical records were searched by lead investigator (MN) to calculate the time to initial sitting and upright activity using electronic keywords (Supplementary Table 1). Initial sitting was defined as the first time a patient was transferred to another surface or completed a sitting balance activity. These activities represent a score on the ICU Mobility Scale of 2 and 3, respectively[21]. Sitting activity did not include sitting up in bed with the bed repositioned into a chair position. The time of initial 'upright activity' was also calculated. Initial upright activity was defined as mobilisation activities including; standing with the assistance of a tilt table, standing, marching on the spot, stand transfer to a seated position or ambulation. These upright activities represent a score on the ICU Mobility Scale from 4 to 10[21].

Minimising potential sources of bias

Selection bias was minimised by analysing all ICU admissions that had a length of stay of over 48 hours over a 5-year period. To minimise information bias, the principal investigator (MN) individually scrutinised medical records to verify that the activity occurred rather than noting a planned intervention not yet completed. Co-investigator (LA) manually checked a series of 100 consecutive records for accuracy plus additional checks at random. These manual checks concurred with the findings of the recorded time to activity (or whether activity had not occurred). Because this study was dependent on routinely recorded clinical records, it is possible that inadvertent omissions or documentation errors occurred when clinicians recorded their clinical notes which was not able to be verified for this historical cohort. As the ICU and acute hospital discharge destination is known for all patients there was no losses to follow-up.

Statistical analysis

Descriptive statistics were used to describe patient and clinical characteristics. Logistic regression models were used to examine patient and clinical factors associated with whether patients i) completed sitting activity ii) completed upright activity in ICU. Cox proportional hazards models were used to examine factors associated with time to i) first completed sitting activity, and ii) first completed an upright activity after neurological, respiratory and cardiovascular stability was achieved. Potential explanatory factors included in these models were admission category (medical, elective surgical, emergency surgical), illness severity (APACHEIII), age, sex, duration of mechanical ventilation, and whether patients received haemodialysis. To adjust for potential clustering attributable to repeat ICU admissions by the same patient, standard error adjustments for cluster-correlated data were applied[22].

Results

There were 11445 patients admitted to ICU over a period of 60 months, of which 3434/11445 (30.0%) had an ICU length of stay longer than 48 hours. A total of 212/3434 (6%) patients (Supplementary Table 3) did not achieve stability. Patients who did not achieve stability were excluded from further analysis. The remaining 3222 ICU admissions (from 2983 unique patients) where stability was achieved were included in further analysis (Figure 1). Patients were predominantly male (67%), had a mean (SD) age of 54 (18) years, the majority were admitted for medical reasons (65%) and stayed in ICU a median (IQR) of 4.9 (3.0 to 9.5) days. During their ICU admission, 1377/3222 (43%) patients achieved stability but did not complete sitting or upright activities (Table 2). Most patients completed sitting activities (57%), but less than half completed upright activities (45%). Three patients completed activity prior to achieving stability and six patients completed activity but never achieved stability (Table 3).

Factors associated with participation in activity

Findings from the logistic regressions examining factors associated with whether or not i) sitting activity or ii) upright activity from when patients had achieved stability was completed are in Table 4. Older patients were more likely to complete sitting activity (OR per 10 years 1.10; 95% CI, 1.05 to 1.15) and upright activities (OR 1.10; 95% CI, 1.05 to 1.15). A higher severity of illness was significantly associated with not completing both sitting (OR per 10 APACHE III 0.92, 95% CI, 0.89 to 0.96) and upright activity (OR 0.92, 95% CI, 0.89 to 0.95). Elective surgical admissions to ICU were more likely to participate in sitting activities (OR 1.76, 95% CI, 1.40 to 2.21) and upright activities (OR 1.59, 95% CI, 1.29 to 1.97) in comparison to medical admissions. In contrast, emergency surgical admissions were less likely to participate with sitting activities (OR 0.64, 95% CI, 0.53 to 0.76) and upright activities (OR 0.68, 95% CI, 0.57 to 0.81). Longer mechanical ventilation time was positively associated with completing sitting activities (OR per day 1.04, 95% CI, 1.02 to 1.06) but not associated with upright activity. There was no association between patients' receiving dialysis and completing sitting activities or upright activities.

Factors associated with time to commence activity following achievement of stability

Findings from the time-to-event analyses are in Table 5. Older age was associated with shorter time to achieve initial sitting activity (HR per 10 years 1.05; 95% CI, 1.02 to 1.08) and upright activity (HR 1.05; 95% CI 1.01 to 1.08). A higher severity of illness delayed the time to commence sitting activities (HR per 10 APACHE III 0.95; 95% CI 0.93 to 0.97) and upright activities (HR 0.93; 95% CI 0.91 to 0.96). Following achievement of stability, patients admitted to ICU following an elective surgical procedure commenced initial sitting activities (HR 1.68; 95% CI 1.47 to 1.92) and upright activities (HR 1.62; 95% CI 1.41 to 1.87) earlier than patients with medical admissions. In contrast, patients admitted to ICU for an emergency surgical procedure were slower to commence initial sitting (HR 0.71, 95% CI 0.62 to 0.80) and upright activity tasks (HR 0.73, 95% CI 0.63 to 0.85). Longer mechanical ventilation duration was associated with a longer time until commencement of sitting activities (HR per day 0.92, 95% CI, 0.90 to 0.94) and upright activities (HR 0.88; 95% CI, 0.87 to 0.91). Receiving dialysis was also associated with a longer time from achievement of stability to commence sitting activities (HR 0.63, 95% CI, 0.53 to 0.74) and upright activities (HR 0.67, 95% CI 0.56-0.82).

Discussion:

Main findings

This study found that 43% of critically ill patients with an ICU length of stay of over 48 hours who achieve neurological, respiratory and cardiovascular stability, did not complete any sitting or upright activities for the duration of their ICU admission. For those patients who did participate in exercise interventions, commencement of activity may have been delayed as it did not occur until a median of more than two days after patients were considered to have achieved stability. This occurred despite published safety considerations[19] indicating that exercise interventions could have commenced considerably earlier than they did in many of these patients.

Comparison to prior research

In the current study, patients who had an ICU length of stay greater than 48 hours commenced activity approximately 3½ days after admission, with slightly more than half of patients completing sitting activities and slightly less than half of patients completing upright activities. This is consistent with the growing body of literature where reports of between 24% and 73% of patients completed exercise interventions within the ICU[9-12, 17, 18, 23-25] and have noted that less than 5% of mechanically ventilated patients completed upright activities [9-12, 26]. A recent prospective study reported that 73% of patients were mobilised during their ICU admission, this proportion may represent something of an upper limit of what is feasible with critically ill patients[17]. Early interventional studies in the United States report a range of times to commence sitting typically between 3 and 9 days[15, 16]. The interval between admission and time of activity reported in the present study is consistent with other reports including a binational observational cohort study where time to mobilisation was 2 days in Australia and 3½ days in Scotland[18], and a historical cohort study from Australia where the time to both sitting and upright activity was 3 days[25]. A 12-centre Australian and New Zealand study reported the time to commence sitting and standing activities was 7 days[27]. However, this study only enrolled patients who were expected to be mechanically ventilated for more than 48 hours from enrolment, potentially contributing to the delay to commence activities[27]. To date, no prior studies have considered the timing of activity commencement relative to the achievement of neurological, cardiovascular and cardiorespiratory stability which renders the current study something of an innovation, albeit caveats are warranted given that pre-specified physiological indicators of stability are not intended to reflect the full gamete of complex clinical reasoning that may precede mobility-related decision making in ICU settings. Given the large sample size this study has also assisted in defining usual care of ICU patients who are admitted for over 48 hours within an Australian setting. This is one step toward the establishment of benchmarks related to mobilisation activities among patient who are critically ill that may assist individual facilities to interpret their own practice[28].

The definition of ‘stability’ utilised in this study is consistent with an expert consensus on the mobilisation of mechanically ventilated patient publication that was published during the study period[20]. The adverse event rate of exercise interventions with critically ill patients is less than 3%

with most adverse events being minor and transient[8]. To date no consensus has been achieved to describe the doses of vasoactive medications that patients could simultaneously receive whilst safely participating in exercise interventions[20]. A recent single centre study reported that cardiothoracic patients were safely able to commence exercise rehabilitation interventions whilst receiving vasoactive medications, with a less than 2% minor adverse event rate[29]. Consequently, the 'stability' definitions utilised could be interpreted as conservative. As bed rest is the only risk factor associated with prolonged weakness[4], determining which patients receiving vasoactive medications can safely exercise remains a priority for future research.

Several studies that have incorporated exercise protocols have demonstrated reductions in time to commence exercise interventions and decreased ventilation and ICU length of stay with critically ill patients[13, 14, 24, 30, 31]. A protocolised approach to early exercise has been recommended by The American Thoracic Society guidelines for the liberation of mechanical ventilation[32]. Patients did not follow an exercise protocol at the study site, however there was a local expectation at the participating facility that elective surgical short stay patients ambulate prior to ICU discharge. These short-stay patients were excluded from the present study to enable the analysis to focus on patients who are at a higher risk of deconditioning. Consequently, the excluded patients were predominately elective surgical patients (66%) (Figure 1). This study has extended the field by highlighting the extent to which higher severity of illness, receiving dialysis, mechanical ventilation time and admission type (e.g., emergency surgical admission) to ICU may contribute to delay until patients complete rehabilitation activities. Effective strategies for reducing the duration of bed rest are likely to represent opportunities to improve patient outcomes. The implementation of an exercise protocol may reduce delays to commence exercise interventions. However, despite recommendations to follow a protocolised approach to implement early activity[32], there is no consensus on exercise dose prescription in terms of frequency, volume and intensity with critically ill patients[33-35] therefore this remains a priority for further research.

Receiving dialysis had a substantial negative association with time to commence exercise interventions. Whilst prior studies have noted that it is safe and feasible for patients receiving dialysis to complete exercise[36, 37], clinicians in real-world clinical practice maybe somewhat reluctant, or find it pragmatically challenging, to commence sitting out of bed or upright activities with their patients who are receiving dialysis in comparison to patients who do not require dialysis. Investigation of pragmatic strategies to facilitate mobility activities among patients receiving dialysis are also a priority for further research.

The present study made use of electronic clinical records. Electronic medical records are being incorporated into standard clinical care internationally and providing new opportunities advancing the quality, safety and effectiveness of clinical care[38]. Additionally, de-identified critical care databases such as the Medical Information Mart for Intensive Care III (MIMIC-III) and Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) are enabling researchers to access clinical data from large cohorts of patients[38] and evaluate the performance of ICUs relative to each other[39]. The ongoing advancement in digitisation of hospital systems is likely to enable others to analyse and report their mobilisation practices, which could enable comparisons between similar ICUs and promote quality improvement activities within critical care settings.

Strengths and limitations

Strengths of this investigation include that it was the largest sample to date in which exercise practices and factors associated with the commencement of exercise interventions were examined. Furthermore, this was the first investigation to have considered the duration of bed rest of critically ill patients' following the achievement of neurological, respiratory and cardiovascular stability. Limitations of this investigation are that it was limited to routinely collected data in a single centre mixed medical, surgical, trauma ICU and times analysed were based on routinely collected observations. It is important to note, that the physiological parameters used in this study were likely to be a conservative indicator of patients' having reached a point of physiological stability. However, it is unlikely that any set of physiological parameters could entirely reflect or substitute for contextualised clinical decision making. Nonetheless, these indicators were useful for highlighting that many patients were likely to have been physiologically stable for some time before they were mobilised. It is worth noting that following the achievement of initial stability patients' may not remain stable or may have achieved 'stability' at times when staffing was not sufficient to enable an exercise intervention to be completed and this may have influenced their time until exercise commencement. Most patients who did not complete exercise interventions survived acute-hospitalisation (76%). This indicates that patients were likely to achieve ‘stability’ and continued to recover. Consequently, it is likely that patients were well enough to participate in some form of exercise whilst in ICU. Results may not be generalisable to dissimilar ICUs or to short-stay post-elective surgery ICU admissions which were intentionally excluded from this investigation. However, this study demonstrated agreement with previous international publications in terms of the proportion of patients who completed exercise interventions whilst in ICU and the duration from ICU admission to commence exercise interventions. It should be noted that the present study did not set-out to define cause and effect relationships related to the timing of activity commencement in ICU. Furthermore, barriers to the implementation of exercise interventions are diverse and include patient, clinician and health care system factors[40]. However, the barriers to early activity commencement were not routinely reported and therefore could not be analysed for this cohort.

Future research

This study has identified that patients either do not complete exercise interventions whilst admitted to the ICU, or the interventions are delayed following achievement of stability. Future prospective work is required to confirm or refute these findings and to examine if barriers exist that could be addressed to optimise the timing of the implementation of exercise interventions with critically ill patients. In addition to research regarding intervention timing, effectiveness and implementation, clinical practice may be further informed by research examining potential physiological mechanisms and biomarkers that may help guide personalised exercise prescription among critically ill patients.

Conclusion:

Critically ill patients who spent more than 48 hours in ICU often did not complete exercise interventions whilst in ICU, and the commencement of exercise was somewhat delayed despite most patients achieving neurological, respiratory and cardiovascular stability relatively early in their ICU admission. A range of patient and clinical factors associated with time-to-commencement of sitting and upright activity were identified that may help inform the development of clinical practice protocols to help reduce unnecessary delays in these activities among critically ill patients.

Ethical Approval: Ethical approval for the study was obtained from the Metro South Human Research Ethics Committee (HREC/12/QPAH/009) and from the Queensland University of Technology University Human Research Ethics Committee (1400000587).

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: None to declare

Acknowledgements: The investigators would like to acknowledge Mr. Rod Hurford (Computer Information Systems Administrator, Intensive Care Unit, Princess Alexandra Hospital) for his expertise and assistance writing SQL queries to enable data to be analysed.

References:

[1] Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364:1293-304.
[2] Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311:1308-16.
[3] Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190:410-20.
[4] Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42:849-59.
[5] Hodgson CL, Udy AA, Bailey M, Barrett J, Bellomo R, Bucknall T, et al. The impact of disability in survivors of critical illness. Intensive Care Med. 2017;43:992-1001.
[6] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310:1591-600.
[7] Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. Intensive Care Med. 2017;43:171-83.
[8] Nydahl P, Sricharoenchai T, Chandra S, Kundt F, Huang MX, Fischill M, et al. Safety of Patient Mobilization and Rehabilitation in the Intensive Care Unit Systematic Review with Meta-Analysis. Annals Of The American Thoracic Society. 2017;14:766-77.
[9] Berney SC, Harrold M, Webb SA, Seppelt I, Patman S, Thomas PJ, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. Crit Care Resusc. 2013;15:260-5.
[10] Jolley SE, Moss M, Needham DM, Caldwell E, Morris PE, Miller RR, et al. Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States. Crit Care Med. 2017;45:205-15.
[11] Nydahl P, Ruhl AP, Bartoszek G, Dubb R, Filipovic S, Flohr HJ, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. Crit Care Med. 2014;42:1178-86.
[12] Sibilla A, Nydahl P, Greco N, Mungo G, Ott N, Unger I, et al. Mobilization of Mechanically Ventilated Patients in Switzerland. J Intensive Care Med. 2017:885066617728486.
[13] Hodgson CL, Bailey M, Bellomo R, Berney S, Buhr H, Denehy L, et al. A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU. Crit Care Med. 2016;44:1145-52.
[14] McWilliams D, Jones C, Atkins G, Hodson J, Whitehouse T, Veenith T, et al. Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. J Crit Care. 2018;44:407-12.
[15] Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36:2238-43.
[16] Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373:1874-82.

[17] Brock C, Marzano V, Green M, Wang J, Neeman T, Mitchell I, et al. Defining new barriers to mobilisation in a highly active intensive care unit - have we found the ceiling? An observational study. Heart Lung. 2018;47:380-5.
[18] Harrold ME, Salisbury LG, Webb SA, Allison GT. Early mobilisation in intensive care units in Australia and Scotland: a prospective, observational cohort study examining mobilisation practises and barriers. Critical Care. 2015;19:336.
[19] Stiller K. Safety issues that should be considered when mobilizing critically ill patients. Crit Care Clin. 2007;23:35-53.
[20] Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. Crit Care. 2014;18:658.
[21] Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart Lung. 2014;43:19-24.
[22] Williams RL. A note on robust variance estimation for cluster-correlated data. Biometrics. 2000;56:645-6.
[23] Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care. 2013;17:R156.
[24] Engel HJ, Tatebe S, Alonzo PB, Mustille RL, Rivera MJ. Physical therapist-established intensive care unit early mobilization program: quality improvement project for critical care at the University of California San Francisco Medical Center. Phys Ther. 2013;93:975-85.
[25] Skinner EH, Haines KJ, Berney S, Warrillow S, Harrold M, Denehy L. Usual Care Physiotherapy During Acute Hospitalization in Subjects Admitted to the ICU: An Observational Cohort Study. Respir Care. 2015;60:1476-85.
[26] Berney SC, Rose JW, Bernhardt J, Denehy L. Prospective observation of physical activity in critically ill patients who were intubated for more than 48 hours. J Crit Care. 2015;30:658-63.
[27] Hodgson C, Bellomo R, Berney S, Bailey M, Buhr H, Denehy L, et al. Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care. 2015;19:81.
[28] Parker A, Tehranchi KM, Needham DM. Critical care rehabilitation trials: the importance of ‘usual care’. Critical Care. 2013;17:183.
[29] Boyd J, Paratz J, Tronstad O, Caruana L, McCormack P, Walsh J. When is it safe to exercise mechanically ventilated patients in the intensive care unit? An evaluation of consensus recommendations in a cardiothoracic setting. Heart Lung. 2018;47:81-6.
[30] Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, et al. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA. 2016;315:2694-702.
[31] McWilliams D, Weblin J, Atkins G, Bion J, Williams J, Elliott C, et al. Enhancing rehabilitation of mechanically ventilated patients in the intensive care unit: a quality improvement project. J Crit Care. 2015;30:13-8.
[32] Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, et al. An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from mechanical ventilation in critically ill adults rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med. 2017;195:120-33.
[33] Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. Cochrane Database Syst Rev. 2018;3:CD010754.

[34] Morris PE, Montgomery-Yates A. Mastering the design for rehabilitation strategies in ICU survivors. Thorax. 2017;72:594-5.
[35] Skinner EH, Berney S, Warrillow S, Denehy L. Rehabilitation and exercise prescription in Australian intensive care units. Physiotherapy. 2008;94:220-9.
[36] Toonstra AL, Zanni JM, Sperati CJ, Nelliot A, Mantheiy E, Skinner EH, et al. Feasibility and Safety of Physical Therapy during Continuous Renal Replacement Therapy in the Intensive Care Unit. Annals of the American Thoracic Society. 2016;13:699-704.
[37] Wang YT, Haines TP, Ritchie P, Walker C, Ansell TA, Ryan DT, et al. Early mobilization on continuous renal replacement therapy is safe and may improve filter life. Crit Care. 2014;18:R161-R.
[38] Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data. 2016;3:160035.
[39] McClean K, Mullany D, Huckson S, van Lint A, Chavan S, Hicks P, et al. Identification and assessment of potentially high-mortality intensive care units using the ANZICS Centre for Outcome and Resource Evaluation clinical registry. Crit Care Resusc. 2017;19:230-8.
[40] Parry SM, Remedios L, Denehy L, Knight LD, Beach L, Rollinson TC, et al. What factors affect implementation of early rehabilitation into intensive care unit practice? A qualitative study with clinicians. J Crit Care. 2017;38:137-43.

Table 1: Definition of patient physiological stability used for the present study examining early exercise interventions in intensive care

Physiological variable	Variable range
Neurological stability	
Glasgow Coma Scale	M6 (able to follow commands)
	E4 (eyes open)
Richmond Agitation-Sedation Score	–1 to +1
Respiratory stability	
Fraction of inspired oxygen	0.6 or less
Positive end expiratory pressure	10 cmH2O or less
Respiratory rate	30 breaths per minute or less
Pulse oximetry oxygen saturations	90% or greater
Cardiovascular stability	
Heart rate	60–120 beats per minute
Mean arterial blood pressure	65–110 mmHg
Vasoactive medication infusions*	Absence of vasoactive medications

*noradrenaline, dopamine, adrenaline, vasopressin, milrinone, glyceryl trinitrate, sodium nitroprusside.

Table 2. Patient characteristics and outcomes for patient admissions where stability was achieved

Variable	Cohort, n= 3222[a] (100%)	Participated in exercise interventions[b], n= 1845 (57%)	Did not participate in exercise interventions, n= 1377 (43%)
Age in years, mean (SD)	53.5 (17.6)	54.4 (17.1)	52.3 (18.2)
Males, n (%)	2169 (67%)	1247 (68%)	922 (67%)
Received dialysis, n (%)	293 (9%)	159 (9%)	134 (10%)
Admission type, n (%)			
Medical (non-surgical)	2096 (65%)	1193 (65%)	903 (66%)
Trauma	455 (14%)	211 (11%)	244 (18%)
Cardiac	421 (13%)	223 (12%)	198 (14%)
Sepsis	343 (11%)	219 (12%)	124 (9%)
Neurological	302 (9%)	150 (8%)	152 (11%)
Respiratory	296 (9%)	206 (11%)	90 (7%)
Abdominal	139 (4%)	82 (4%)	57 (4%)
Other	140 (4%)	102 (6%)	38 (3%)
Emergency surgical	652 (20%)	311 (17%)	341 (25%)
Trauma surgery	254 (8%)	86 (5%)	168 (12%)
Cardiac and vascular surgery	125 (4%)	83 (4%)	42 (3%)
Abdominal surgery	120 (4%)	74 (4%)	46 (3%)
Neurological surgery	80 (2%)	28 (2%)	52 (4%)
Other emergency surgery	73 (2%)	40 (2%)	33 (2%)
Elective surgical	474 (15%)	341 (19%)	133 (10%)
Cardiac and vascular surgery	281 (9%)	219 (12%)	62 (5%)
Cancer related surgery	50 (2%)	34 (2%)	16 (1%)
Liver transplant	49 (2%)	39 (2%)	10 (1%)
Neurological surgery	45 (1%)	19 (1%)	26 (2%)
Other elective surgery	49 (2%)	30 (2%)	19 (1%)
APACHE III score, median (IQR)	57 (42, 75)	56 (42, 73)	59 (42, 77)
Required MV, n (%)	2969 (92%)	1711 (93%)	1258 (91%)
Length of MV, days, median (IQR)[c]	1.5 (0.5, 3.6)	1.6 (0.6, 3.8)	1.5 (0.5, 3.3)

ICU length of stay[d], days, median (IQR)	4.9 (3.0, 9.5)	4.9 (3.0, 9.9)	4.8 (3.0, 9.1)
Hospital stay[e], days, median (IQR)	19.9 (11.3, 34.6)	17.4 (10.5, 31.2)	24.4 (13.7, 39.6)
ICU discharge destination, n (%)			
Acute hospital ward	2979 (93%)	1809 (98%)	1170 (85%)
Died in ICU	200 (6%)	10 (1%)	190 (14%)
Transferred to other acute hospital	24 (1%)	12 (1%)	12 (1%)
Home	16 (1%)	11 (1%)	5 (<1%)
Transferred to rehabilitation facility	3 (<1%)	3 (<1%)	0 (0%)
Acute hospital discharge destination, n (%)			
Home	1888 (59%)	1274 (69%)	614 (45%)
Died in Hospital	421 (13%)	92 (5%)	329 (24%)
Transferred to a rehabilitation facility	630 (20%)	313 (17%)	317 (23%)
Other acute hospital	282 (9%)	166 (9%)	116 (8%)
Palliative care hospital	1 (<1%)	0 (0%)	1 (<1%)

[a] 2983 unique individuals representing 3222 ICU admissions during study period
[b] Participated in exercise: completed either sitting activity or upright activity (or both) in ICU
[c] Calculated for those who were invasively mechanically ventilated
[d] Length of stay for patients who survived ICU admission
[e] Length of stay for patients who survived acute hospital admission
SD, standard deviation, n, number; APACHE III = Acute Physiology and Chronic Health Evaluation III severity of illness score (0-299); IQR, interquartile range; MV, mechanical ventilation; ICU, intensive care unit.

Table 3: Description of whether sitting and upright activity occurred in patients who achieved physiological stability, and time to these activities (n = 3222)

Outcome	Sitting activity	Upright activity
Completed activity after achieving stability, n (% of admissions[a])	1842 (57.2%)	1454 (45.1%)
Time from stability to first complete activity, days, median (IQR)	2.7 (1.5, 5.7)	2.3 (1.3, 4.4)
Time from ICU admit to first complete activity, days, median (IQR)	3.6 (2.0, 7.7)	3.3 (2.0, 6.7)
Achieved stability but not activity, n (% of admissions[a])	1377 (42.7%)	1768 (54.9%)
Completed activity prior to achieving stability, n (% of admissions[a])	3 (0.1%)	1 (<0.1%)
Completed activity but never achieved stability, n (% of admissions[b])	6 (0.2%)	6 (0.2%)

[a] cohort of patients who achieved physiological stability
[b] all admissions
ICU, intensive care unit, IQR, interquartile range; n, number.

Table 4: Findings from the logistic regression examining patient and clinical factors associated with whether i) sitting activity, and ii) 'upright activity' occurred in ICU for patients who achieved stability n=3222

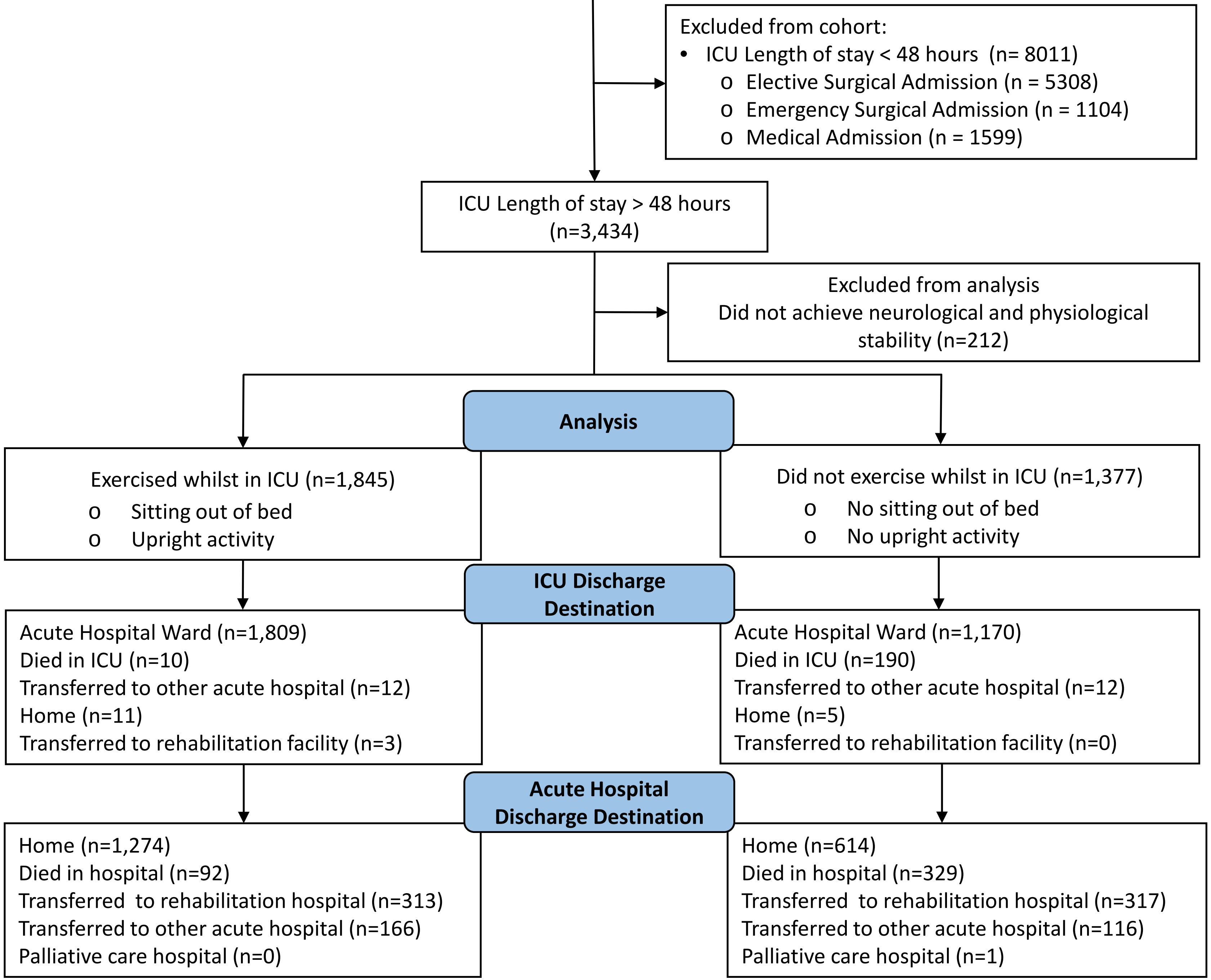
Activity achieved	Independent variables	Odds ratio	95% CI	p-value
i) Achieved sitting activity in ICU	Age (per 10 years)	1.10	(1.05-1.15)	<0.001
	Male	1.00	(0.86-1.16)	0.99
	APACHE III (per 10)	0.92	(0.89-0.96)	<0.001
	Admission type			
	Medical admission	Referent		
	Elective surgical admission	1.76	(1.40-2.21)	<0.001
	Emergency surgical admission	0.64	(0.53-0.76)	<0.001
	MV time (days)	1.04	(1.02-1.06)	<0.001
	Received dialysis	0.96	(0.74-1.25)	0.76
i) Achieved upright activity in ICU	Age (per 10 years)	1.10	(1.05-1.15)	<0.001
	Male	1.03	(0.89-1.20)	0.69
	APACHE III (per 10)	0.92	(0.89-0.95)	<0.001
	Admission type			
	Medical admission	Referent		
	Elective surgical admission	1.59	(1.29-1.97)	<0.001
	Emergency surgical admission	0.68	(0.57-0.81)	<0.001
	MV time (days)	0.99	(0.97-1.01)	0.29
	Received dialysis	1.00	(0.77-1.31)	0.97

CI, confidence interval; p, probability; APACHE III = Acute Physiology and Chronic Health Evaluation III severity of illness score; MV, mechanical ventilation; ICU, intensive care unit.

Table 5: Hazard Ratios from a Cox regression examining the factors associated with time to commencement of sitting activity and upright activity in ICU since stability

Time to activity	Independent variables	Hazard ratio[a]	95% CI	p-value
i) Time to sitting activity[b] in ICU since stability	Age (per 10 years)	1.05	(1.02-1.08)	<0.01
	Male	0.97	(0.88-1.07)	0.54
	APACHE III (per 10)	0.95	(0.93-0.97)	<0.001
	Admission type			
	Medical admission	Referent		
	Elective surgical admission	1.68	(1.47-1.92)	<0.001
	Emergency surgical admission	0.71	(0.62-0.80)	<0.001
	MV time (days)	0.92	(0.90-0.94)	<0.001
	Received dialysis	0.63	(0.53-0.74)	<0.001
ii) Time to upright activity[c] in ICU since stability	Age (per 10 years)	1.05	(1.01-1.08)	<0.01
	Male	1.00	(0.89-1.11)	0.95
	APACHE III (per 10)	0.93	(0.91-0.96)	<0.001
	Admission type			
	Medical admission	Referent		
	Elective surgical admission	1.62	(1.41-1.87)	<0.001
	Emergency surgical admission	0.73	(0.63-0.85)	<0.001
	MV time (days)	0.88	(0.87-0.91)	<0.001
	Received dialysis	0.67	(0.56-0.82)	<0.001

CI, confidence interval; p, probability; APACHE III = Acute Physiology and Chronic Health Evaluation III severity of illness; MV, mechanical ventilation; ICU, intensive care unit.,
[a]Hazard ratio greater than 1.0 indicates a shorter time to event.
[b]n=3219 (3434 observations, 212 patients did not achieve stability and 3 individuals completed activity without achieving stability excluded from analysis)
[c]n=3221 (3434 observations, 212 patients did not achieve stability and 1 individual completed activity without achieving stability excluded from analysis)


Excluded from cohort:
• ICU Length of stay < 48 hours (n= 8011)
o Elective Surgical Admission (n = 5308)
o Emergency Surgical Admission (n = 1104)
o Medical Admission (n = 1599)
ICU Length of stay > 48 hours (n=3,434)
Excluded from analysis
Did not achieve neurological and physiological stability (n=212)
Analysis
Exercised whilst in ICU (n=1,845)
o Sitting out of bed
o Upright activity
Did not exercise whilst in ICU (n=1,377)
o No sitting out of bed
o No upright activity
ICU Discharge Destination
Acute Hospital Ward (n=1,809)
Died in ICU (n=10)
Transferred to other acute hospital (n=12)
Home (n=11)
Transferred to rehabilitation facility (n=3)
Acute Hospital Ward (n=1,170)
Died in ICU (n=190)
Transferred to other acute hospital (n=12)
Home (n=5)
Transferred to rehabilitation facility (n=0)
Acute Hospital Discharge Destination
Home (n=1,274)
Died in hospital (n=92)
Transferred to rehabilitation hospital (n=313)
Transferred to other acute hospital (n=166)
Palliative care hospital (n=0)
Home (n=614)
Died in hospital (n=329)
Transferred to rehabilitation hospital (n=317)
Transferred to other acute hospital (n=116)
Palliative care hospital (n=1)

Supplementary Table 1: Keywords used to search electronic medical records for exercise interventions

Inclusion	Keywords
Sitting Activity	edge, lie to sit, oxford chair, patslide, sit* (sit out of bed, sitting balance, sitting out, sitting over), SOEOB, SOOB.
Upright Activity	FASF, mob* (mobile, mobilise, mobility), MOS, on spot, rollator, stand, spot, step, stood, “sit to stand”, STS, tilt, table, walk.
Excluding	plan, P:, P/, chair position, nil, not, unable, sit up

SOEOB; sit on edge of bed, SOOB; sitting out of bed, FASF; forearm support frame, MOS; march on spot, STS; sit to stand P: plan, P/; plan.

Supplementary Table 2: Description of outcomes for patients relative to achieving physiological stability (n = 3434)

Outcome	Cohort (n = 3434)
Achieved physiological stability, n (% of admissions)	3222 (93.8%)
Did not achieve physiological stability, n (% of admissions)	212 (6.2%)
Time from ICU admission to achieve stability, median (IQR)	0.6 (0.2,1.5)
Acute Hospital Mortality of patients who achieved stability, n (% of admissions[a])	395 (12.3%)
Acute Hospital Mortality of patients who did not achieve stability, n (% of admissions[b])	186 (87.7%)

[a] cohort of patients who achieved physiological stability
[b] cohort of patients who did not achieve physiological stability
ICU, intensive care unit; IQR, interquartile range; n, number.

Supplementary Table 3. Patient characteristics and outcomes for patient admissions where stability was not achieved

Variable	Cohort, n= 212[a] (100%)
Age in years, mean (SD)	54.2 (17.5)
Males, n (%)	139 (65.6%)
Received dialysis, n (%)	25 (11.8%)
Admission type, n (%)	
Medical	140 (66.0%)
Elective surgical	40 (18.9%)
Emergency surgical	32 (15.1%)
APACHE III score, median (IQR)	56 (42, 73)
Required MV, n (%)	173, (81.6%)
Length of MV, days, median (IQR)[b]	1.0 (0.2, 2.7)
ICU length of stay, days, median (IQR)	3.9 (2.8, 6.9)
Hospital stay, days, median (IQR)	5.0 (3.2, 8.7)
ICU discharge destination, n (%)	
Acute hospital ward	54 (25.5%)
Died in ICU	157 (74.1%)
Transferred to other acute hospital	1 (0.5%)
Home	0 (0%)
Transferred to rehabilitation facility	0 (0%)
Acute hospital discharge destination, n (%)	
Home	12 (5.7%)
Died in Hospital	186 (87.7%)
Transferred to a rehabilitation facility	4 (1.9%)
Other acute hospital	10 (4.7%)

[a] 208 unique individuals representing 212 ICU admissions during study period
[b] Calculated for those who were invasively mechanically ventilated
SD, standard deviation, n, number; APACHE III = Acute Physiology and Chronic Health Evaluation III severity of illness score (0-299); IQR, interquartile range; MV, mechanical ventilation; ICU, intensive care unit.