EDITORIAL

The Challenging Task of Improving the Recovery of ICU Survivors

Shannon L. Goddard, MD; Neill K. J. Adhikari, MDCM, MSc

Survivors of critical illness encounter a variety of challenges, even after the acute illness has resolved. Observational studies have documented physical, cognitive,[1] and mental[2] impairments affecting survivors after a stay in the intensive care unit (ICU). As these data have accumulated, clinicians have sought to better understand what is now called "post-ICU syndrome"[3] and to develop interventions both during and after the ICU stay to attenuate the effects.

Related articles pages 2694 and 2703

In this issue of *JAMA*, Morris and colleagues[4] report a randomized clinical trial of early ICU-based mobility involving 300 patients with acute hypoxemic respiratory failure from 1 US center. Patients in the intervention group (n = 150, including 84 who completed 6-month follow-up) received an intensive daily regimen of range of motion, strength training, and functional mobility training, whereas patients in the control group (n = 150, including 81 who completed 6-month follow-up) received physical therapy during weekdays, when ordered by the clinical team. The investigators demonstrated significant separation of treatment between the intervention and control groups, with faster initiation (median, 3 days vs 7 days) and more days of physical therapy (median, 5 days vs 1 day).

Despite successful intervention implementation, there was no effect on the primary outcome, hospital length of stay (median, 10 days in both groups). Similarly, there were no differences in most secondary outcomes, particularly hospital-free days (median, 18 days in both groups), ventilator-free days (median, 24 days in both groups), and ICU length of stay (median, 7.5 days vs 8 days).

Also in this issue of *JAMA*, Schmidt and colleagues[5] report a randomized clinical trial of a complex program delivered after the hospital stay to 291 survivors of sepsis treated in the ICU at 9 German centers. In the intervention group (n = 148), nurse case managers and primary care clinicians, with access to a consulting physician, were trained to assess a broad spectrum of physical, psychological, and cognitive symptoms and to intervene as necessary according to severity and urgency of the symptoms. In the usual care group (n = 143), primary care physicians provided direct patient care, including periodic contacts, referrals to specialists, and prescription of medications and other treatments. The primary outcome was a mental health–related quality-of-life measure: change in 36-Item Short Form Health Survey mental component summary score from ICU discharge to 6 months.

There was no difference in the primary outcome between the intervention and control groups. The mental component summary scores from baseline to 6 months increased from 49.1 to 52.9 in the intervention group and from 49.3 to 51.0 in the control group); the mean between-group treatment effect was 2.15 (95% CI −1.79 to 6.09; P = .28). In fact, the scores at ICU discharge were close to population means in both the treatment and the control groups. The investigators included 32 secondary outcomes at 2 different time points. There was no difference in most secondary outcomes except for 6-month assessments of physical function, physical disability, and impairment of activities of daily living that favored the intervention group. Given multiple statistical tests, the authors correctly label these findings as exploratory.

The field of ICU rehabilitation and care after ICU discharge is at a crossroads. These 2 rigorous trials add to research that largely demonstrates no effect of interventions to improve longer-term outcomes of ICU survivors. Although studies aiming to improve recovery after ICU discharge are often considered together because of this common aim, it is important to consider substantial heterogeneity of study methods when interpreting results and considering future trials.

First, interventions to ameliorate post-ICU syndrome have been implemented in the ICU,[6] in the hospital ward,[7] and in the outpatient clinic or home[8] and have differed in duration and intensity. These interventions have involved strategies for physical rehabilitation, activities of daily living, and case management. However, patient populations have been similar and broad. Attempts to identify a subgroup both at risk for poor outcomes and responsive to the intervention—an essential design strategy in randomized trials—have been limited to patients receiving mechanical ventilatation and with a minimum ICU length of stay. Intuitively reasonable yet broad patient selection criteria highlight that the current understanding of trajectories of post-ICU syndrome is still in its infancy.

Second, although numerous observational studies have documented clinical evidence of ICU-acquired weakness, impaired function, and psychiatric and cognitive impairments, an understanding of the pathophysiology of these symptoms is still developing. For example, only recently have studies characterized muscle biology,[9] morphologic features on ultrasound,[10] and electrophysiology.[9] Gaining an understanding of the biology of ICU-acquired weakness over time across the ICU stay and recovery period, together with clinical associations, may identify key features needed for the design of future trials: which muscle groups are functioning poorly yet potentially responsive to rehabilitation; the optimal timing of the intervention; and the specific interventions to be tested. In the trial by Morris et al,[4] the intervention had no effect on patient-reported measures of physical function at hospital discharge, but there was some improvement at both 3 and 6 months. However, these changes did not correlate with objective strength measured by handheld dynamometry. The explanation for this discordance is unclear but may relate to bias when exposure to the intervention cannot not be blinded and the outcome is patient-reported. Another potential limitation, that the intervention was not sufficiently intense to improve hospital-based outcomes, seems highly unlikely given

results of a related trial that also showed no effect of more intensive physiotherapy in the ICU.[11]

Third, complex interventions such as case management or a rehabilitation regimen adjusted to a patient's evolving clinical situation are difficult to deliver. Morris et al demonstrated unequivocal separation in physical therapy between groups. Schmidt et al also collected detailed data on processes of care (eg, referrals to specialists and number of treatments given), but groups were similarly treated, which may have reflected insufficient intensity of the intervention or high-performing care by primary care clinicians in the usual care group. The careful documentation of processes of care linked to the intervention and delivered by usual care in the control group should be a standard for future trials of complex interventions targeting ICU survivors.

Fourth, selecting the right outcome for these trials continues to challenge investigators, as shown in a recent review of the literature that found a total of 250 instruments to measure health-related quality of life, physical function, cognition, and mental health outcomes in studies of ICU survivors.[12] This multiplicity illustrates the complexity of the post-ICU survivor experience and the uncertainty over how to record that experience quantitatively. However, the extensive data collection may be burdensome to study participants, and the divergent outcome measurements limit opportunities for meta-analysis. To minimize bias, and when feasible for investigators and acceptable to patients, studies should include assessor-blinded objective measures paired with patient-reported measures. Ongoing work to identify the most valid and reliable instruments for survivorship research will be critical to harmonize outcomes and compare studies.

As these complex patients transition from the geographic and team-based confines of the ICU to the community-based environment, the quest to improve outcomes becomes more daunting. For instance, individual outpatient physicians ordinarily provide care for few ICU survivors; in the trial by Schmidt et al,[5] more than 90% of the enrolled patients had outpatient clinicians who cared for only 1 study patient. However, this point is relevant only if ICU survivors have different needs from the more common group of patients presenting to primary care after an acute illness without an ICU stay.[13] Centralized care is an attractive solution to low-volume care but may not be feasible for patients who have to travel long distances to specialist clinics. Furthermore, recent work that describes groups of ICU survivors with distinct trajectories and needs[14] shows that specialty clinic–based care will not eliminate the need for individual attention traditionally associated with attentive community physicians. The situation is similar to that of complex high-cost general medical outpatients, who can be divided into subgroups with distinct needs that include management of end-stage organ disease, mental health issues, and traditional disease risk factors. Perhaps most importantly, many ICU survivors either recover without limitations or simply may not benefit from rehabilitation. The latter group may live at the end of the spectrum of noncritically ill hospital survivors with more serious illness, for whom efforts to describe and manage the posthospital syndrome are ongoing.[13]

Attitudes and clinical practice involving hospital-based mobilization have clearly progressed since "the dangers of going to bed" were identified nearly 70 years ago.[15] These 2 trials also provide information that will be helpful for clinicians and their patients. Within the ICU, trials support restrained approaches to sedation using either protocols or daily interruption of infusions, but not specific additional physiotherapy regimens beyond the current standard of care. After discharge from the ICU, astute primary care clinicians, and increasingly patients and their caregivers, will need to be aware of the range of clinical problems encountered by ICU survivors and the help available from specialist physicians and rehabilitation programs. Pending results of additional interventional trials, patients and their caregivers should continue to access these existing services.

ARTICLE INFORMATION

Author Affiliations: Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, and Interdepartmental Division of Critical Care, University of Toronto, Toronto Ontario, Canada.

Corresponding Author: Neill Adhikari, MDCM MSc, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room D1.08, Toronto, ON M4N 3M5 Canada (neill.adhikari@utoronto.ca).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Brummel NE, Balas MC, Morandi A, et al. Understanding and reducing disability in older adults following critical illness. *Crit Care Med*. 2015;43(6):1265-1275.

2. Davydow DS, Gifford JM, Desai SV, et al. Depression in general intensive care unit survivors. *Intensive Care Med*. 2009;35(5):796-809.

3. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit. *Crit Care Med*. 2012;40(2):502-509.

4. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure. *JAMA*. doi:10.1001/jama.2016.7201.

5. Schmidt K, Worrack S, Von Korff M, et al; SMOOTH Study Group. Effect of a primary care management intervention on mental health–related quality of life among survivors of sepsis. *JAMA*. doi:10.1001/jama.2016.7207.

6. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients. *Lancet*. 2009;373(9678):1874-1882.

7. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge. *JAMA Intern Med*. 2015;175(6):901-910.

8. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness. *BMJ*. 2009;339:b3723.

9. Dos Santos C, Hussain SN, Mathur S, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay: a pilot study [published online April 8, 2016]. *Am J Respir Crit Care Med*. doi:10.1164/rccm.201512-2344OC.

10. Bunnell A, Ney J, Gellhorn A, Hough CL. Quantitative neuromuscular ultrasound in intensive care unit–acquired weakness: a systematic review. *Muscle Nerve*. 2015;52(5):701-708.

11. Moss M, Nordon-Craft A, Malone D, et al. A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med*. 2016;193(10):1101-1110.

12. Turnbull AE, Rabiee A, Davis WE, et al. Outcome measurement in ICU survivorship research from 1970 to 2013 [published online March 27, 2016]. *Crit Care Med*. http://journals.lww.com/ccmjournal/Abstract/publishahead/Outcome_Measurement_in_ICU_Survivorship_Research.96956.aspx.

13. Krumholz HM. Post-hospital syndrome—an acquired, transient condition of generalized risk. *N Engl J Med*. 2013;368(2):100-102.

14. Herridge MS, Chu LM, Matte A, et al. The RECOVER program: disability risk groups & one year outcome after ≥7 days of mechanical ventilation [published online March 14, 2016]. *Am J Respir Crit Care Med*. 2016. doi:10.1164/rccm.201512-2343OC.

15. Asher RA. The dangers of going to bed. *Br Med J*. 1947;2(4536):967.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Primary Care Management Intervention on Mental Health–Related Quality of Life Among Survivors of Sepsis
A Randomized Clinical Trial

Konrad Schmidt, MD; Susanne Worrack, MSc; Michael Von Korff, ScD; Dimitry Davydow, MD, MPH; Frank Brunkhorst, MD; Ulrike Ehlert, PhD; Christine Pausch, PhD; Juliane Mehlhorn, MD; Nico Schneider, MSc; André Scherag, MSc, PhD; Antje Freytag, PhD; Konrad Reinhart, MD; Michel Wensing, PhD; Jochen Gensichen, MD, MSc, MPH; for the SMOOTH Study Group

IMPORTANCE Survivors of sepsis face long-term sequelae that diminish health-related quality of life and result in increased care needs in the primary care setting, such as medication, physiotherapy, or mental health care.

OBJECTIVE To examine if a primary care–based intervention improves mental health–related quality of life.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted between February 2011 and December 2014, enrolling 291 patients 18 years or older who survived sepsis (including septic shock), recruited from 9 intensive care units (ICUs) across Germany.

INTERVENTIONS Participants were randomized to usual care (n = 143) or to a 12-month intervention (n = 148). Usual care was provided by their primary care physician (PCP) and included periodic contacts, referrals to specialists, and prescription of medication, other treatment, or both. The intervention additionally included PCP and patient training, case management provided by trained nurses, and clinical decision support for PCPs by consulting physicians.

MAIN OUTCOMES AND MEASURES The primary outcome was change in mental health–related quality of life between ICU discharge and 6 months after ICU discharge using the Mental Component Summary (MCS) of the 36-Item Short-Form Health Survey (SF-36 [range, 0-100; higher ratings indicate lower impairment; minimal clinically important difference, 5 score points]).

RESULTS The mean age of the 291 patients was 61.6 years (SD, 14.4); 66.2% (n = 192) were men, and 84.4% (n = 244) required mechanical ventilation during their ICU stay (median duration of ventilation, 12 days [range, 0-134]). At 6 and 12 months after ICU discharge, 75.3% (n = 219 [112 intervention, 107 control]) and 69.4% (n = 202 [107 intervention, 95 control]), respectively, completed follow-up. Overall mortality was 13.7% at 6 months (40 deaths [21 intervention, 19 control]) and 18.2% at 12 months (53 deaths [27 intervention, 26 control]). Among patients in the intervention group, 104 (70.3%) received the intervention at high levels of integrity. There was no significant difference in change of mean MCS scores (intervention group mean at baseline, 49.1; at 6 months, 52.9; change, 3.79 score points [95% CI, 1.05 to 6.54] vs control group mean at baseline, 49.3; at 6 months, 51.0; change, 1.64 score points [95% CI, −1.22 to 4.51]; mean treatment effect, 2.15 [95% CI, −1.79 to 6.09]; $P = .28$).

CONCLUSIONS AND RELEVANCE Among survivors of sepsis and septic shock, the use of a primary care–focused team-based intervention, compared with usual care, did not improve mental health–related quality of life 6 months after ICU discharge. Further research is needed to determine if modified approaches to primary care management may be more effective.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN61744782

JAMA. 2016;315(24):2703-2711. doi:10.1001/jama.2016.7207

Editorial page 2671

Related article page 2694

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The SMOOTH Study Group members are listed at the end of this article.

Corresponding Author: Jochen Gensichen, MD, MSc, MPH, Institute of General Practice and Family Medicine, Jena University Hospital, Friedrich-Schiller-University, School of Medicine, Bachstrasse 18, D-07740 Jena, Germany (jochen.gensichen@med.uni-jena.de).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

Sepsis is a major health problem worldwide.[1] It has been estimated that sepsis occurred in 2% of hospitalized patients in the United States in 2008, and incidence is expected to increase further in the future, with an even higher incidence in developing countries.[2] The risk of dying from sepsis has decreased in recent decades, owing to earlier detection and more effective treatment.[3] Although more patients survive sepsis and are increasingly discharged from the hospital,[4] they often experience functional disability, cognitive impairment, and psychiatric morbidity,[5,6] resulting in diminished health-related quality of life,[7] increased health care costs,[8,9] and burden on patients and their families.[7,10]

Many survivors of sepsis have multiple medical comorbidities that are typically managed in primary care. Yet interventions for managing sepsis sequelae in primary care have not been developed.[5,11] A systematic review of outpatient interventions for patients surviving critical illnesses showed heterogeneous and small effects on clinical outcomes such as depression and symptoms of posttraumatic stress disorder (PTSD).[12] Studies with post-intensive care unit (ICU) follow-ups of 6 months or more are rare.[7]

The purpose of this randomized clinical trial was to assess whether a primary care-based intervention[13] would improve mental health–related quality of life among survivors of sepsis compared with usual care.

Methods

Study Design and Population

A multicenter, unblinded, 2-group randomized clinical trial was performed. The institutional review board of the Jena University Hospital approved the study protocol (protocol available in Supplement 1). All patients and primary care physicians (PCPs) in the study provided written informed consent. Serious adverse events were reported to a data and safety monitoring board. Patients were recruited in 9 ICU study centers across Germany between February 2011 and December 2013. Follow-up assessments were completed in December 2014. Patients were eligible for inclusion if they were adult (≥18 years) survivors of severe sepsis, (now defined as "sepsis"[14]) or septic shock and fluent in the German language.

Clinical diagnoses of sepsis were made by intensivists according to *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes (R65.1/R57.2) and American College of Chest Physicians/Society of Critical Care Medicine consensus criteria.[15] Baseline interviews of patients were conducted by the study team within 1 month of ICU discharge. The key exclusion criterion was cognitive impairment, as determined by the Telephone Interview of Cognitive Status (score ≤27).[16] After determining patient eligibility, the study team invited each patient's PCP to participate in the trial.

Randomization was stratified by ICU study centers and performed using computer-generated random permutated blocks (block size range, 2-6) provided by an independent center for clinical trials at the University of Leipzig.

Intervention

The intervention was based on the chronic care model.[17] Its core components included case management focusing on proactive patient symptom monitoring, clinical decision support for the PCP, and training for both patients and their PCPs in evidence-based care. Three nurses with ICU experience were trained as outpatient case managers for survivors of sepsis in an 8-hour workshop. The training included information on sepsis sequelae, communication skills, telephone monitoring, and behavioral activation of patients that included goal setting (Sepsis Case Manager Manual in Supplement 2). Each case manager worked with 38 to 65 patients, starting with a 60-minute face-to-face training on sepsis sequelae (Sepsis Help Book in Supplement 2) that took place a median of 8 days after ICU discharge (interquartile range [IQR], 2-20). This was followed by monthly telephone contact for 6 months, then once every 3 months for the final 6 months. Case managers monitored patients' symptoms using validated screening tools (Sepsis Monitoring Checklist in Supplement 2) to assess critical illness polyneuropathy/myopathy, wasting, neurocognitive deficits, PTSD, depressive and pain symptoms, as well as patient self-management behaviors focusing on physical activity and individual self-management goals. Each case manager reported results to 1 of 3 assigned consulting physicians (medical doctors with background in primary and critical care), who supervised the case managers and provided clinical decision support to the PCPs using a structured written report that included the Sepsis Monitoring Checklist (Supplement 2; eFigure 3 in Supplement 3). The reports were stratified by urgency using a traffic-light scheme: red signified "immediate intervention recommended"; yellow, "intervention should be considered"; and green, "acceptable clinical status." Evidence-based sepsis aftercare training for the patients' PCPs was provided in person on an individual basis by the consulting physicians (Sepsis PCP Manual in Supplement 2). Intervention delivery was considered to have high integrity if the training was delivered both to patients and to PCPs and the patient was monitored 5 or more times.

Patients in the control group received care as usual from their PCPs without additional information or monitoring. Usual sepsis aftercare included periodic contacts, referrals to specialists, and prescription of medication and therapeutic aids at quantities comparable with those for other populations with multiple chronic conditions.[18] In Germany, most primary care practices are privately operated by 1 or 2 PCPs, with limited access to specialist care.[19] There are no outpatient postsepsis/ICU follow-up clinics or national treatment guidelines for sepsis aftercare in Germany.

Baseline Data and Outcomes

Baseline data were collected at in-person interviews with patients while they were still hospitalized. Further clinical data were obtained from their ICU records. Since the majority of patients remained hospitalized and incapacitated, baseline data collection of activities of daily living (ADL), physical function, and insomnia was not feasible.

The primary outcome was change in mental health–related quality of life between ICU discharge and 6 months after

ICU discharge, as assessed by the Mental Component Summary (MCS) score of the 36-Item Short Form Health Survey (SF-36 [range, 0-100; higher scores indicate lower levels of impairment[20]]). The SF-36 consists of 8 subscores and is valid and reliable in both post-ICU discharge[21] and German primary care populations.[22]

Secondary outcomes at 6 months were derived from (1) the other SF-36 scales (range, 0-100; higher scores indicate lower levels of impairment); (2) overall survival; (3) mental health outcomes, including the Major Depression Inventory (range, 0-50; higher scores indicate greater impairment[23]), the Posttraumatic Symptom Scale (range, 10-70; higher scores indicate greater impairment[24]), and the Telephone Interview of Cognitive Status (range, 0-50; higher scores indicate greater impairment[16]); (4) functional outcomes including ADL (range, 0-11; higher scores indicate lower levels of impairment[25]), the Extra Short Musculoskeletal Function Assessment regarding physical function (XSFMA-F) and disability (XSMFA-B [range for both, 0-100; higher scores indicate greater impairment[26]), the Graded Chronic Pain Scale including a Disability Score and Pain Intensity (range, 0-100; higher scores indicate greater impairment[27]), the Neuropathy Symptom Score (range, 0-10; higher scores indicate greater impairment[28]), the Malnutrition Universal Screening Tool (range, 0-2; higher scores indicate greater impairment[29]) including body mass index,[30] and the Regensburg Insomnia Scale (range 0-40; higher scores indicate greater impairment[31]).

Process-related outcomes included the Patient Assessment of Care for Chronic Conditions (range, 0-10; higher scores indicate lower levels of impairment)[32,33] and measures of medication adherence, the modified Morisky questionnaire (range 1-5; higher scores indicate greater impairment,[34] and the Short Form for Medication Use (range, 0-12; higher scores indicate greater impairment.[35] In addition, process-related data from PCP documentation were derived, including PCP contacts (No.), referrals to specialists (No.), level of nursing, inability to work (days), remedies and therapeutic aids (No.), and length of stay in the hospital and rehabilitation clinic (days). All 31 secondary outcomes prespecified in the statistical analysis plan (Supplement 4) are reported in eTables 2-8 in Supplement 3.

In addition, we also included as secondary outcomes all of the above measured at 12 months after ICU discharge. Outcome assessment was conducted by nonblinded assessors by telephone.

Initially, the MCS as well as the Physical Component Summary score of the SF-36 were chosen for primary outcome to provide a multicomponent score reflecting health-related quality of life (as noted in the study protocol[13] and the ISRCTN registration). However, based on review of the literature[12] highlighting the importance of mental health outcomes in post-ICU care, the primary outcome was specified to the MCS.

Statistical Analysis

The aim of the study was to detect a difference at 6 months of 5 points or more in mean MCS scores, since this amount of change is thought to be clinically meaningful.[22] A common standard deviation of 10 was assumed on the basis of a typical German population with acute and chronic diseases.[36] At a 2-sided significance level of $\alpha = .05$, a total of $2 \times 86 = 172$ patients were required to detect the above-mentioned effect with a power of 90%. Allowing for an additional approximately 40% for dropouts and mortality, an initial sample size of 287 was required.

The confirmatory test for the primary outcome was the Welch *t* test for independent groups, which was run in the intention-to-treat population. The confirmatory analyses did not consider intrapractice clustering because 155 (96.9%) of intervention practices and 141 (95.1%) of control practices included only 1 patient. The effect clustering and missing values were explored using, for example, linear mixed models and imputations by regression models. Details on methods and results of exploratory sensitivity analyses are provided in the eMethods in Supplement 3.

All secondary outcome analyses were exploratory and not adjusted for multiple tests. These analyses were performed using the *t* test, Fisher exact test, and the Wilcoxon-Mann-Whitney test, as appropriate. Overall survival was estimated using the Kaplan-Meier method, with study groups compared using the log-rank test. A confirmatory and exploratory 2-sided significance level of $\alpha = .05$ was applied, and effect size estimates with 95% confidence intervals were reported.

All statistical analyses were performed using R version 3.2.3 (R Project for Statistical Computing).[37]

Results

Baseline Characteristics

A total of 361 patients were eligible, of which 291 (80.6%) agreed to participate, with 148 patients randomized to the intervention and 143 patients to the control group (**Figure**). Overall, baseline characteristics were well balanced (**Table**). The mean age of the cohort was 61.6 years (SD, 14.4); 244 patients (84.4%) received mechanical ventilation, and the median ICU length of stay was 26 days (IQR, 13-46). Mental health–related quality of life was close to that of the normal population (mean MCS score, 49.0 [SD, 12.5]), physical health–related quality of life was low (mean SF-36 [Physical Component Summary] score, 25.3 [SD, 8.8]); 68 of 281 (24.2%) had substantial depressive symptoms, 41 of 281 (14.6%) reported substantial PTSD symptoms, and 54 of 276 (19.6%) indicated severe pain (Table). Among the entire cohort, 164 of 277 (59.2%) reported neuropathic symptoms.

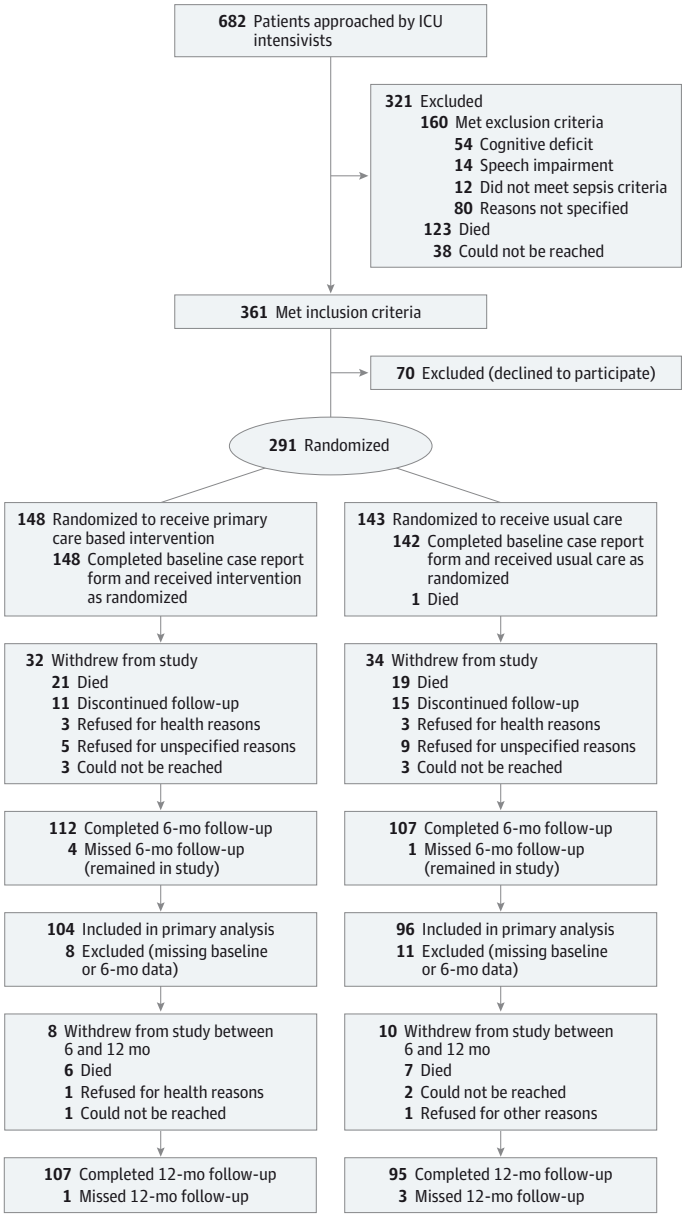
Follow-up

All included 291 patients were cared for by 159 intervention PCPs and 148 control PCPs. Because of some patient-initiated PCP changes, the number of PCPs was slightly larger than the number of patients (eMethods in Supplement 3). Among the 307 assigned PCPs, 294 (95.8%) were willing to participate. Loss to follow-up due to withdrawal or nonresponse totaled 66 patients (22.7%) at 6 months and an additional 18 patients (6.2%) at 12 months after ICU discharge and was evenly distributed across study groups (Figure).

Intervention Delivery

Of the 148 patients assigned to the intervention, 130 (87.8%) received patient training from case managers; 125 (84.5%) of

Figure. CONSORT Flow Diagram of Patient Recruitment and Retention During the Study



ICU indicates intensive care unit.

their PCPs received training from a consulting physician. There was a mean gap of 62.38 days (IQR, 36-99) between ICU discharge and PCP training, caused by the wide range of patient clinical courses. One hundred-four patients (70.3%) in the intervention group received the planned intervention at high levels of intervention integrity (eFigure 2 in Supplement 3). Incomplete intervention was usually attributable to death of the patient (24 [54%] of those with fewer than 5 monitoring calls). Reduction of motor function (204 [27.1%]) and pain intensity (201 [27.2%]) were the postsepsis symptoms most rated "red" (ie, "immediate intervention recommended") in all 756 structured monitoring reports (eTable 10 in Supplement 3).

No adverse events related to the intervention were reported.

Primary Outcome

There was no significant difference between groups in the primary outcome: The mean change MCS score was 3.79 score points (95% CI, 1.05 to 6.54) for the intervention group and 1.64 score points (95% CI, 1.22 to 4.51) for the control group, leading to a mean treatment effect of 2.15 (95% CI, −1.79 to 6.09); P = .28; baseline mean, 49.1 for intervention vs 49.3 for control; 6-month mean, 52.9 for intervention vs 51.0 for control (all data related to n = 200 patients [n = 104 intervention, n = 96 control]), with both MCS scores available at baseline and 6 months; due to rounding, change scores presented may not add up precisely). These results were unchanged in several sensitivity analyses (eTable 1 in Supplement 3).

Table. Baseline Characteristics

Characteristic	All (N = 290)	Intervention (n = 148)	Control (n = 142)	Not Available	
				Intervention	Control
Sociodemographics					
Age, mean (SD), y	61.6 (14.4)	62.1 (14.1)	61.2 (14.9)	0	0
Men, No. (%)	192 (66.2)	105 (70.9)	87 (61.3)	0	0
Married, No. (%)	148 (52.1)	84 (57.9)	64 (46.0)	3	3
Educational status <high school, No. (%)	98 (34.0)	54 (36.7)	44 (31.1)	1	1
Care Measures					
Recent surgical history, No. (%)				2	1
Emergency	106 (36.8)	49 (33.6)	57 (40.1)		
Elective	62 (21.5)	34 (23.3)	28 (19.7)		
No history	73 (25.3)	39 (26.7)	34 (23.9)		
Source of infection, No. (%)					5
Community acquired	102 (36.0)	54 (37.2)	48 (34.8)		
Nosocomial					
ICU or intermediate care	139 (49.1)	70 (48.3)	69 (50.0)		
General ward or nursing home	42 (14.8)	21 (14.5)	21 (15.2)		
ICU length of stay, d				16	11
Mean (SD)	34.4 (27.2)	31.5 (27.7)	35.2 (26.7)		
Median (IQR)	26 (4-27)	23 (4-26)	29 (5-28)		
Mechanical ventilation, No. (%)	244 (84.4)	121 (82.3)	123 (86.6)	1	1
If applicable, d				5	4
Mean (SD)	18.5 (19.2)	17.0 (17.5)	19.9 (20.7)		
Median (IQR)	12 (4-27)	10 (4-26)	14 (5-28)		
Renal replacement therapy, No. (%)	82 (28.5)	43 (29.3)	39 (27.7)	1	2
If applicable, d				5	5
Mean (SD)	12.3 (13.2)	11.9 (13.7)	12.8 (12.8)		
Median (IQR)	8 (4-15)	7 (4-14)	8 (5-16)		
Clinical Measures					
Charlson Comorbidity Index, mean (SD)[a]	4.0 (2.9)	4.0 (3.0)	4.0 (2.9)	1	1
ICD-10 diagnoses, No.				6	7
Median	9	9	10		
Mean (SD)	10.1 (4.7)	9.6 (4.4)	10.6 (5.1)		
BMI, mean (SD)	27.3 (6.0)	27.3 (6.0)	27.3 (5.9)	3	9
Depression				3	6
MDI, mean (SD)[b]	18.1 (10.0)	18.4 (9.8)	17.8 (10.1)		
Depressive symptoms, No. (%)	68 (24.2)	36 (24.8)	32 (23.5)		
PTSD				3	6
PTSS-10, mean (SD)[c]	23.6 (10.4)	24.0 (11.0)	23.2 (9.7)		
Score >35, No. (%)	41 (14.6)	22 (15.2)	19 (14.0)		
TICS-M, mean (SD)[d]	33.4 (3.6)	33.7 (3.4)	33.1 (3.9)	1	0
Neuropathic symptoms				4	9
NSS, mean (SD)[e]	3.6 (3.2)	3.6 (3.3)	3.7 (3.1)		
Score 3-10, No. (%)	164 (59.2)	83 (57.6)	81 (60.9)		
Pain					
Intensity: GCPS PI, mean (SD)[f]	43.8 (24.4)	43.7 (25.6)	43.9 (23.1)	5	9
Disability: GCPS DS, mean (SD)[f]	36.2 (34.6)	36.0 (34.5)	36.4 (34.8)	7	12
Severe pain: GCPS category >1, No. (%)	54 (19.6)	26 (18.2)	28 (21.0)	5	9
Health-Related Quality of Life, Mean (SD)[g]					
SF-36				12	15
MCS	49.0 (12.5)	48.8 (12.5)	49.2 (12.6)		
PCS	25.3 (8.8)	25.9 (9.4)	24.7 (8.0)		

Abbreviations: BMI, body mass index; GCPS DS, Graded Chronic Pain Scale Disability Score; GCPS PI, Graded Chronic Pain Scale Pain Intensity; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ICU, intensive care unit; MDI, Major Depression Inventory; NSS, Neuropathic Symptom Score; PTSD, Posttraumatic Stress Disorder; PTSS, Posttraumatic Symptom Scale; SF-36 MCS, Short Form 36 Health Survey Mental Component Score; SF-36 PCS, Short Form 36 Health Survey Physical Component Score; TICS-M, modified Telephone Interview for Cognitive Status.

[a] Range of possible scores, 0-37. High score indicates high impairment.

[b] Range of possible scores, 0-50. High score indicates high impairment.

[c] Range of possible scores, 10-70. High score indicates high impairment.

[d] Range of possible scores, 0-50; includes only values greater than 27 (inclusion criterion). High score indicates low impairment.

[e] Range of possible scores, 0-10. High score indicates high impairment.

[f] The range of possible scores is 0-100. High score indicates high impairment.

[g] Range of possible scores, 0-100. High score indicates low impairment.

Secondary Outcomes

A total of 63 secondary outcomes were analyzed at both 6 and 12 months (including the 12-month MCS score).

A respective 28 (6 months) and 30 (12 months) outcomes did not show significant differences (at an uncorrected α = .05) between both groups, including physical health-related quality of life and mental health outcomes (eTable 2 and eTable 3 in Supplement 3). Overall mortality was 13.7% (n = 40) at 6 months after ICU discharge and 18.2% (n = 53) at 12 months after ICU discharge (eFigure 1 in Supplement 3). If any, potential intervention effects were observed in measures of functional outcomes only: at 6 months, sepsis survivors receiving the intervention had better physical functioning (mean XSFMA-F score, 38.0 [95% CI, 32.5 to 43.5] vs 46.9 [95% CI, 40.9 to 52.9]; *P* = .04; difference, −8.9 [95% CI, −17.02 to −0.78]), less physical disability (mean XSFMA-B score, 42.5 [95% CI, 36.6 to 48.4] vs 52.4 [95% CI, 46.2 to 58.7]; *P* = .03; difference, −9.9 [95% CI, −18.49 to −1.31]), and fewer ADL impairments (mean, 8.6 [95% CI, 8.0 to 9.1] vs 7.6 [95% CI, 7.0 to 8.2]; *P* = .03; difference, 1.0 [95% CI, 0.16 to 1.84]) than usual care. After adjusting for prespecified baseline covariates, these potential effects were persistent. In addition, survivors of sepsis receiving the intervention had potentially fewer sleep impairments at 12 months after ICU discharge than controls (mean Regensburg Insomnia Scale score, 10.3 [95% CI, 9.2 to 11.4] vs 12.1 [95% CI, 10.8 to 13.4]; difference, −1.8 [95% CI, −3.5 to −0.10]).

In addition, the PCP documentation data at 6 and 12 months provided no evidence for group differences in PCP care (eTable 8 in Supplement 3).

Discussion

Among survivors of sepsis, a primary care–based intervention, compared with usual care, did not improve mental health-related quality of life.

To our knowledge, this is the first large-scale, randomized controlled clinical trial of an intervention to improve outcomes in survivors of sepsis in primary care.

This sample of survivors of sepsis had similar mean ages and rates of existing comorbidities as compared with other cohorts.[38,39] The prevalence of depressive and PTSD symptoms was slightly less than that among other populations of survivors of critical illness,[40,41] whereas neuropathic symptoms and severe pain were more frequent.[42,43] Physical function, as measured by the SF-36 Physical Function subscore, was substantially lower than in the German population (mean, 85.71 [SD, 22.1]; n = 2886)[36] and also lower than in some comparable cohorts[44,45] and intervention studies.[46,47] Thus, patients may have been more sensitive to the intervention's focus on increasing motivation to be physically active.

Study patients were exposed to longer durations of mechanical ventilation and ICU length of stay than reported in other studies.[4] ICU length of stay and duration of mechanical ventilation were shown to generally be longer in Europe than in the United States, especially in survivors of sepsis.[48,49] In addition, extensive ICU length of stay may have facilitated patient identification by the intensivists.

There was no evidence for a differential treatment effect on the study's primary outcome, postsepsis MCS scores. This finding is similar to those from previous trials of care management interventions following critical illness.[12,46,47,50] The absence of an intervention effect on the primary and most secondary outcomes can be considered using the PICO (Population, Intervention, Controls, Outcome) frameworks.[51]

Population

The studied cohort experienced heterogeneous clinical multiple conditions. This primary care–based intervention may not have been sufficiently focused to address all their diverse medical and psychological needs.[52] Future trials may evaluate interventions in different patient subgroups targeting specific postsepsis sequelae. Larger samples should be included to address smaller but potentially still clinically relevant effects of primary care interventions.

Intervention

The exploratory analyses indicated no intervention effects on mental health symptoms. These results may reflect lack of intervention intensity and specificity or absence of clinically effective interventions. However, there is growing evidence that after critical illness, mental health outcomes can be improved through effective psychological interventions targeting specific syndromes.[52,53]

Controls

According to process data derived from control PCPs (eTable 8 in the Supplement), usual sepsis aftercare in Germany seems to be highly intensive. PCP training and consultation may have been insufficient to yield a meaningful improvement in the level of care. Observational research may provide more insights into existing usual sepsis aftercare in diverse health care systems.

Outcome

The wide range of postsepsis sequelae may not be adequately reflected in a rather global outcome measure, such as change in SF-36 MCS score. Furthermore, the cohort's baseline mental health-related quality of life was similar to healthy population norms in Germany, reflecting a limited potential for improvement in the MCS score. Last, the exclusion of patients with more severe cognitive dysfunction may have led to a ceiling effect compared with other trials. For future trials, more specific primary outcomes should be considered.

Up to years after the ICU discharge, many patients seem to share their needs with a reliable medical professional.[54] Yet the PCP is not involved systematically in post-ICU care.[55,56] This study may shed light on PCP relevance, addressing major concerns recently identified as "barriers to practice."[57] These include checks on transition from ICU through to community reintegration, linkage, and clinical decision support to primary care, inclusion of a case manager, and educational information for patients and PCPs. Compared with the large-scale PRACTICAL trial on follow-up care in ICU clinics,[47] this study defines a clear

function for the PCP in sepsis aftercare. Follow-up care combining specialized ICU clinics and integrated PCPs may improve outcomes.

This study's exploratory findings suggest possible improvements of physical function and ADL impairments. Additional research is needed to confirm these results. Possible mechanisms of action for these findings may include increased patient motivation (despite the presence of pain) to partake in physical activity owing to regular case manager telephone calls with goal-setting and basic behavioral activation. Increased PCP supportiveness in the intervention group may also have motivated patients to be more proactive, possibly reflected by the increased rating in number of Patient Assessment of Care for Chronic Conditions items (eTable 9 in Supplement 3).

This study has strengths and limitations. It was possible to enroll a large number of patients in spite of the challenges of recruiting critically ill patients for research.[58] Intervention integrity went as planned[59] (eFigure 2 in Supplement 3), including the acceptance of an external medical consultant by the patient's PCP. These findings are encouraging for further interventions in the primary care setting.

Loss to follow-up was balanced between the groups and low, in contrast to sample size calculations that allowed for 40% dropout. Baseline values were missing for some secondary outcomes owing to patients' severely impaired clinical condition. A carryover effect (from treatment to control) may have occurred for 1 PCP, inducing a bias toward a null effect. Calling control patients to collect follow-up data may have led to an intervention effect, possibly leading to underestimation of the intervention effects.[60] In addition, nonblinded outcome assessments also may have biased the results.[61] The intervention is not generalizable to all survivors of sepsis in various outpatient settings.

Conclusions

Among survivors of sepsis or septic shock, the use of a primary care–focused team-based intervention, compared with usual care, did not improve mental health–related quality of life 6 months after ICU discharge. Further research is needed to determine if modified approaches to primary care management may be more effective.

ARTICLE INFORMATION

Author Affiliations: Institute of General Practice and Family Medicine, Jena University Hospital, Jena, Germany (Schmidt, Worrack, Mehlhorn, Schneider, Freytag, Wensing, Gensichen); Center of Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany (Schmidt, Worrack, Brunkhorst, Pausch, Scherag, Reinhart, Gensichen); Group Health Research Institute, Group Health Cooperative, Seattle, Washington (Von Korff); Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle (Davydow); Center of Clinical Studies, Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany (Brunkhorst); Department of Psychology, University of Zuerich, Zuerich, Switzerland (Ehlert); Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany (Pausch); Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany (Reinhart); Department of General Practice and Health Services, University of Heidelberg Hospital, Heidelberg, Germany (Wensing).

Author Contributions: Drs Schmidt and Gensichen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schmidt, Davydow, Brunkhorst, Ehlert, Freytag, Reinhart, Wensing, Gensichen.
Acquisition, analysis, or interpretation of data: Schmidt, Worrack, Von Korff, Pausch, Mehlhorn, Schneider, Scherag, Reinhart, Wensing, Gensichen.
Drafting of the manuscript: Schmidt, Davydow, Schneider, Scherag, Wensing, Gensichen.
Critical revision of the manuscript for important intellectual content: Schmidt, Worrack, Von Korff, Davydow, Brunkhorst, Ehlert, Pausch, Mehlhorn, Freytag, Reinhart, Wensing, Gensichen.
Statistical analysis: Schmidt, Worrack, Pausch, Schneider, Scherag, Freytag, Wensing, Gensichen.
Obtained funding: Reinhart, Gensichen.
Administrative, technical, or material support: Worrack, Brunkhorst, Mehlhorn, Schneider, Freytag, Gensichen.
Study supervision: Schmidt, Davydow, Brunkhorst, Ehlert, Scherag, Wensing, Gensichen.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Von Korff reported serving as principal investigator on grants from Pfizer to Group Health Research Institute for research on prescription opioids, outside the submitted work. Dr Pausch reported receiving a grant from the German Federal Ministry of Education and Research. Dr Scherag reported receiving a grant from the German Federal Ministry of Education and Research. Dr Reinhart reported receiving personal fees from Adrenomed and that he holds shares in InflaRx. Dr Wensing reported receiving a grant from the Department of General Practice, University of Jena. Dr Gensichen reported receiving personal fees from The Primary Health Care Foundation and receiving a grant from the German Federal Ministry of Education and Research. No other authors reported disclosures.

SMOOTH Study Group: The authors and Anne Bindara-Klippel, Carolin Fleischmann, MD, Ursula Jakobi, MD, Susan Kerth, Heike Kuhnsch, Friederike Mueller, MD, Mercedes Schelle, Paul Thiel, MD (Institute of General Practice and Family Medicine, Jena University Hospital); Mareike Baenfer, Sabine Gehrke-Beck, MD, Christoph Heintze, MD (Charité University Medicine Berlin); Andrea Geist, Torsten Schreiber, MD (Zentralklinik Bad Berka); Christian Berhold, MD, Marcel Corea, MD, Adrian Freytag, MD, Herwig Gerlach, MD, MBA, Rainer Kuehnemund, MD, Josefa Lehmke, MD, Peter Lehmkuhl, MD, Lorenz Reil, MD, Guenter Tiedemann, MD, Susanne Toissaint, MD, Siegfried Veit, MD (Vivantes Clinics Berlin); Anton Goldmann, MD, Michael Oppert, MD, Didier Keh, MD, Sybille Rademacher, MD, Claudia Spies, MD, Lars Toepfer, MD (Charite University Medicine Berlin); Frank Klefisch, MD (Paulinen Hospital Berlin); Ute Rohr, MD, Hartmut Kern, MD (DRK Clinics Berlin); Armin Sablotzki, MD (St Georgs Hospital Leipzig); Frank Oehmichen, MD, Marcus Pohl, MD (Bavaria Clinic Kreischa); Andreas Meier-Hellmann, MD (Helios Clinic Erfurt); Farsin Hamzei, MD (Moritz-Clinic Bad Klosterlausnitz); Christoph Engel, MD (Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig); Michael Hartmann, MBA, MPH, Christiane Hartog, MD (Jena University Hospital); Jürgen Graf, MD (University Clinic Frankfurt); Günter Ollenschlaeger, MD, PhD (ÄZQ Berlin); Gustav Schelling, MD (University Clinic LMU Munich).

Funding/Support: The study was supported by the Center for Sepsis Control and Care (CSCC), funded by the German Federal Ministry of Education and Research (grant 01 EO 1002) and the German Sepsis Society. Dr Davydow is supported by the National Institutes of Health (grant KL2 TR000421). Dr Brunkhorst is supported by the Thuringian Ministry of Education, Science and Culture (grant PE 108-2) and the Thuringian Foundation for Technology, Innovation and Research.

Role of the Funder/Sponsor: The funding organizations are public institutions and had no role in the design and conduct of the study; collection, management, and analysis of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication.

REFERENCES

1. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(21):2063.

2. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief*. 2011;(62):1-8.

3. Iwashyna TJ, Angus DC. Declining case fatality rates for severe sepsis: good data bring good news with ambiguous implications. *JAMA*. 2014;311(13):1295-1297.

4. 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(13):1308-1316.

5. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794.

6. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. *Am J Geriatr Psychiatry*. 2013;21(9):887-897.

7. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.

8. Goodwin AJ, Rice DA, Simpson KN, Ford DW. Frequency, cost, and risk factors of readmissions among severe sepsis survivors. *Crit Care Med*. 2015;43(4):738-746.

9. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA*. 2015;313(10):1055-1057.

10. Lee H, Doig CJ, Ghali WA, Donaldson C, Johnson D, Manns B. Detailed cost analysis of care for survivors of severe sepsis. *Crit Care Med*. 2004;32(4):981-985.

11. McGovern M, McGovern C, Parker R. Survivors of critical illness: victims of our success? *Br J Gen Pract*. 2011;61(593):714-715.

12. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. *Crit Care Med*. 2014;42(5):1263-1271.

13. Schmidt K, Thiel P, Mueller F, et al; Smooth Study Group. Sepsis survivors monitoring and coordination in outpatient health care (SMOOTH): study protocol for a randomized controlled trial. *Trials*. 2014;15(1):283.

14. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.

15. Bone RC, Balk RA, Cerra FB, et al; The ACCP/SCCM Consensus Conference Committee, American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101(6):1644-1655.

16. de Jager CA, Budge MM, Clarke R. Utility of TICS-M for the assessment of cognitive function in older adults. *Int J Geriatr Psychiatry*. 2003;18(4):318-324.

17. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q*. 1996;74(4):511-544.

18. van den Bussche H, Schön G, Kolonko T, et al. Patterns of ambulatory medical care utilization in elderly patients with special reference to chronic diseases and multimorbidity—results from a claims data based observational study in Germany. *BMC Geriatr*. 2011;11:54.

19. Zentralinstitut für die kassenärztliche Versorgung in Deutschland. ZI-Praxis-Panel: Jahresbericht 2012—Wirtschaftliche Situation und Rahmenbedingungen in der vertragsärztlichen Versorgung der Jahre 2008 bis 2010. https://www.zi-pp.de/pdf/ZiPP_Jahresbericht_2012.pdf. Accessed March 24, 2015.

20. Ware JE, Snow KK, Kosinski M. *SF-36 Version 2 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: Quality Metric Inc; 2000.

21. Chrispin PS, Scotton H, Rogers J, Lloyd D, Ridley SA. Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. *Anaesthesia*. 1997;52(1):15-23.

22. Bullinger M; International Quality of Life Assessment. German translation and psychometric testing of the SF-36 Health Survey: preliminary results from the IQOLA Project. *Soc Sci Med*. 1995;41(10):1359-1366.

23. Cuijpers P, Dekker J, Noteboom A, Smits N, Peen J. Sensitivity and specificity of the Major Depression Inventory in outpatients. *BMC Psychiatry*. 2007;7:39.

24. Stoll C, Kapfhammer HP, Rothenhäusler HB, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. *Intensive Care Med*. 1999;25(7):697-704.

25. Fonda S, Herzog AR. *HRS/AHEAD Documentation Report: Documentation of Physical Functioning Measured in the Heath and Retirement Study and the Asset and Health Dynamics Among the Oldest Old Study*. Ann Arbor, MI: Survey Research Center, University of Michigan; 2004.

26. Wollmerstedt N, Kirschner S, Böhm D, Faller H, König A. Design and evaluation of the Extra Short Musculoskeletal Function Assessment Questionnaire XSMFA-D [in German]. *Z Orthop Ihre Grenzgeb*. 2003;141(6):718-724.

27. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133-149.

28. Haslbeck M, Luft D, Neundörfer B, Stracke H, Hollenrieder V, Bierwirth R. Diabetische Neuropathie. *Diabetologie*. 2007;2(suppl 2):150-156.

29. Marinos E; British Association for Parenteral and Enteral Nutrition (BAPEN). The"MUST" Report: Nutritional Screening for Adults: A Multidisciplinary Responsibility. BAPEN website. http://www.bapen.org.uk/pdfs/must/must_exec_sum.pdf., 2003.

30. Garrouste-Orgeas M, Troché G, Azoulay E, et al. Body mass index: an additional prognostic factor in ICU patients. *Intensive Care Med*. 2004;30(3):437-443.

31. Crönlein T, Langguth B, Popp R, et al. Regensburg Insomnia Scale (RIS): a new short rating scale for the assessment of psychological symptoms and sleep in insomnia; study design: development and validation of a new short self-rating scale in a sample of 218 patients suffering from insomnia and 94 healthy controls. *Health Qual Life Outcomes*. 2013;11:65.

32. Rosemann T, Laux G, Droesemeyer S, Gensichen J, Szecsenyi J. Evaluation of a culturally adapted German version of the Patient Assessment of Chronic Illness Care (PACIC 5A) questionnaire in a sample of osteoarthritis patients. *J Eval Clin Pract*. 2007;13(5):806-813.

33. Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med Care*. 2005;43(5):436-444.

34. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.

35. Watzl H, Rist S, Höcker W, Miehle K. Entwicklung eines Fragebogens zum Medikamentenmißbrauch bei Suchtpatienten. In: Heide N, Lieb H, eds. *Sucht und Psychosomatik*. Bonn: Fachverbandes Sucht e.V.; 1991.

36. Bullinger M, Kirchberger I. *SF36 Fragebogen zum Gesundheitszustand: Handanweisungen*. Göttingen, Bern: Hogrefe Verlag für Psychologie; 1998.

37. R Core Team. R: A language and environment for statistical computing. R Project for Statistical Computing website. http://www.r-project.org/. Accessed May 21, 2015.

38. Karlsson S, Varpula M, Ruokonen E, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med*. 2007;33(3):435-443.

39. Hofhuis JG, Spronk PE, van Stel HF, Schrijvers AJ, Rommes JH, Bakker J. The impact of severe sepsis on health-related quality of life: a long-term follow-up study. *Anesth Analg*. 2008;107(6):1957-1964.

40. Davydow DS, Zatzick D, Hough CL, Katon WJ. A longitudinal investigation of posttraumatic stress and depressive symptoms over the course of the year following medical-surgical intensive care unit admission. *Gen Hosp Psychiatry*. 2013;35(3):226-232.

41. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Crit Care Med*. 2015;43(5):1121-1129.

42. Marx G, Zimmer A, Rothaug J, Mescha S, Reinhart K, Meissner W. Chronic pain after surviving sepsis. *Crit Care*. 2006;10(suppl 1):421.

43. Griffiths J, Fortune G, Barber V, Young JD. The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review. *Intensive Care Med*. 2007;33(9):1506-1518.

44. Battle CE, Davies G, Evans PA. Long term health-related quality of life in survivors of sepsis in South West Wales: an epidemiological study. *PLoS One*. 2014;9(12):e116304.

45. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis: Short Form 36: a valid and reliable measure of health-related quality of life. *Crit Care Med*. 2000;28(11):3599-3605.

46. Elliott D, McKinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Crit Care*. 2011;15(3):R142.

47. Cuthbertson BH, Rattray J, Campbell MK, et al; PRaCTICaL Study Group. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ*. 2009;339:b3723.

48. Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med*. 2007;33(4):606-618.

49. Levy MM, Artigas A, Phillips GS, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. *Lancet Infect Dis*. 2012; 12(12):919-924.

50. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chronically critically ill patients: health-related quality of life and resource use after a disease management intervention. *Am J Crit Care*. 2007;16(5):447-457.

51. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995; 123(3):A12-A13.

52. Jackson JC, Ely EW, Morey MC, et al. Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Crit Care Med*. 2012; 40(4):1088-1097.

53. Jones C, Bäckman C, Capuzzo M, et al; RACHEL Group. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care*. 2010;14(5): R168.

54. Czerwonka AI, Herridge MS, Chan L, Chu LM, Matte A, Cameron JI. Changing support needs of survivors of complex critical illness and their family caregivers across the care continuum: a qualitative pilot study of Towards RECOVER. *J Crit Care*. 2015;30(2):242-249.

55. Van Der Schaaf M, Bakhshi-Raiez F, Van Der Steen M, Dongelmans DA, De Keizer NF. Recommendations for intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. *Minerva Anestesiol*. 2015;81 (2):135-144.

56. Egerod I, Risom SS, Thomsen T, et al. ICU-recovery in Scandinavia: a comparative study of intensive care follow-up in Denmark, Norway and Sweden. *Intensive Crit Care Nurs*. 2013; 29(2):103-111.

57. Elliott D, Davidson JE, Harvey MA, et al. Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. *Crit Care Med*. 2014;42(12): 2518-2526.

58. Burns KE, Zubrinich C, Tan W, et al; Canadian Critical Care Trials Group. Research recruitment practices and critically ill patients: a multicenter, cross-sectional study (the Consent Study). *Am J Respir Crit Care Med*. 2013;187(11):1212-1218.

59. Thomas BH, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs*. 2004;1(3):176-184.

60. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne effect: a randomised, controlled trial. *BMC Med Res Methodol*. 2007;7:30.

61. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. *BMJ*. 2000;321 (7259):504.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure
A Randomized Clinical Trial

Peter E. Morris, MD; Michael J. Berry, PhD; D. Clark Files, MD; J. Clifton Thompson, RN; Jordan Hauser, MS; Lori Flores, RN; Sanjay Dhar, MD; Elizabeth Chmelo, MS; James Lovato, MS; L. Douglas Case, PhD; Rita N. Bakhru, MD, MS; Aarti Sarwal, MD; Selina M. Parry, PhD; Pamela Campbell, RN; Arthur Mote; Chris Winkelman, PhD; Robert D. Hite, MD; Barbara Nicklas, PhD; Arjun Chatterjee, MD, MS; Michael P. Young, MD

IMPORTANCE Physical rehabilitation in the intensive care unit (ICU) may improve the outcomes of patients with acute respiratory failure.

OBJECTIVE To compare standardized rehabilitation therapy (SRT) to usual ICU care in acute respiratory failure.

DESIGN, SETTING, AND PARTICIPANTS Single-center, randomized clinical trial at Wake Forest Baptist Medical Center, North Carolina. Adult patients (mean age, 58 years; women, 55%) admitted to the ICU with acute respiratory failure requiring mechanical ventilation were randomized to SRT (n=150) or usual care (n=150) from October 2009 through May 2014 with 6-month follow-up.

INTERVENTIONS Patients in the SRT group received daily therapy until hospital discharge, consisting of passive range of motion, physical therapy, and progressive resistance exercise. The usual care group received weekday physical therapy when ordered by the clinical team. For the SRT group, the median (interquartile range [IQR]) days of delivery of therapy were 8.0 (5.0-14.0) for passive range of motion, 5.0 (3.0-8.0) for physical therapy, and 3.0 (1.0-5.0) for progressive resistance exercise. The median days of delivery of physical therapy for the usual care group was 1.0 (IQR, 0.0-8.0).

MAIN OUTCOMES AND MEASURES Both groups underwent assessor-blinded testing at ICU and hospital discharge and at 2, 4, and 6 months. The primary outcome was hospital length of stay (LOS). Secondary outcomes were ventilator days, ICU days, Short Physical Performance Battery (SPPB) score, 36-item Short-Form Health Surveys (SF-36) for physical and mental health and physical function scale score, Functional Performance Inventory (FPI) score, Mini-Mental State Examination (MMSE) score, and handgrip and handheld dynamometer strength.

RESULTS Among 300 randomized patients, the median hospital LOS was 10 days (IQR, 6 to 17) for the SRT group and 10 days (IQR, 7 to 16) for the usual care group (median difference, 0 [95% CI, −1.5 to 3], P= .41). There was no difference in duration of ventilation or ICU care. There was no effect at 6 months for handgrip (difference, 2.0 kg [95% CI, −1.3 to 5.4], P= .23) and handheld dynamometer strength (difference, 0.4 lb [95% CI, −2.9 to 3.7], P = .82), SF-36 physical health score (difference, 3.4 [95% CI, −0.02 to 7.0], P= .05), SF-36 mental health score (difference, 2.4 [95% CI, −1.2 to 6.0], P = .19), or MMSE score (difference, 0.6 [95% CI, −0.2 to 1.4], P = .17). There were higher scores at 6 months in the SRT group for the SPPB score (difference, 1.1 [95% CI, 0.04 to 2.1, P = .04), SF-36 physical function scale score (difference, 12.2 [95% CI, 3.8 to 20.7], P = .001), and the FPI score (difference, 0.2 [95% CI, 0.04 to 0.4], P = .02).

CONCLUSIONS AND RELEVANCE Among patients hospitalized with acute respiratory failure, SRT compared with usual care did not decrease hospital LOS.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00976833

JAMA. 2016;315(24):2694-2702. doi:10.1001/jama.2016.7201

Editorial page 2671

Related article page 2703

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Peter E. Morris, MD, Division of Pulmonary, Critical Care and Sleep Medicine, University of Kentucky, 740 S Limestone, L-543, Kentucky Clinic, Lexington, KY 40536 (peter.morris@uky.edu).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

Acute respiratory failure is associated with high mortality and prolonged morbidity, with impaired physical function for many survivors. Interventions directed at attenuating the profound muscle wasting in patients with acute respiratory failure are patient-centered.[1] Such therapies designed to improve patient-reported weakness and impaired physical function could reduce recovery time in patients with acute respiratory failure. As well, such interventions could potentially improve long-term health-related quality of life, which for this population is commonly below normal following hospital discharge.[2-4] Reports have suggested that a rehabilitation program, delivered by an intensive care unit (ICU) rehabilitation team, may be associated with reduced length of stay (LOS) and improved physical function, although findings to the contrary exist as well.[5-11] This randomized clinical trial was designed to test the hypothesis that early delivery of a standardized, multifaceted ICU and hospital rehabilitation program would decrease hospital LOS and improve physical function for patients with acute respiratory failure.

Methods

Study Design and Oversight

The institutional review board at the enrolling hospital approved the clinical trial. Written consent was obtained from participants or their legally authorized representative. Race and ethnicity data were collected per the National Institutes of Health reporting policy and determined by patient or surrogate self-reporting based on fixed categories. The study was a single-center, assessor-blinded, randomized investigation with 2 groups: standardized rehabilitation therapy (SRT) and usual care conducted at Wake Forest Baptist Medical Center in Winston Salem, North Carolina. The SRT group received rehabilitation therapy 7 days a week, from enrollment through hospital discharge, including days spent in a regular floor bed. The usual care group received routine care as dictated by the patient's attending physician from Monday through Friday. SRT ended at hospital discharge. Both groups underwent testing at ICU and hospital discharge, and at 2, 4, and 6 months after enrollment by research personnel blinded to the randomization assignment.

Study Patients

Inclusion criteria were admission to a medical ICU, being 18 years or older, mechanical ventilation via endotracheal tube or noninvasive ventilation by mask, and an arterial oxygen partial pressure to fractional inspired oxygen (Pao_2/FIO_2) ratio less than 300. Exclusion criteria were inability to walk without assistance prior to the acute ICU illness (use of cane or walkers were not exclusions), cognitive impairment prior to acute ICU illness described by surrogate, as nonverbal, acute stroke, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 50, neuromuscular disease impairing weaning from mechanical ventilation, acute hip fracture, unstable cervical spine or pathologic fracture, mechanically ventilated more than 80 hours or current hospitalization (including transferring hospital) more than 7 days, orders for do not intubate on admission, considered to be moribund by the primary attending, or enrolled in another research study.

Randomization

Patients were randomly assigned, using a computer-generated variably sized approach (in block sizes of 2, 4, 6, or 8), to SRT or usual care.

Study Measurements and Procedures

The SRT protocol contained 3 exercise types: passive range of motion, physical therapy, and progressive resistance exercises, and was administered by a rehabilitation team for a total of 3 separate sessions every day of hospitalization for 7 days per week.[6] The team comprised a physical therapist, an ICU nurse, and a nursing assistant. Passive range of motion included 5 repetitions for each upper and lower extremity joint. Physical therapy included bed mobility, transfer training, and balance training. These exercises included transfer to the edge of the bed; safe transfers to and from bed, chair, or commode; seated balance activities; pregait standing activities (forward and lateral weight shifting, marching in place); and ambulation. Progressive resistance exercise included dorsiflexion, knee flexion and extension, hip flexion, elbow flexion and extension, and shoulder flexion. Resistance was added through the use of elastic resistance bands (TheraBand, Hygienic Corporation). Both the physical therapy and resistance training targeted lower extremity functional tasks and activities of daily living (for further details of the implementation of SRT modalities, see trial protocol in Supplement 1).

The patient's level of consciousness determined suitability for receipt of physical therapy or progressive resistance exercise, and ability to complete the exercises.[12] When patients were unconscious, the 3 sessions consisted of passive range of motion. Once the patient gained consciousness, physical therapy and progressive resistance exercise were introduced. Being free from mechanical ventilation was not a prerequisite for any of the exercise sessions. The usual care group received no rehabilitation per treatment protocol. Physical therapy could be ordered as part of routine care, but only Monday through Friday.

Study Outcomes

The primary end point was hospital LOS, defined to include hospital calendar days (or any portion of a calendar day) at the enrolling hospital and at any long-term acute care facility to which the patient was directly transferred. Research team members were not involved in the decision for hospital discharge (ie, the primary end point). Hospital floor medical teams separate from the ICU teams were responsible for hospital discharge. Study days were days of hospitalization following randomization.

Secondary outcomes included physical function and health-related quality of life. Physical function was measured using both performance-based and self-report instruments. Performance-based tests included the Short Performance Physical Battery (SPPB) and muscular strength as determined by handgrip dynamometer (Jamar, Lafayette Instrument) and from a handheld dynamometer (microFET2, Hoggan Health Industries).

SPPB scores were derived from performance of 3 components: a 4-meter walk, chair sit-to-stand, and a balance test.[13] Muscular strength of the shoulder flexors, elbow flexors and extensors, hip flexors, knee flexors and extensors, and ankle dorsiflexors was measured thrice bilaterally. The maximum values from each test were averaged to produce a single composite value of muscular strength. Self-report tests consisted of the short form Functional Performance Inventory (FPI),[14] and the physical functioning scale of the medical outcomes study 36-Item Short Form Health Survey (SF-36 PFS).[15] Health-related quality of life was measured using the SF-36 physical health survey (SF-36 PHS) and mental health survey (SF-36 MHS) component summary scores and Mini-Mental State Examination (MMSE) score. Measures of physical function were obtained at ICU discharge, hospital discharge and 2, 4, and 6 months after enrollment. Health-related quality-of-life measures were obtained at hospital discharge and 2, 4, and 6 months after enrollment. The SF-36 and the FPI were not administered at ICU discharge as they were not considered relevant to the patient at this time. The FPI was not administered at hospital discharge for the same reason. Post-hoc outcomes were the number of days that patients were alive and breathing without ventilator assistance (ventilator-free days), ICU-free and hospital-free days to day 28.[16] Adverse events were quantified by deaths, device removals, reintubations, and patient falls during physical therapy (for classification of adverse events, see trial protocol in Supplement 1).

Statistical Analysis

The initial plan was to accrue 326 participants to provide 80% power for detecting a 30% decrease in the median hospital LOS at the 5% 2-sided level of significance assuming an exponential LOS distribution, a 20% in-hospital mortality, and that 5% of the remaining patients would withdraw prior to discharge, resulting in 247 discharges.

The projected 30% decrease in the primary outcome (hospital LOS) is slightly larger than the decrease observed in a previous quality improvement report,[6] but, as described below, there was a greater expected effect with the current intervention due to a greater potential for exposure to the SRT after ICU discharge in this study. An important feature of the previous quality improvement report was that the intervention was delivered only in the ICU. Hence, the effect reported was for intervention delivered only in the ICU, not after ICU discharge. Despite the intervention being limited to the ICU, there was a 24% adjusted reduction in hospital LOS (hazard ratio [HR], 1.31). The current study design delivered the SRT from ICU admission through hospital discharge and due to the addition of progressive resistance exercise, there was a much greater clinical effect expected.

The in-hospital mortality and dropout were both less than expected and enrollment was stopped after 300 patients were accrued, 257 of whom were discharged.

Kaplan-Meier methods were used to estimate hospital LOS, and a log-rank test was used to assess the difference between groups. Patients who died or dropped out before discharge were censored in the analyses. A Cox proportional hazards regression model was used to estimate the hazard ratio. Because there were concerns that censoring (particularly from deaths) might be informative, 2 extremes were considered—assuming all the patients who died would have been discharged on the day of their death and that all the patients who died would have had the longest hospital stays. The same assumptions were made regarding the patients who simply withdrew even though there is less reason to believe that those would be informative. Analyses were repeated under the possible combinations of assumptions regarding the deaths and dropouts. For each of these scenarios, unadjusted analyses and analyses adjusted for those variables related to in-hospital death (sex, mean arterial pressure, partial pressure of carbon dioxide [$Paco_2$], Pao_2, FIo_2, and Acute Physiology and Chronic Health Evaluation [APACHE] score) were conducted. χ^2 Tests were used to assess group differences in-hospital and after discharge deaths and Wilcoxon rank-sum tests were used to assess group differences in ventilator-free and ICU-free days. Median differences of medians and 95% confidence intervals were generated using bootstrap methods with 10 000 bootstrap samples. The significance threshold was $P < .05$ for each outcome and testing was 2-sided. Due to the lack of adjustment for multiple testing, the secondary analyses should be considered exploratory. The statistical software was SAS (SAS Institute), version 9.4.

For secondary outcomes assessed longitudinally, a mixed-effects repeated measures analysis of variance model was used to assess differences in these measures between the SRT and usual care groups at discharge, 2, 4, and 6 months. An unstructured covariance matrix was used to account for the within-patient correlation over time.

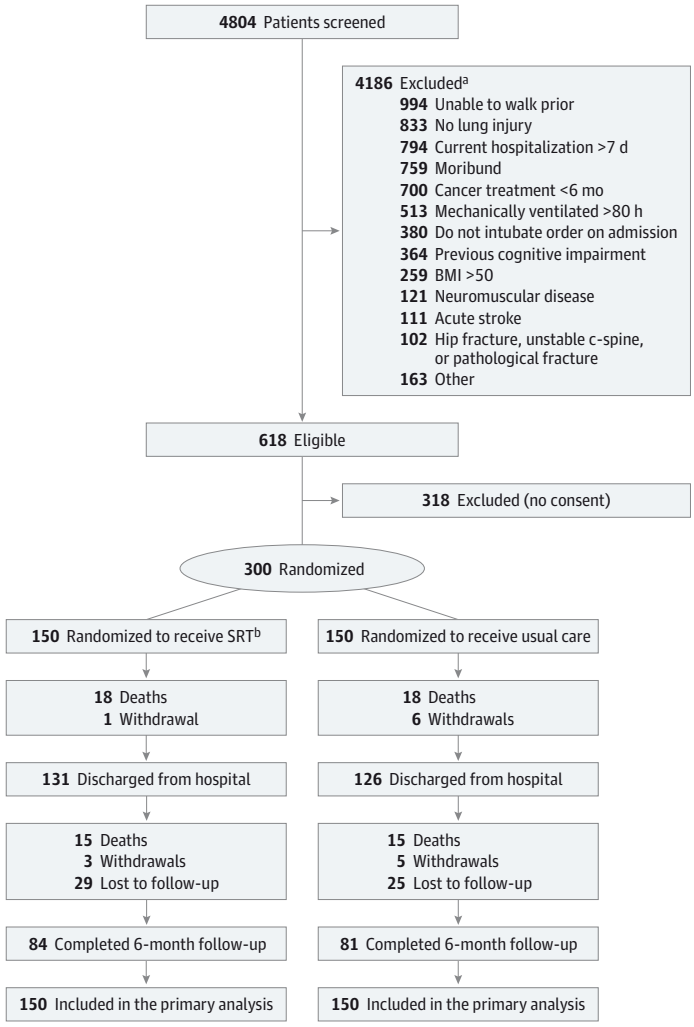
χ^2 and Wilcoxon rank-sum tests were used to assess differences in patient characteristics between those patients with and without missing data. Those characteristics predictive of missingness (due either to death or withdrawal) were included in the longitudinal mixed models. These covariates included age, race, BMI, ICU diagnosis, mean arterial pressure, $Paco_2$, Pao_2/FIo_2 ratio, APACHE score, and number of comorbid conditions. Multiple imputation was also used to assess the sensitivity of the results to the missing at random assumption. To be conservative, it was assumed that all dropouts would follow a pattern similar to that seen among the control patients (usual care group).[17] One hundred data sets were generated using the SAS MI procedure (SAS Institute), a repeated measures mixed model was run on each data set, and results were combined using the SAS MIANALYZE procedure (SAS Institute).[18] Covariates related to missing data were included in the imputations and in the adjusted mixed models. The imputation analyses included all patients.

Results

Study Patients

From October 2009 through November 2014, 4804 patients with acute respiratory failure were screened, 618 were eligible, and 300 were randomized (**Figure 1**) and followed up for up to 6 months after the enrollment date (last follow-up visit, November 2014). There were 84 patients in the SRT group (56%) vs 81 in the usual care group (54%) who com-

Figure 1. Flow of Patients Through the Study of Rehabiliation for Patients With Acute Respiratory Failure



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); SRT, standardized rehabilitation therapy.

[a] Patients could have more than 1 exclusion. Either patient or surrogate may have provided or refused consent.

[b] One patient after completing intervention was deemed technically ineligible; the patient was consented and randomized to SRT but was found to be unable to walk prior to study and included in the primary analysis.

pleted the 6-month follow-up. There were no clinically important differences in baseline characteristics between the 2 groups (**Table 1**).

Study Interventions

For the SRT group, the median days to first therapy exercise were 1 (interquartile range [IQR], 0-2) for passive range of motion, 3 (IQR, 1-6) for physical therapy, and 4 (IQR, 2-7) for progressive resistance exercise, whereas the days to first therapy exercise for the usual care group were 7 (IQR, 4-10). The mean percentage of study days SRT patients received therapy was 87.1% (SD, 18.4%) for passive range of motion, 54.6% (SD, 27.2%) for physical therapy, and 35.7% (SD, 23.0%) for progressive resistance exercise. The mean percentage of study days usual care patients received physical therapy was 11.7% (SD, 14.5%). For the SRT group, the median days of delivery of therapy per participant was 8.0 (IQR, 5.0-14.0) for passive range of motion, 5.0 (IQR, 3.0-8.0) for physical therapy, and 3.0 (IQR, 1.0-5.0) for progressive resistance exercise. The median days of delivery of physical therapy for the usual care group was 1.0 (IQR, 0.0-8.0).

Primary Outcomes and Hospital Data

The median hospital LOS was 10 days (IQR, 6 to 17) for the SRT group and 10 days (IQR, 7 to 16) for the usual care group (median difference, 0 [95% CI, −1.5 to 3], P = .41) (**Table 2** and **Figure 2**). The estimated hazard ratio (SRT to usual care) was 1.11 (95% CI, 0.86 to 1.45). There were no differences between groups in the number of days taking a vasopressor, Confusion Assessment Method for the ICU-positive days, days receiving intravenous sedative drugs, days with restraint, or net ICU-related fluid balance (Table 2). Sensitivity analyses were performed for the primary outcome as described in the methods. The assumptions regarding the censored observations made little difference to the outcome, with a median 9 to 10 days in the SRT group and 10 days in the usual care group across the various scenarios. Hazard ratios ranged from 1.03 to 1.11 (with SRT patients more likely to get discharged) unadjusted for covariates and from 1.06 to 1.18 after adjusting for those covariates predictive of in-hospital death. The difference between groups was nonsignificant in each sensitivity analysis (P >.22).

Table 1. Baseline Characteristics for Patients With Acute Respiratory Failure Receiving Standard Rehabilitation Therapy (SRT) vs Usual Care

	No. (%)		
	All (N = 300)	SRT (n = 150)	Usual Care (n = 150)
Age, mean (SD), y	56 (15)	55 (17)	58 (14)
Sex			
Women	166 (55.3)	84 (56.0)	82 (54.7)
Men	134 (44.7)	66 (44.0)	68 (45.3)
Race/ethnicity			
Hispanic or Latino	4 (1.3)	2 (1.3)	2 (1.3)
Black or African American	64 (21.3)	33 (22.0)	31 (20.7)
White	232 (77.3)	115 (76.7)	117 (78.0)
APACHE III score, mean (SD)[a]	76 (27)	76 (26)	75 (27)
Intensive care unit diagnosis			
Coma	5 (1.7)	1 (0.7)	4 (2.7)
Acute respiratory failure			
Without chronic lung disease	203 (67.7)	98 (65.3)	105 (70.0)
With chronic lung disease	92 (30.7)	51 (34.0)	41 (27.3)
Home oxygen	59 (19.7)	32 (21.3)	27 (18.0)
Dialysis prehospital	24 (8.0)	13 (8.7)	11 (7.3)
Mean arterial pressure, mean (SD), mm Hg	75.1 (22.4)	76.2 (22.3)	74.1 (22.5)
$PaCo_2$, mean (SD), mm Hg	44.1 (17.2)	44.4 (18.2)	43.8 (16.2)
Pao_2 /FIo_2 ratio, mean (SD)	178.6 (83.8)	182.0 (81.2)	175.1 (86.4)
Noninvasive ventilation	21 (7.0)	11 (7.3)	10 (6.7)
Shock	69 (23.0)	36 (24.0)	33 (22.0)

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

[a] APACHE III[19] score ranged from 0 to 299. A higher score indicates an increased risk of mortality.

Secondary Outcomes

Performance-based and self-reported measures of physical function are shown in **Table 3**. None of the scores were significantly different between groups at either ICU or hospital discharge. Strength values from handgrip and from handheld dynamometer did not differ between treatment groups at any of the measurement time points. The SPPB, SF-36 PFS, and FPI scores were not significantly different between groups at 2 or 4 months. However, each of these outcomes was significantly greater in the SRT group at the 6-month follow-up visit. At hospital discharge there was no difference in the proportion of SRT patients who could perform the 4-meter walk vs usual care (71% vs 61%, $P = .15$). By 6 months, those percentages had increased to 96% for the SRT group vs 88% for the usual care group ($P = .037$).

Health-related quality-of-life measures are shown in Table 3. SF-36 PHS, SF-36 MHS, and MMSE scores were not significantly different between groups at any time points.

The estimated intervention effects when analyses were repeated using multiple imputation assuming conservatively that all dropouts followed the pattern seen in the control group were decreased by approximately 40%. For example, the intervention effects at 6 months decreased from 1.06 to 0.60 for SPPB, 12.2 to 7.3 for SF-36 PFS, 0.21 to 0.12 for FPI, and 3.39 to 2.12 for SF-36 PHS. Only the SF-36 PFS effect remained significant ($P = .04$); the other P values were .11 for FPI, .16 for SPPB, and .19 for SF-36 PHS.

Outpatient physical therapy was not an intervention per treatment protocol; there was no difference in the number of patients (self-reported at each follow-up visit) who received outpatient or home physical therapy between hospital discharge and the 6-month follow-up visit (41 SRT patients vs 39 usual care patients, $P = .69$).

There were no differences in discharge destination between the SRT group and the usual care group (ie, home, long-term acute care, skilled nursing, or rehabilitation hospital) (eTable 1 in Supplement 2). Similarly, there were no differences between groups in post-index hospitalization readmissions or discharge emergency department visits without a hospital readmission. The percentage of each study group discharged from the hospital who were alive and hospital readmission-free at 6 months was 48.7% for the SRT group and 44.7% for the usual care group ($P = .63$). Post-hoc analyses indicated that the median number of ventilator-free days was 24 for both groups (median difference, 0 [95% CI, −2 to 1], $P = .59$), and the median number of ICU-free days was 19 for both groups (median difference, 0 [95% CI, −1.5 to 3], $P = .83$).

Missing Data

Death during the hospital stay was less than expected (12% observed vs 20% expected) as was death during the follow-up period (12% observed vs 15% expected). Dropout during the hospital stay was also less than expected (2% observed vs 5% expected). However, dropout during follow-up was greater than expected (24% observed from discharge to 6-month follow-up vs 10% expected). Neither dropout nor mortality differed between the study groups. Characteristics of those with and without missing data and those who did and did not drop out are shown in eTable 2 and eTable 3 in Supplement 2. Characteristics were fairly well balanced for those patients who re-

Table 2. Outcomes for Standard Rehabilitation Therapy (SRT) vs Usual Care Among Patients With Acute Respiratory Failure

	Median (IQR)			
	SRT (n = 150)	Usual Care (n = 150)	Median Difference (95% CI)	*P* Value
Hospital days (primary outcome)	10.0 (6 to 17)	10.0 (7 to 16)	0 (−1.5 to 3)	.41[a]
Free days[b]				
Hospital	18 (7 to 22)	18 (9 to 21)	0 (−3 to 1.5)	.96[c]
Ventilator	24 (19 to 26)	24 (20 to 26)	0 (−2 to 1)	.59[c]
Intensive care unit				
Days	7.5 (4 to 14)	8.0 (4 to 13)	0 (−2.5 to 2)	.68[a]
Free days[b]	19 (8 to 23)	19 (12 to 24)	0 (−1.5 to 3)	.83[c]
Intravenous sedation[d]				
Days	2 (1 to 5)	2 (0 to 4)	0 (0 to 1.5)	.11
Days, %	30.8 (0.8 to 54.1)	27.1 (0 to 50.0)	3.8 (−5.5 to 14.5)	.14
Vasopressor				
Days	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	>.99
Days, %	0 (0 to 6.7)	0 (0 to 8.3)	0 (0 to 0)	.90
ICU fluid balance, cc	−68.5 (−806.6 to 664.4)	−148.8 (−766.8 to 520.2)	53.9 (−270.3 to 281.2)	.89
Restraint				
Days	1 (0 to 4)	1 (0 to 3)	0 (−1 to 1)	.71
Days, %	25.0 (0 to 55.8)	25.0 (0 to 50.0)	0 (−16.7 to 12.3)	.82
CAM-ICU[e]				
Negative				
Days	2 (0 to 3)	2 (0 to 4)	0 (−1 to 1)	.88
Days, %	24.5 (0 to 44.8)	20 (0 to 50.0)	3.4 (−5.0 to 10.1)	.91
Positive				
Days	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	.77
Days, %	0 (0 to 12.5)	0 (0 to 9.1)	0 (0 to 0)	.71
RASS score of 4 or 5[f]				
Days	1 (0 to 4)	1 (0 to 3)	0 (−1 to 1)	.43
Days, %	14.6 (0 to 36.9)	14.3 (0 to 33.3)	1.8 (−6.7 to 10.5)	.71

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit[20]; IQR, interquartile range; RASS, Richmond Agitation Sedation Scale.[21]

[a] Log-rank test.

[b] All free days are based on 28 days.

[c] Wilcoxon ranked sum.

[d] Intravenous sedation days were defined as any part of a day a continuous intravenous delivery occurred of fentanyl, morphine, midazolam, lorazepam, propofol or dexmedetomidine. Percentage of restraint days, CAM-ICU–positive days, CAM-ICU–negative days, and RASS score 4 or 5 days represent the percentage of ventilator days.

[e] CAM-ICU scores were positive or negative for delirium.

[f] RASS score ranged from −3 (moderate sedation) to 4 (combative).

mained in the study. Of the patients included in the follow-up analyses, APACHE III scores were lower (better) in the usual care group.

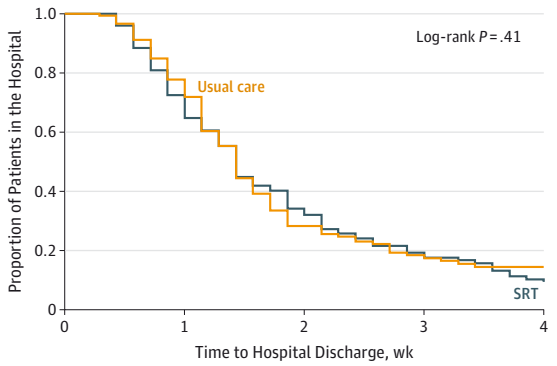
Adverse Events

There were no differences in adverse event reporting between study groups (eTable 4 in Supplement 2). The majority of adverse events captured were not specifically related to SRT delivery. Specific to SRT, there were no untoward events such as endotracheal tube removal, vascular access device removal, patient near-fall or fall, or cardiac arrest. However, there was an episode of asymptomatic bradycardia during a progressive resistance exercise session lasting less than 1 minute, with the patient completing the session afterwards.

Discussion

In this randomized, assessor-blinded study of SRT vs usual care for patients with acute respiratory failure, there was no difference in hospital LOS between groups. Similarly, SRT did not affect ventilator-free days or ICU-free days. Functional-related and health-related quality-of-life outcomes were similar for the 2 study groups at hospital discharge.

Figure 2. Length of Stay for Patients With Acute Respiratory Failure Receiving SRT vs Usual Care



No. at risk

SRT	150	102	44	22	10
Usual care	150	107	34	18	14

SRT indicates standardized rehabilitation therapy. Time zero indicates time of randomization.

The amount of exercise delivered and performed while in-hospital was substantially different between SRT and usual care groups. The usual care group received physical therapy for only

Table 3. Secondary Outcomes: Physical Function Measures and Health-Related Quality of Life for Patients With Acute Respiratory Failure, by Group

Measurement	Group	ICU Discharge		Hospital Discharge		2-Month Follow-up		4-Month Follow-up		6-Month Follow-up	
		Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data
Physical Function											
Short Physical Performance Battery score[a]	SRT	1.6 (1.0 to 2.2)	86	4.7 (4.0 to 5.4)	106	8.7 (8.1 to 9.4)	88	8.9 (8.2 to 9.6)	88	9.0 (8.3 to 9.7)	84
	Usual care	1.9 (1.3 to 2.4)	98	4.7 (4.0 to 5.4)	98	7.8 (7.1 to 8.5)	76	8.0 (7.2 to 8.7)	79	8.0 (7.2 to 8.7)	81
	Difference	−0.3 (−1.1 to 0.5)		−0.01 (−1.0 to 0.9)		0.9 (−0.01 to 1.9)		1.0 (−0.03 to 1.9)		1.1 (0.04 to 2.1)	
	P Value[b]	.46		.97		.05		.06		.04	
Dynamometer strength, lb	SRT	20.3 (17.9 to 22.8)	67	23.7 (21.6 to 25.8)	100	28.5 (26.3 to 30.8)	84	28.8 (26.5 to 31.0)	85	31.1 (28.8 to 33.4)	78
	Usual care	22.8 (20.4 to 25.1)	77	23.9 (21.7 to 26.2)	86	28.0 (25.6 to 30.4)	73	29.6 (27.2 to 31.9)	75	30.8 (28.4 to 33.1)	77
	Difference	−2.4 (−5.8 to 1.0)		−0.2 (−3.3 to 2.9)		0.5 (−2.8 to 3.8)		−0.8 (−4.1 to 2.5)		0.4 (−2.9 to 3.7)	
	P Value[b]	.16		.90		.76		.63		.82	
Handgrip strength, kg	SRT	20.0 (17.8 to 22.3)	78	22.6 (20.6 to 24.6)	104	27.2 (25.1 to 29.2)	87	29.0 (26.8 to 31.2)	87	29.3 (26.9 to 31.6)	83
	Usual care	20.9 (18.7 to 23.1)	88	24.3 (22.2 to 26.4)	94	26.0 (23.8 to 28.1)	74	27.2 (24.9 to 29.4)	77	27.2 (24.8 to 29.6)	81
	Difference	−0.8 (−4.0 to 2.3)		−1.7 (−4.6 to 1.2)		1.2 (−1.8 to 4.2)		1.8 (−1.3 to 5.0)		2.0 (−1.3 to 5.4)	
	P Value[b]	.60		.25		.43		.25		.23	
SF-36 physical functioning scale score[c]	SRT			38.4 (33.2 to 43.7)	108	47.4 (41.8 to 53.1)	89	52.2 (46.7 to 57.7)	86	55.9 (50.0 to 61.7)	82
	Usual care			38.3 (32.8 to 43.8)	100	43.0 (37.0 to 49.0)	77	47.2 (41.4 to 53.0)	77	43.6 (37.5 to 49.7)	79
	Difference			0.1 (−7.6 to 7.8)		4.4 (−3.9 to 12.7)		5.0 (−3.0 to 13.0)		12.2 (3.8 to 20.7)	
	P Value[b]			.97		.29		.22		.001	
Functional Performance Inventory score[d]	SRT					2.0 (1.9 to 2.1)	89	2.2 (2.1 to 2.3)	86	2.2 (2.1 to 2.4)	83
	Usual care					2.0 (1.9 to 2.1)	75	2.1 (1.9 to 2.2)	77	2.0 (1.9 to 2.2)	79
	Difference					−0.03 (−0.2 to 0.1)		0.1 (−0.03 to 0.3)		0.2 (0.04 to 0.4)	
	P Value[b]					.74		.11		.02	
Health-Related Quality of Life											
SF-36 physical health summary score[e]	SRT			30.2 (28.4 to 32.1)	108	33.4 (31.4 to 35.5)	89	36.0 (33.8 to 38.2)	86	36.9 (34.6 to 39.3)	82
	Usual care			30.3 (28.4 to 32.2)	100	32.2 (31.0 to 34.4)	77	33.7 (31.4 to 36.0)	77	33.5 (31.1 to 36.0)	79
	Difference			−0.1 (−2.8 to 2.7)		1.2 (−1.8 to 4.3)		2.3 (−0.9 to 5.5)		3.4 (−0.02 to 7.0)	
	P Value[b]			.96		.43		.16		.05	
SF-36 mental health summary score[e]	SRT			43.6 (41.5 to 45.7)	108	46.3 (43.8 to 48.8)	89	47.8 (45.5 to 50.2)	86	48.8 (46.3 to 51.3)	82
	Usual care			43.3 (41.2 to 45.5)	100	46.2 (43.6 to 48.8)	77	47.7 (45.2 to 50.1)	77	46.4 (43.8 to 49.0)	79
	Difference			0.3 (−2.7 to 3.3)		0.1 (−3.5 to 3.7)		0.2 (−3.2 to 3.6)		2.4 (−1.2 to 6.0)	
	P Value[b]			.86		.96		.91		.19	
Mini-Mental State Examination score[c]	SRT			25.4 (24.7 to 26.1)	114	26.7 (25.9 to 27.5)	88	27.6 (27.0 to 28.2)	86	27.6 (27.0 to 28.2)	84
	Usual care			25.1 (24.3 to 25.8)	104	26.8 (26.0 to 27.7)	75	27.2 (26.5 to 27.8)	78	27.0 (26.4 to 27.6)	81
	Difference			0.3 (−0.7 to 1.3)		−0.1 (−1.3 to 1.1)		0.4 (−0.5 to 1.3)		0.6 (−0.2 to 1.4)	
	P Value[b]			.55		.86		.37		.17	

Abbreviations: ICU, intensive care unit; SRT, standardized rehabilitation therapy.

Metric conversion factor: To convert pounds to kilograms, divide by 0.45.

[a] Short Physical Performance Battery minimal clinically important difference is 1 unit.[13,22]

[b] Treatment effect at the given visit.

[c] SF-36 physical functioning scale and Mini-Mental State Examination were performed on hospital discharge and following appointments.

[d] Functional Performance Inventory was performed starting at first outpatient follow-up. Self-report mechanisms use higher scores to indicate greater levels of functioning.

[e] SF-36 mental and physical health summary minimal clinically important differences are 3 to 5 units.[15]

12% of the study days and never received resistance training. In contrast, in the SRT group, passive range of motion occurred in 87% of study days, physical therapy in 55%, and progressive resistance exercise in 36%, with no significant hospital-based outcome differences observed. The volume of exercise delivered to SRT patients was delivered with 7 days per week availability. This structure may differ from the current practice in many US ICUs.[23] Others have also reported on the real-life delivery of ICU-related exercise being less than expected by ICU practitioners.[24-26] In view of these data, it is unclear what ICU exercise dose is required to affect outcomes by hospital discharge for patients with acute respiratory failure.

Following discharge, handgrip strength or strength measured by handheld dynamometer and health-related quality of life remained similar for the 2 groups. But from these exploratory analyses, the physical function measures (SPPB, SF-36 PFS, and FPI) were different at 6 months. The separation of the 2 groups' self-reported and objectively measured functional data over 6 months of follow-up contrasts with the lack of difference for hospital-centered outcomes.

These findings from the exploratory analyses may highlight the emerging role of placing long-term outcomes within critical care clinical trial design not only as a secondary outcome, but possibly as the primary outcome.[27-30] In view of the SPPB, SF-36 PFS, and FPI data at 6 months, the SRT group demonstrated a potential signal of improvement compared with the usual care group that was not evident at hospital discharge. It is not obvious what aspect of the SRT may have accounted for the differences at 6 months; however, both the physical therapy and the progressive resistance training emphasized lower extremity function. The exposure in the hospital may have inclined the SRT group to have greater movement while in the outpatient setting.

The findings from this study contrast with the outcomes of the study by Schweickert and colleagues,[7] which found greater improvements in activities of daily living at hospital discharge in an early ICU rehabilitation group than the control group, but no difference in hospital LOS either. The study by Walsh and colleagues[31] reported post-ICU hospital-based rehabilitation, including increased physical and nutritional therapy, did not improve physical recovery or quality-of-life scores at 3 months after enrollment. Outpatient-focused patient-level functional outcome differences were not detected in the study by Denehy and colleagues,[9] which linked an inpatient rehabilitation exercise repertoire with outpatient exercise instructions for a cohort of patients who were critically ill. Moss and colleagues[32] found that an intensive physical therapy program compared with a standard physical therapy program in which the intensive program continued for up to 28 days from randomization, including the outpatient setting, did not improve long-term physical functional performance at 6 months.

Study limitations include a higher than expected dropout (lost to follow-up and withdrawals, 24%) following hospital discharge. Also, there was no intervention following discharge; future study of ICU-initiated rehabilitation programs may need to include a bridge program of some outpatient exercise content to further optimize outcomes.[31,33]

Another potential limitation was that there was no explicit sedation protocol; the lack of a sedation protocol may have allowed patients in both groups to spend unnecessary days either unconscious or with a positive Confusion Assessment Method score.[34,35] Given that the intervention group had approximately 30% of ventilator days associated with intravenous continuous drip medications, and patients were unarousable on 15% of ventilator days, sedation may have been a barrier to receipt of early exercise. These data indicate the challenge of delivering a treatment modality requiring a conscious, engaged patient. Other modalities have been proposed such as functional electrical stimulation for the unconscious patient.[36] Additionally, multiple tests may have led to a spurious significant finding for the functional tests.

Conclusions

Among patients hospitalized with acute respiratory failure, SRT compared with usual care did not decrease hospital LOS.

ARTICLE INFORMATION

Author Affiliations: Division of Pulmonary, Critical Care, and Sleep Medicine, University of Kentucky, Lexington (Morris); Department of Health and Exercise Science, Wake Forest University, Winston Salem, North Carolina (Berry, Hauser); Section on Pulmonary, Critical Care, Allergy, and Immunologic Disease, Wake Forest University, Winston Salem, North Carolina (Files, Thompson, Flores, Dhar, Chmelo, Bakhru, Campbell, Mote, Chatterjee, Young); Department of Biostatistical Sciences, Wake Forest University, Winston Salem, North Carolina (Lovato, Case); Department of Neurology, Wake Forest University, Winston Salem, North Carolina (Sarwal); Physiotherapy Department, University of Melbourne, Melbourne, Australia (Parry); Francis Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, Ohio (Winkelman); Department of Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio (Hite); Division of Geriatrics, Wake Forest University, Winston Salem, North Carolina (Nicklas).

Author Contributions: Dr Morris had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Morris, Berry, Hauser, Dhar, Chmelo, Case, Hite, Nicklas.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Morris, Berry, Thompson, Hauser, Case, Parry, Mote, Chatterjee.
Critical revision of the manuscript for important intellectual content: Berry, Files, Flores, Dhar, Chmelo, Lovato, Case, Bakhru, Sarwal, Parry, Campbell, Winkelman, Hite, Nicklas, Chatterjee, Young.
Statistical analysis: Lovato, Case, Chatterjee.
Obtained funding: Morris, Berry, Hite.
Administrative, technical, or material support: Morris, Berry, Files, Thompson, Hauser, Flores, Dhar, Bakhru, Sarwal, Parry, Mote, Nicklas, Chatterjee.
Study supervision: Morris, Berry, Files, Thompson, Dhar, Chatterjee.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bakhru reports consulting for Hill Rom Company. Dr Chatterjee reports part-time employment with the US Department of Veterans Affairs and the US Navy. No other disclosures were reported.

Funding/Support: This work was supported by the National Institutes of Health, National Institute of Nursing Research, and National Heart, Lung, and Blood Institute.

Role of the Funder/Sponsor: The sponsors did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The opinions contained in this article are those of the authors and do not represent the opinions of the US Department of Veterans Affairs nor the US Department of Defense.

Previous Presentation: Selected data in this article were presented at the Australian Physiotherapy Association meeting; October 3-6, 2015; Brisbane, Australia.

REFERENCES

1. Hermans G, Van Mechelen H, Clerckx B, 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(4):410-420.

2. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.

3. Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a 2-year longitudinal prospective study. *Crit Care Med*. 2014;42(4):849-859.

4. Pandharipande PP, Girard TD, Jackson JC, et al; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306-1316.

5. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med*. 2007;35(1):139-145.

6. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med*. 2008;36(8):2238-2243.

7. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.

8. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med*. 2009;37(9):2499-2505.

9. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care*. 2013;17(4):R156.

10. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness [published correction appears in *JAMA*. 2014;311(6):625]. *JAMA*. 2013;310(15):1591-1600.

11. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil*. 2010;91(4):536-542.

12. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859-2867.

13. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94.

14. Leidy NK, Hamilton A, Becker K. Assessing patient report of function: content validity of the Functional Performance Inventory-Short Form (FPI-SF) in patients with chronic obstructive pulmonary disease (COPD). *Int J Chron Obstruct Pulmon Dis*. 2012;7:543-554.

15. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med*. 2001;33(5):350-357.

16. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.

17. Ratitch B, O'Kelly M. Implementation of pattern-mixture models using standard SAS/STAT procedures. http://pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf. Accessed May 26, 2016.

18. SAS Institute. *SAS/STAT 9.3 SAS User's Guide*. Cary, NC: SAS Institute; 2011.

19. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100(6):1619-1636.

20. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2001;29(7):1370-1379.

21. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.

22. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006;54(5):743-749.

23. Hodgin KE, Nordon-Craft A, McFann KK, Mealer ML, Moss M. Physical therapy utilization in intensive care units: results from a national survey. *Crit Care Med*. 2009;37(2):561-566.

24. Nydahl P, Ruhl AP, Bartoszek G, et al. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. *Crit Care Med*. 2014;42(5):1178-1186.

25. Hodgson C, Bellomo R, Berney S, et al; TEAM Study Investigators. Early mobilization and recovery in mechanically ventilated patients in the ICU: a binational, multicentre, prospective cohort study. *Crit Care*. 2015;19:81.

26. Berney SC, Harrold M, Webb SA, et al. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. *Crit Care Resusc*. 2013;15(4):260-265.

27. Hudson LD, Lee CM. Neuromuscular sequelae of critical illness. *N Engl J Med*. 2003;348(8):745-747.

28. Elliott D, Davidson JE, Harvey MA, et al. Exploring the scope of postintensive care syndrome therapy and care: engagement of noncritical care providers and survivors in a second stakeholders meeting. *Crit Care Med*. 2014;42(12):2518-2526.

29. Iwashyna TJ. Trajectories of recovery and dysfunction after acute illness, with implications for clinical trial design. *Am J Respir Crit Care Med*. 2012;186(4):302-304.

30. Cooper DJ, Rosenfeld JV, Murray L, et al; DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med*. 2011;364(16):1493-1502.

31. Walsh TS, Salisbury LG, Merriweather JL, et al; RECOVER Investigators. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *JAMA Intern Med*. 2015;175(6):901-910.

32. Moss M, Nordon-Craft A, Malone D, et al. A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med*. 2016;193(10):1101-1110.

33. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med*. 2014;40(3):370-379.

34. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.

35. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.

36. Parry SM, Berney S, Koopman R, et al. Early rehabilitation in critical care (eRiCC): functional electrical stimulation with cycling protocol for a randomised controlled trial. *BMJ Open*. 2012;2(5):e001891.