ORIGINAL ARTICLE

Early Active Mobilization during Mechanical Ventilation in the ICU

The TEAM Study Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND

Intensive care unit (ICU)–acquired weakness often develops in patients who are undergoing invasive mechanical ventilation. Early active mobilization may mitigate ICU-acquired weakness, increase survival, and reduce disability.

METHODS

We randomly assigned 750 adult patients in the ICU who were undergoing invasive mechanical ventilation to receive increased early mobilization (sedation minimization and daily physiotherapy) or usual care (the level of mobilization that was normally provided in each ICU). The primary outcome was the number of days that the patients were alive and out of the hospital at 180 days after randomization.

RESULTS

The median number of days that patients were alive and out of the hospital was 143 (interquartile range, 21 to 161) in the early-mobilization group and 145 days (interquartile range, 51 to 164) in the usual-care group (absolute difference, –2.0 days; 95% confidence interval [CI], –10 to 6; P=0.62). The mean (±SD) daily duration of active mobilization was 20.8±14.6 minutes and 8.8±9.0 minutes in the two groups, respectively (difference, 12.0 minutes per day; 95% CI, 10.4 to 13.6). A total of 77% of the patients in both groups were able to stand by a median interval of 3 days and 5 days, respectively (difference, –2 days; 95% CI, –3.4 to –0.6). By day 180, death had occurred in 22.5% of the patients in the early-mobilization group and in 19.5% of those in the usual-care group (odds ratio, 1.15; 95% CI, 0.81 to 1.65). Among survivors, quality of life, activities of daily living, disability, cognitive function, and psychological function were similar in the two groups. Serious adverse events were reported in 7 patients in the early-mobilization group and in 1 patient in the usual-care group. Adverse events that were potentially due to mobilization (arrhythmias, altered blood pressure, and desaturation) were reported in 34 of 371 patients (9.2%) in the early-mobilization group and in 15 of 370 patients (4.1%) in the usual-care group (P=0.005).

CONCLUSIONS

Among adults undergoing mechanical ventilation in the ICU, an increase in early active mobilization did not result in a significantly greater number of days that patients were alive and out of the hospital than did the usual level of mobilization in the ICU. The intervention was associated with increased adverse events. (Funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand; TEAM ClinicalTrials.gov number, NCT03133377.)

The members of the writing committee (Carol L. Hodgson, Ph.D., Michael Bailey, Ph.D., Rinaldo Bellomo, Ph.D., Kathy Brickell, R.G.N., Tessa Broadley, B.Biomed.Sci., Heidi Buhr, M.Sc.Med., Belinda J. Gabbe, Ph.D., Doug W. Gould, Ph.D., Meg Harrold, Ph.D., Alisa M. Higgins, Ph.D., Sally Hurford, P.G.Dip., Theodore J. Iwashyna, Ph.D., Ary Serpa Neto, Ph.D., Alistair D. Nichol, Ph.D., Jeffrey J. Presneill, Ph.D., Stefan J. Schaller, M.D., Janani Sivasuthan, M.P.H., Claire J. Tipping, Ph.D., Steven Webb, Ph.D., and Paul J. Young, M.B., Ch.B., Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Dr. Hodgson can be contacted at carol.hodgson@monash.edu or at the Australian and New Zealand Intensive Care Research Centre, 553 St. Kilda Rd., Melbourne, VIC 3004, Australia.

*A complete list of the TEAM trial investigators and the ANZICS Clinical Trials Group is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 13 million to 20 million people worldwide receive treatment in intensive care units (ICUs) annually.[1] ICU-acquired weakness, which is defined as clinically detected weakness with no plausible explanation except for critical illness,[2] occurs in approximately 40% of such patients[3] and is associated with an increased risk of death, prolonged hospitalization, and impaired recovery.[4-8]

Among patients in the ICU who have undergone mechanical ventilation for more than 48 hours, wasting of skeletal muscles occurs rapidly.[9] Although immobilization may contribute to ICU-acquired weakness, such weakness appears to be part of the pathophysiology of critical illness and is not just due to disuse.[9] It is associated with disruption of myofilament organization,[10] damage to the sarcoplasmic reticulum, decreased electrical excitability, and mitochondrial dysfunction.[11] Although some data suggest that early mobilization of patients in the ICU may reduce the length of hospital stay[12] and improve function at the time of hospital discharge,[13,14] many barriers to early mobilization exist.[15-17] Moreover, early mobilization may not be sufficient to prevent ICU-acquired weakness affecting patient-important outcomes and may be associated with risks.[12,18] The Pain, Agitation–Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) guidelines recommended mobilization of critically ill adults but do not offer advice on the appropriate timing or regimen.[19]

Accordingly, we conducted a clinical trial, called Treatment of Mechanically Ventilated Adults with Early Activity and Mobilization (TEAM), to test the hypothesis that early active mobilization would increase the number of days that patients were alive and out of the hospital at day 180 as compared with the usual level of mobilization in the ICU in adults who were undergoing mechanical ventilation.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this international, multicenter, randomized, controlled trial, we evaluated the effects of early mobilization (sedation minimization and daily physiotherapy) or usual care (mobilization level that was normally provided in each ICU) among adults in the ICU who were undergoing mechanical ventilation that was expected to continue beyond the calendar day after randomization. In the early-mobilization group, senior physiotherapists led the intervention and participated in interdisciplinary discussions and reviews of a safety checklist. The trial was funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand. The management committee designed the trial, which was endorsed by the Australian and New Zealand Intensive Care Society and the Irish Critical Care Trials Group. The institutions that managed the trial and monitored data quality are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org). An independent data and safety monitoring committee oversaw the trial and reviewed a planned interim analysis after 400 patients had reached 28 days of follow-up. No commercial support was provided.

The protocol (available at NEJM.org), which was reported before the completion of enrollment, was approved by the ethics committee at each participating institution.[20] Written informed consent for enrollment, or consent to continue and to use data, was obtained from each patient or from a legal surrogate. In cases in which a patient died before consent could be obtained, data were included if such inclusion was allowed by local regulations and approved by an ethics committee. The authors all contributed to the writing of the article and the decision to submit the manuscript for publication. They also vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were adults (≥18 years of age) who were expected to undergo mechanical ventilation in the ICU beyond the calendar day after randomization and whose condition was sufficiently stable to make mobilization potentially possible. Key exclusion criteria were dependency in any activity of daily living in the month before hospitalization, rest-in-bed orders, and proven or suspected acute primary brain or spinal injury. A full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix. We defined subgroups using baseline characteristics including prehospitalization disability level, age, illness severity, diagnosis, and frailty, as described in the Supplementary Appendix.

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RANDOMIZATION AND TREATMENT

We randomly assigned patients in a 1:1 ratio to receive early mobilization or usual care using a centralized Web-based interface. The trial statistician generated the assignment sequence using computer-generated random numbers stratified according to the trial center with variable block sizes.

We followed the guidelines of the Medical Research Council for evaluating complex interventions[21] and the Template for Intervention Description and Replication.[22] Our intervention, which included minimization of sedation as required, was hierarchical and began after randomization with daily physiotherapy, which could be provided in one or more sessions. The sessions were individually tailored to achieve the highest possible level of mobilization that was deemed to be safe for the patient at the initiation of daily therapy. The highest level of mobilization was provided for as long as possible before a step-down to lower levels of activity if the patient became fatigued,[23] as measured on the ICU Mobility Scale.[24] This validated scale rates the level of mobilization from 0 to 10, with 0 indicating no mobilization and 10 indicating independent walking.[25] Patients who were assigned to the usual-care group received a level of mobilization that was normally provided at each site. In both groups, concomitant care was guided by treating clinicians. Details regarding the treatments and monitoring are provided in the Supplementary Appendix.

Patients received the trial treatment while they were in the ICU for up to 28 days after randomization. Blinding of mobilization in the ICU was not possible; however, trained staff who were unaware of trial-group assignments ascertained patient-reported outcomes, and the statistical analysis was performed in a blinded manner.

OUTCOMES

The primary outcome was the number of days that patients were alive and out of the hospital at day 180. The time that patients were out of the hospital was defined as the number days that they were at home or in an accommodation that was not a health care facility (i.e., a rehabilitation hospital or nursing home). Patients who had died by day 180 were defined as having zero days alive and out of the hospital.

Key secondary outcomes were mortality at 180 days, the number of ventilator-free days and days out of the ICU from randomization to day 28, and patient-reported outcome measures, including quality of life and function in survivors at day 180. We defined ventilator-free days as the number of days of unassisted breathing during the first 28 days after randomization; deaths by day 28 were assigned zero ventilator-free days. ICU-free days were defined analogously.

We assessed health-related quality of life using the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L), which evaluates mobility, personal care, usual activities, pain or discomfort, and anxiety or depression and categorizes each of these into five levels that range from no problems to extreme problems,[26] and the EQ utility score, which ranges from −0.6 to 1.0, with 1.0 indicating the best health state.[27] The EQ Visual Analogue Scale provided a global rating of patient-perceived health from 0 to 100, with higher scores indicating better health.[28] Independent activities of daily living were measured with the Barthel Activities of Daily Living (ADL) Index, which scores 10 activities of daily living that include feeding, bathing, and dressing from 0 (dependent) to 100 (independent),[29] and the Lawton Instrumental Activities of Daily Living Scale (IADL), which scores 8 independent living skills that include shopping, laundry, and housekeeping from 0 (dependent) to 8 (independent).[30,31] The 12-item World Health Organization Disability Assessment Schedule (WHODAS 2.0) measured generic function for mobility, self-care, life activities, and participation.[32] It incorporated scores from 0 (no difficulty) to 4 (extreme difficulty) for each item on a scale of 0 to 48, with higher scores representing greater disability; this score is expressed as a percentage of maximum disability.[32,33] Details regarding additional outcomes, including cognitive and psychological function, are provided in the Supplementary Appendix.

Prespecified serious adverse events were falls to the floor, cardiac arrest, atrial fibrillation with a ventricular response of more than 150 bpm, other dangerous arrhythmias, oxygen-saturation level on pulse oximetry of less than 80% for more than 3 minutes, and unplanned extubation or removal of the intravascular line resulting in urgent replacement. Site investigators reported other ad-

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verse events that were potentially caused by active mobilization, as described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The statistical analysis plan was reported before the completion of enrollment.[20] The sample size was based on the standard deviation of the primary outcome in the pilot study.[14,34] We determined that the enrollment of 750 patients would provide 90% power to detect a 7-day between-group difference with a two-sided alpha of 0.05 after allowing for 15% inflation to account for a nonparametric distribution[35] and 5% loss to follow-up.

The analysis of the primary outcome was performed in the intention-to-treat population, which was defined as all the patients who had been enrolled except for those who had withdrawn consent for use of data. Between-group differences in the primary outcome and continuous secondary outcomes were calculated with the use of median regression with cluster-robust standard errors to account for site; results were reported as a difference of medians with 95% confidence intervals.[36] Further analyses of the primary outcome included evaluating the intervention effect across the range of quantiles, ordinal logistic regression, and sensitivity to missingness. Prespecified subgroup analyses were conducted with the use of median regression with heterogeneity determined by fitting an interaction between treatment assignment and subgroup with results reported in a forest plot. Binomial secondary outcomes were compared with the use of logistic regression to derive odds ratios with cluster-robust standard errors reported with 95% confidence intervals, according to the statistical analysis plan; however, odds ratios may overestimate the relative risk.

Analyses were conducted with the use of R software, version 4.0.2,[37] and SAS statistical software, version 9.4 (SAS Institute). Statistical significance for the primary outcome was determined with the use of a two-sided hypothesis test with an alpha of 0.05. Because there was no correction for multiple comparisons in secondary outcomes, P values have not been reported for these comparisons and the results are considered to be exploratory. Multiple imputation was performed for all outcomes without complete data. Additional details regarding the analyses are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From February 27, 2018, to November 19, 2021, a total of 750 patients at 49 hospitals in 6 countries underwent randomization to the early-mobilization group (372 patients) or usual-care group (378 patients) (Fig. 1). Full consent was withdrawn by 1 patient in the early-mobilization group and 8 patients in the usual-care group, which left 371 in the early-mobilization group and 370 in the usual-care group. Three patients in the usual-care group were lost to follow-up, and 5 patients — 2 in the early-mobilization group and 3 in the usual-care group — withdrew consent for follow-up of the primary outcome but not for the use of other data. Accordingly, the primary outcome was available for 733 of 736 patients (99.6%) in the intention-to-treat population (369 in the early-mobilization group and 364 in the usual-care group). The trial groups had similar characteristics at baseline (Table 1 and Tables S1 through S5 in the Supplementary Appendix). Table S6 describes the representativeness of the population.

ACTIVITY AND MOBILIZATION

Mobilization milestones of active exercise, standing, and walking according to treatment group are shown in Table 2 and Figure 2. The mean (±SD) daily duration of active mobilization per patient in the ICU was 20.8±14.6 minutes in the early-mobilization group and 8.8±9.0 minutes in the usual-care group (absolute difference, 12 minutes per day; 95% confidence interval [CI], 10.4 to 13.6). Additional details regarding mobilization according to group are shown in Table S7 and Figures S1, S2, and S3. Compliance with the intervention was high (Fig. S4). The major barriers to mobilization in the early-mobilization group were protocol-compliant and included sedation, agitation, and physiological instability.

PRIMARY OUTCOME

At day 180, the median number of days that patients were alive and out of the hospital was 143 days (interquartile range, 21 to 161) in the early-mobilization group and 145 days (interquartile range, 51 to 164) in the usual-care group (absolute difference, –2 days; 95% CI, –10 to 6; P=0.62) (Table 3). Consistent with the results of the primary analysis were the findings in com-

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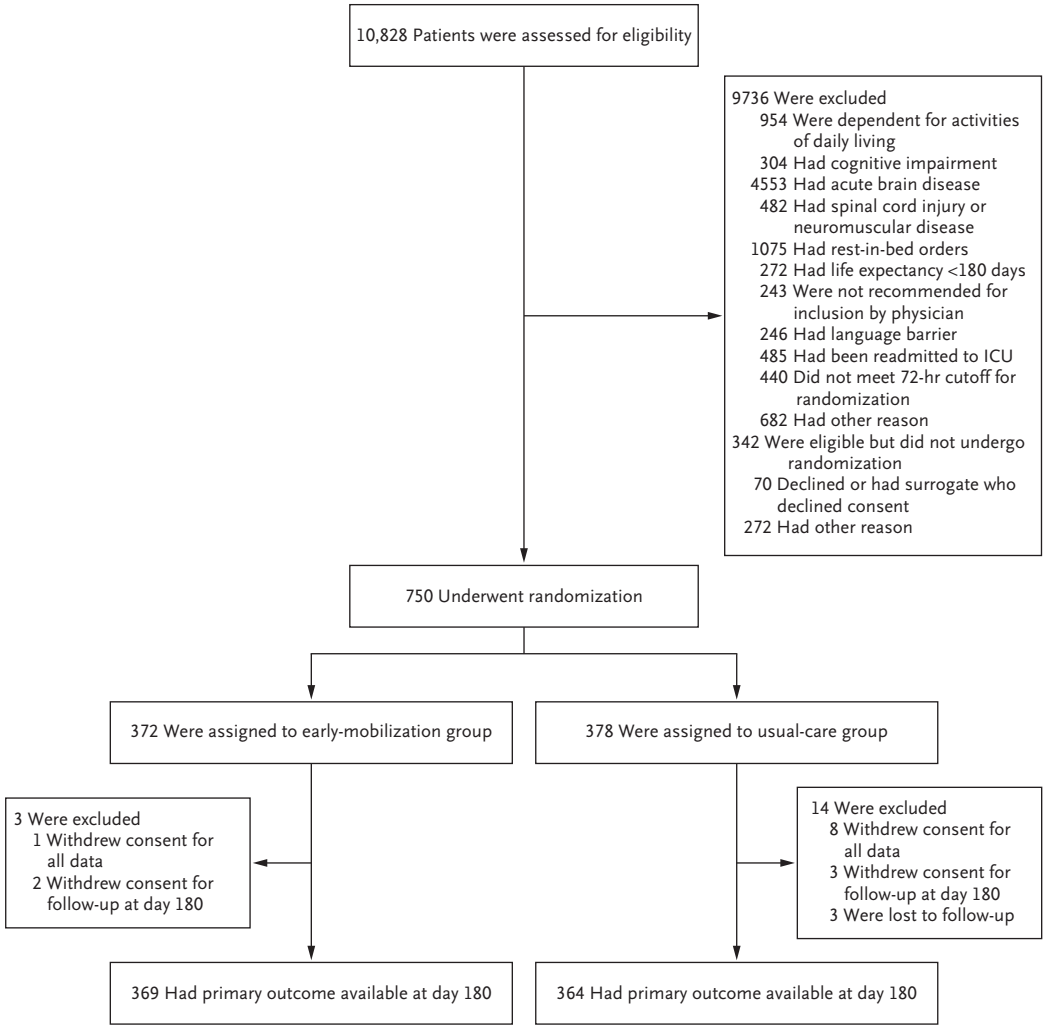

Figure 1. Randomization and Outcomes.

In this trial involving patients who were undergoing invasive mechanical ventilation, early mobilization included sedation minimization and daily physiotherapy and usual care included the level of mobilization that was normally provided in each intensive care unit (ICU).

plete-case analyses, sensitivity analyses for missingness, evaluation of the intervention effect estimate across quantiles and according to country, and analyses of the primary outcome as an ordinal categorical variable (Tables S8 through S10 and Fig. S5).

SECONDARY OUTCOMES

By day 180, deaths were reported in 83 of 369 patients (22.5%) in the early-mobilization group and in 71 of 364 (19.5%) in the usual-care group (odds ratio, 1.15; 95% CI, 0.81 to 1.65) (Table 3 and Fig. S6). The number of ventilator-free days and ICU-free days at day 28 were similar in the two groups.

The scheduled 180-day follow-up occurred at a median of 186 days (interquartile range, 182 to 194) after randomization. Among the 579 survivors, patient-reported outcomes were evaluated in 286 patients in the early-mobilization group and 293 in the usual-care group. The numbers of patients who completed each assessment and findings regarding quality of life, activities of daily living, and disability were similar in the two

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Early Mobilization (N=371)	Usual Care (N=370)
Age — yr	60.5±14.8	59.5±15.2
Female sex — no. (%)	128 (34.5)	146 (39.5)
Body-mass index†	29.9±7.9	30.4±7.8
Frailty and function		
Median score on Clinical Frailty Scale (IQR)‡	3 (2 to 4)	3 (2 to 4)
Median score on Functional Comorbidity Index (IQR)§	2 (1 to 3)	2 (1 to 3)
Median score on WHODAS 2.0 (IQR)¶	10.4 (2.1 to 25.0)	8.7 (2.1 to 22.7)
Highest score on the ICU Mobility Scale in wk before ICU admission‖	9.9±0.6	9.8±0.7
Median interval from hospital admission to randomization (IQR) — hr	88.3 (50.5 to 137.0)	81.6 (48.2 to 147.0)
Median interval from ICU admission to randomization (IQR) — hr	60.1 (35 to 92.3)	61.3 (33.8 to 96.1)
ICU admission type — no. (%)		
Planned ICU admission after elective surgery	68 (18.3)	58 (15.7)
Unplanned ICU admission	303 (81.7)	312 (84.3)
Median RASS score at randomization (IQR)**	−3 (−4 to −2)	−3 (−4 to −2)
Measurements and interventions at randomization††		
Positive end-expiratory pressure — cm of water	8.9±3.0	8.8±3.1
Pao_2:FIO_2	226±79.1	230±85.2
Receipt of vasopressors by infusion — no. (%)	228 (61.5)	231 (62.4)
Receipt of renal-replacement therapy — no. (%)	82 (22.1)	79 (21.4)
APACHE II score‡‡	18.2±6.8	18±6.9
Diagnosis subgroup — no. (%)§§		
Sepsis¶¶	246 (66.3)	245 (66.2)
Trauma	15 (4.0)	14 (3.8)
Covid-19	7 (1.9)	10 (2.7)

* Plus–minus values are means ±SD. Patients in the usual-care group received the level of mobilization that was normally provided in each intensive care unit (ICU). Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission, as confirmed by their next of kin or surrogate.

§ The Functional Comorbidity Index includes 18 diagnoses and scores from 0 to 18, with the score equal to the number of specified coexisting illnesses present. Higher scores are associated with greater level of physical limitation.

¶ The 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 covers six domains of functioning (with multiple questions for each domain), with scores ranging from 0 (no difficulty) to 4 (extreme difficulty) and a total score ranging from 0 to 48, with higher scores representing greater disability. The total score is divided by 48 and multiplied by 100 to convert it to a percentage of maximum disability. The WHODAS 2.0 score was available for 322 patients in the early-mobilization group and 310 patients in the usual-care group. At randomization, the WHODAS 2.0 was completed by the patient's next of kin or surrogate.

‖ Scores on the ICU Mobility Scale include 0 (lying in bed), 1 (sitting and exercising in bed), 2 (passive movement from bed to chair, no standing), 3 (sitting on edge of bed), 4 (standing), 5 (transferring from bed to chair), 6 (marching in place at bedside), 7 (walking with assistance of 2 or more people), 8 (walking with assistance of 1 person), 9 (walking independently with gait aid), and 10 (walking independently without gait aid). The score was obtained from the patient's next of kin or surrogate at the time of randomization.

** Scores on the Richmond Agitation Sedation Scale (RASS) range from −5 (unarousable) to 4 (combative). A score of −4 to −2 indicates deep to light sedation. This score was available for 358 patients in the early-mobilization group and 357 patients in the usual-care group.

†† Data regarding positive end-expiratory pressure were available for all the patients in the early-mobilization group and 369 patients in the usual-care group. Data regarding the ratio of arterial partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (FIO_2) were available for 369 patients and 368 patients, respectively.

‡‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

§§ Subgroups of this category were the only prespecified diagnoses that were evaluated and were not mutually exclusive. Data regarding the ICU admission source and diagnosis are provided in Table S4.

¶¶ Sepsis was defined as suspected or confirmed infection plus a score on the Sequential Organ Failure Assessment (SOFA) of 2 or more if there was no known preexisting organ dysfunction or an increase from baseline in the SOFA score of more than 2 points if there was preexisting organ dysfunction.

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Table 2. Mobilization in the ICU.*

Characteristic	Early Mobilization (N=371)	Usual Care (N=370)	Between-Group Difference (95% CI)†
Patients who were assessed by a physiotherapist on day of randomization — no./total no. (%)	320/370 (86.5)	265/363 (73.0)	13.5 (6.7 to 20.3)
No. of days per patient when physiotherapy assessment occurred	0.94±0.11	0.81±0.24	0.14 (0.12 to 0.16)
No. of minutes of active mobilization per day	20.8±14.6	8.8±9.0	12.0 (10.4 to 13.6)
Mobilization milestones‡			
IMS 3 or higher			
Patients — no. (%)	331 (89.2)	330 (89.2)	0 (–4.3 to 4.3)
Median no. of days since randomization (IQR)	3 (1 to 6)	4 (2 to 7)	–1 (–2.2 to –0.2)
IMS 4 or higher			
Patients — no. (%)	287 (77.4)	286 (77.3)	0.1 (–6.0 to 6.1)
Median no. of days since randomization (IQR)	3 (2 to 7)	5 (3 to 8)	–2 (–3.4 to –0.6)
IMS 7 or higher			
Patients — no. (%)	176 (47.4)	150 (40.5)	6.9 (–0.2 to 14.0)
Median no. of days since randomization (IQR)	5 (3 to 8)	7 (4 to 13)	–2 (–3.4 to –0.7)
Median peak IMS (IQR)	6 (4 to 8)	6 (4 to 8)	0 (–1 to 1)

* Plus–minus values are means ±SD.
† Between-group differences were calculated after adjustment for trial site.
‡ A score of 3 on the ICU mobility scale (IMS 3) (sitting on the edge of the bed) could involve assistance of a staff member but required that the patient was actively sitting with some trunk control. IMS 4 (standing) required weight bearing through the feet with or without assistance or the use of a standing lifter or tilt-table device. IMS 5 (transferring from bed to chair) required active transfer of weight from one leg to another to move to the chair; if standing was accomplished with the assistance of a medical device, stepping into the chair was required. IMS 6 (marching in place) required that the patient lift alternate feet at least four times (twice on each foot) with or without assistance. IMS 7 (walking with assistance of ≥2 people), IMS 8 (walking with the assistance of 1 person), IMS 9 (walking independently with a gait aid), and IMS 10 (walking independently without a gait aid) required walking at least 5 m away from the bed or chair.

groups (Tables S11 and S12). Additional secondary outcomes, including 28-day mortality and cognitive and psychological function, were also similar (Table S13).

PROCESS OF CARE MEASURES AND SUBGROUP ANALYSES

Process-of-care measures — which included the use of tracheostomy, neuromuscular blockers, glucocorticoids, new renal-replacement therapy, reintubation, and vasopressor-free days — were similar in the two groups (Table S14). Daily sedation scores are shown in Figure S7, and the proportion of patients in the ICU with delirium each day is shown in Figure S8. Daily ventilatory support is shown in Figure S9. There was no evidence of heterogeneity in the effect of early mobilization on the primary outcome among patients in any of the prespecified subgroups (Fig. S10).

SAFETY OUTCOMES

Adverse events that were potentially due to mobilization were reported in 34 of 371 patients (9.2%) in the early-mobilization group and in 15 of 370 (4.1%) in the usual-care group (P=0.005); cardiac arrhythmia, altered blood pressure, and oxygen desaturation were the most commonly reported events (Table 3). A total of 8 serious adverse events were reported, of which 7 occurred in the early-mobilization group (5 arrhythmias, a desaturation episode, and a cerebrovascular accident), and 1 occurred in the usual-care group (a desaturation episode) (Table S15). All serious adverse events required medical intervention. All events resolved except for the cerebrovascular accident, which resulted in persistent unilateral weakness. No instances of falling to the floor, cardiac arrest, unplanned extubation, or intravascular line removal resulting in urgent replacement were reported.

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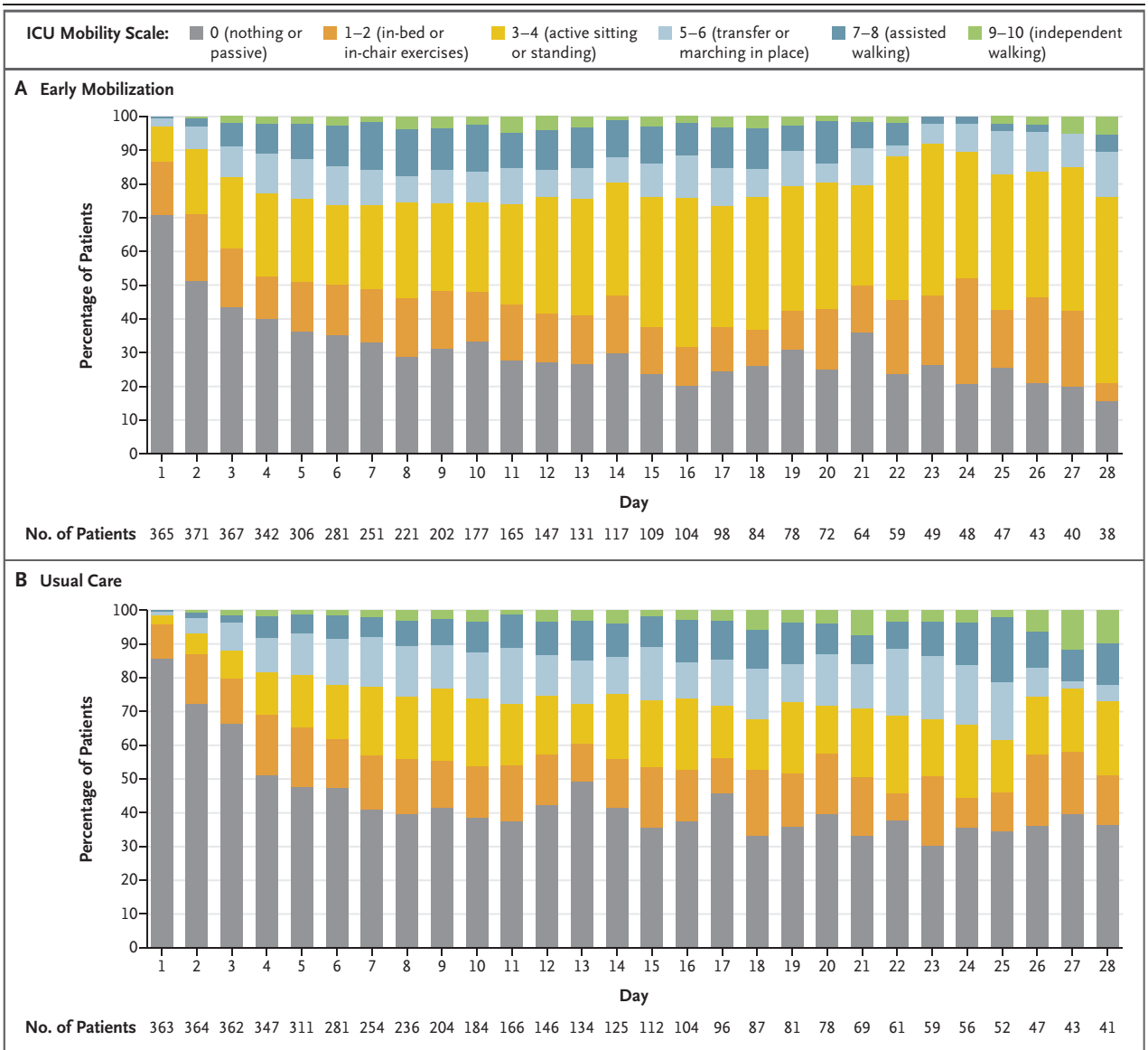

Figure 2. Mobilization in the Intensive Care Unit, According to Treatment Group.

DISCUSSION

In this international, randomized, controlled trial involving adults who were undergoing mechanical ventilation, the numbers of days that patients were alive and out of the hospital at 180 days were similar in the early-mobilization group and the usual-care group. Adverse events and serious adverse events were reported more commonly in the early-mobilization group.

Our findings are at variance with a meta-analysis showing that active mobilization in the ICU, particularly when delivered early, significantly increased the number of days that patients were alive and out of the hospital at 180 days.[14] However, in this meta-analysis, both the intensity and duration of mobilization in the control groups varied greatly, a factor that made it difficult to draw comparisons across the trials. Our trial avoided some of the methodologic shortcomings of studies that were included in this meta-analysis, such as small sample sizes,[34,38] single-center designs,[39] and use of historical controls.[39]

Some randomized, controlled trials of early mobilization that have shown potential benefits have focused on outcomes other than days alive

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Table 3. Primary Outcome, Key Secondary Outcomes, and Adverse Events.*

Outcome	Early Mobilization (N=371)	Usual Care (N=370)	Difference or Odds Ratio (95% CI)†	P Value
Primary outcome				
Days alive and out of hospital at day 180‡				
Median no. (IQR)	143 (21 to 161)	145 (51 to 164)	−2.0 (−10 to 6)	0.62
Key secondary outcomes				
Death at day 180				
Patients — no. (%)	83/369 (22.5)	71/364 (19.5)	1.15 (0.81–1.65)§	
Median no. of days since randomization (IQR)	17 (9 to 41)	19 (12 to 50)	−2.0 (−12.0 to 8.0)	
Median no. of ventilator-free days at day 28 (IQR)	21 (8 to 25)	21 (11 to 25)	0.0 (−1.4 to 1.4)	
Median no. of ICU-free days at day 28 (IQR)	16 (0 to 21)	17 (3 to 22)	−1.0 (−3.1 to 1.1)	
Functional outcomes in survivors at day 180¶				
Score on EQ-5D-5L utility score‖	0.7±0.3	0.7±0.3	0.0 (−0.0 to 0.1)	
Score on EQ Visual Analogue Scale**	70.2±19.7	69.0±20.1	2.0 (−5.7 to 9.7)	
Median score on Barthel Index of ADL (IQR)††	100 (100 to 100)	100 (95 to 100)	0	
Median score on IADL (IQR)‡‡	8.0 (7.0 to 8.0)	8.0 (6.0 to 8.0)	0.2 (−0.9 to 1.3)	
Median score on WHODAS 2.0 (IQR)§§	12.5 (2.1 to 33.3)	14.6 (4.2 to 38.9)	−1.8 (−6.9 to 3.4)	
Adverse events — no. (%)¶¶				
Patients with ≥1 adverse event potentially due to mobilization — no. (%)	34 (9.2)	15 (4.1)	2.55 (1.33–4.89)§	0.005
Adverse events per patient — no. (%)				0.02
0	337 (90.8)	355 (95.9)		
1	19 (5.1)	11 (3.0)		
2	4 (1.1)	2 (0.5)		
≥3	11 (3.0)	2 (0.5)		
Type of adverse events — no. (%)‖‖				
Altered blood pressure	13 (3.5)	8 (2.2)		0.27
Cardiac arrhythmia	13 (3.5)	4 (1.1)		0.03
Oxygen desaturation	8 (2.2)	1 (0.3)		0.02
Pain or agitation	4 (1.1)	1 (0.3)		0.37
Removal of invasive line	2 (0.5)	2 (0.5)		1.00
Gastrointestinal	2 (0.5)	1 (0.3)		1.00
Tachypnea	3 (0.8)	0		0.25
Altered neurologic state	1 (0.3)	1 (0.3)		1.00
Other	4 (1.1)	0		0.12

* Plus–minus values are means ±SD.
† Values are between-group differences unless otherwise indicated. All differences in medians were calculated with the use of quantile regression after adjustment for trial site. Multiple imputation for missingness was used for primary and key secondary outcomes.
‡ Data for the primary and secondary outcomes were available for 733 patients (369 in the early-mobilization group and 364 in the usual-care group).
§ This value is an odds ratio that was calculated after adjustment for the trial site as a random effect with the use of multiple imputation to account for missingness.
¶ Of 579 survivors, 286 in the early-mobilization group and 293 in the usual-care group were contacted to complete functional outcome assessments.
‖ The EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) includes of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Scores on the utility scale range from −0.6 to 1, with the maximum score indicating the best health state. The utility score was missing for 38 patients in the early-mobilization group and 38 in the usual-care group.
** The EQ Visual Analogue Scale provides a single global rating of self-perceived health and is scored on a scale of 0 to 100, with higher scores indicating better health. Data on this scale were missing for 40 patients in the early-mobilization group and 39 in the usual-care group.
†† The Barthel Index of Activities of Daily Living (ADL) measures functional disability in 10 ADLs by quantifying patient performance. Increments of 5 points are used in scoring, with a maximal score of 100 indicating full independence in physical functioning and a lowest score of 0 indicating a completely bed-bound state. The ADL was missing for 39 patients in the early-mobilization group and 43 in the usual-care group.
‡‡ The Lawton Instrumental Activities of Daily Living (IADL) Scale is an assessment of independent living skills across eight domains of function. A summary score ranges between from 0 and 8 with higher scores indicating greater levels of independence. The IADL score was missing for 37 patients in the early-mobilization group and 43 in the usual-care group.
§§ The WHODAS 2.0 score was missing for 52 patients in the early-mobilization group and 52 in the usual-care group.
¶¶ Adverse events include events that were reported as probably, possibly, or definitely related to mobilization. These do not include serious adverse events, which are reported separately in Table S15.
‖‖ In cases in which a patient had a particular adverse event on more than one occasion, each event was only counted once.

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and out of the hospital. In a trial that involved patients being treated in a medical ICU, early mobilization with an interruption of sedation increased the level of independent function at the time of hospital discharge.[13] In that trial, mobilization milestones in the usual-care group were met at a similar time as were those in our trial. However, in contrast to the previous trial, which began mobilization sessions with low levels of activity, we sought to begin mobilizing patients at the highest level of activity possible. In one study involving patients in a surgical ICU, early mobilization reduced the length of stay in the ICU and increased functional mobility at hospital discharge.[12] However, as in our trial, patients in the early-mobilization group in that trial had an increased risk of adverse events. Moreover, the interpretation of that study in surgical patients was complicated by markedly higher in-hospital mortality in the early-mobilization group.

Our findings are broadly consistent with the results of three randomized, controlled trials that were conducted during the past 6 years.[40-42] In two of these trials, investigators compared intensive physiotherapy with usual care among patients in the ICU and reported no between-group difference among survivors with respect to physical function at 1 month and at 6 months, respectively.[40,41] The third trial compared standardized rehabilitation therapy with usual ICU care in adults with acute respiratory failure and showed no difference between groups in the length of hospital stay.[42]

Our trial has some limitations. Patients in our usual-care group received a higher level of mobilization than those in some cohort studies[43,44] and in the control groups of some previous trials.[12,41] However, the mobilization levels that were achieved in our usual-care group were consistent with those outlined in international guidelines,[19,45] were similar to those in a recent multicenter cohort study,[46] and were similar to those in the control group of a previous clinical trial showing benefits from early mobilization.[13] Although practitioners in our trial provided treatments according to the protocol, changes in practice that could have affected treatment in the usual-care group may have occurred in specific sites or countries. Our protocol stipulated that whenever it was feasible to do so, patients in the usual-care group should receive treatment from physiotherapy staff members who were not involved in delivering early mobilization in the intervention group, but we did not record whether this occurred. Despite separation between groups in timing and duration of mobilization, factors including sedation, agitation, and physiological instability often precluded mobilization. This meant that some patients were not actively mobilized in the ICU. Patients who were not mobilized reduced the statistical power to detect a difference between groups. Our protocol did not stipulate details regarding rehabilitation beyond the ICU or call for an assessment of function at hospital discharge. The observation of a greater frequency of adverse events with early mobilization than with usual care may have been subject to surveillance bias because the treatment assignments were unblinded. In contrast, for patient-reported outcomes at day 180, we used centralized assessors who were unaware of trial-group assignments to avoid bias. Because these outcomes could be compared only among survivors, they do not represent randomized comparisons. Some data related to patient-reported outcomes at day 180 were missing. These data may not have been missing at random because patients with better (or worse) outcomes might have been harder to contact or less likely to complete interviews. For our primary outcome, missing data were rare and our findings were consistent in a range of sensitivity analyses. Odds ratio may overestimate the relative risk and be misinterpreted.

Mobilizing critically ill patients early requires clinical expertise, time, and resources. Although we used a safety checklist,[23] conducted interdisciplinary discussion with the medical team, and required that senior physiotherapists direct early active mobilization, our trial suggests greater safety with usual care than with the additional early mobilization that was provided in our trial. Thus, for adults undergoing mechanical ventilation in the ICU, increased early active mobilization did not affect the number of days that they were alive and out of the hospital as compared with the usual level of mobilization received in the ICU.

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APPENDIX

The affiliations of the members of the writing committee are as follows: the Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine (C.L.H., M.B., R.B., T.B., A.M.H., A.S.N., A.D.N., J.J.P., J.S., S.W., P.J.Y.), School of Public Health and Preventive Medicine (B.J.G.), Monash University, the Data Analytics Research and Evaluation Centre, University of Melbourne and Austin Hospital (R.B., A.S.N.), the Department of Critical Care (C.L.H., R.B., A.S.N., J.J.P., P.J.Y.) and the School of Medicine (J.J.P.), University of Melbourne, the Department of Intensive Care (A.D.N.) and the Intensive Care Unit and Physiotherapy Department (C.L.H., C.J.T.), Alfred Hospital, and the Department of Intensive Care, Royal Melbourne Hospital (R.B., J.J.P.), Melbourne, VIC, the Critical Care Division, the George Institute for Global Health (C.L.H., A.M.H.), and Intensive Care Services, Royal Prince Alfred Hospital (H.B.), Sydney, the Curtin School of Allied Health, Curtin University, Bentley, WA (M.H.), and the Department of Physiotherapy, Royal Perth Hospital (M.H.), and the Intensive Care Unit, St. John of God Subiaco Hospital (S.W.), Perth, WA — all in Australia; the Intensive Care Unit, Wellington Hospital (P.J.Y.), and the Medical Research Institute of New Zealand (S.H., P.J.Y.) — both in Wellington, New Zealand; the Department of Anesthesiology and Intensive Care, School of Medicine, Technical University of Munich, School of Medicine, Klinikum Rechts der Isar, Munich, and the Department of Anesthesiology and Operative Intensive Care Medicine, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin — both in Germany (S.J.S); the Department of Internal Medicine Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor (T.J.I.); the Department of Medicine Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore (T.J.I.); the Clinical Trials Unit, Intensive Care National Audit and Research Centre, London (D.W.G.); the Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo (A.S.N.); and University College Dublin–Clinical Research Centre at St. Vincent's University Hospital, Dublin (K.B., A.D.N.).

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