Rehabilitation Interventions for Postintensive Care Syndrome: A Systematic Review*

Juliane Mehlhorn, MD[1]; Antje Freytag, PhD[1]; Konrad Schmidt, MD[1]; Frank M. Brunkhorst, MD[2,3]; Juergen Graf, MD[4]; Ute Troitzsch[5]; Peter Schlattmann, PhD[6]; Michel Wensing, PhD[1,7]; Jochen Gensichen, MD, MPH, MSc[1]

Objective: An increasing number of ICU patients survive and develop mental, cognitive, or physical impairments. Various interventions support recovery from this postintensive care syndrome. Physicians in charge of post-ICU patients need to know which interventions are effective.

Data Sources: Systematic literature search in databases (MEDLINE, EMBASE, Cochrane CENTRAL, PsycInfo, CINAHL; 1991–2012), reference lists, and hand search.

Study Selection: We included comparative studies of rehabilitation interventions in adult post-ICU patients if they considered health-related quality of life, frequency/severity of postintensive care syndrome symptoms, functional recovery, need for care, autonomy in activities of daily living, mortality, or hospital readmissions.

Data Extraction: Two reviewers extracted data and assessed risk of bias independently.

Data Synthesis: From 4,761 publications, 18 studies with 2,510 patients were included. Studies addressed 20 outcomes, using 45 measures, covering inpatient ($n = 4$ trials), outpatient ($n = 9$), and mixed ($n = 5$) healthcare settings. Eight controlled trials with moderate to high quality were considered for evaluation of effectiveness. They investigated inpatient geriatric rehabilitation, ICU follow-up clinic, outpatient rehabilitation, disease management, and ICU diaries. Five of these trials assessed posttraumatic stress disorder, with four trials showing positive effects: first, ICU diaries reduced new-onset posttraumatic stress disorder (5% vs 13%, $p = 0.02$) after 3 months and second showed a lower mean Impact of Event Scale-Revised score (21.0 vs 32.1, $p = 0.03$) after 12 months. Third, aftercare by ICU follow-up clinic reduced Impact of Event Scale for women (20 vs 31; $p < 0.01$). Fourth, a self-help manual led to fewer patients scoring high in the Impact of Event Scale after 8 weeks ($p = 0.026$) but not after 6 months. For none of the other outcomes did more than one study report positive impacts.

Conclusion: Interventions which have substantial effects in post-ICU patients are rare. Positive effects were seen for ICU-diary interventions for posttraumatic stress disorder. More interventions for the growing number of ICU survivors are needed. (*Crit Care Med* 2014; 42:1263–1271)

Key Words: aftercare; critical illness; intensive care; posttraumatic stress disorder; rehabilitation; review literature as topic

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[1]Institute of General Practice and Family Medicine, Jena University Hospital, Jena, Germany.

[2]Paul-Martini-Research Group, Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany.

[3]Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany.

[4]Medical Directorate, Central Hospital Stuttgart, Stuttgart, Germany.

[5]Thuringian State and University Library, Jena, Germany.

[6]Department of Medical Statistics, Computer Sciences and Documentation, Jena University Hospital, Jena, Germany.

[7]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

This study was performed at Institute of General Practice and Family Medicine, Friedrich Schiller University/Jena University Hospital, Jena, Germany.

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For information regarding this article, E-mail: jochen.gensichen@med.uni-jena.de

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The aging population and expanding boundaries of medical treatment have led to an increasing number of patients treated in ICUs (1), mostly because of a life-threatening critical illness (2). Millions of patients require ICU treatment annually in the United States (3), and with recent advances in

critical care medicine, more patients survive ICU stays (4). But after ICU discharge, patients often experience persistent physical, mental, and cognitive symptoms (5, 6), which have recently been described as postintensive care syndrome (PICS) (7). Post-ICU patients may need long-term medical interventions to support recovery in inpatient and in outpatient settings. Data on effective intervention is scattered across scientific literature.

Post-ICU patients may suffer from physical problems like critical illness polyneuromyopathy (CIPNM; ICU-acquired weakness) (2, 5), dysphagia (8), cachexia or wasting syndrome (9, 10), organ dysfunction (11), chronic pain (12), sexual dysfunction (13, 14), etc., as well as mental health problems like depression, anxiety, or posttraumatic stress disorder (PTSD) (15–17) and neurocognitive impairments like new or worsening cognitive impairment or delirium (18). The impact of these problems is reduced quality of life (19–21), reduced functional status (6, 22), and reduced daily functioning (5, 6).

Post-ICU patients challenge healthcare systems, driving high costs through repeated hospital admissions (23). In Germany, productivity loss for sepsis patients alone is about 5.6 million € per year (24).

So far, research on interventions to support the recovery of post-ICU patients is scarce. The purpose of this systematic review is to assess, for the first time, the effectiveness of rehabilitation interventions in adult post-ICU patients.

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (25, 26). According to these guidelines, we established a detailed study protocol in advance, which is available on request.

Data Sources and Searches

We systematically searched MEDLINE (via OvidSP), EMBASE, Cochrane CENTRAL, PsycInfo, and CINAHL. We used a combination of the following search blocks to perform a keyword search in title and abstract and a MeSH term search: critical illness (e.g., critical illness, sepsis, and respiratory distress syndrome), state after intensive care (e.g., after/postintensive care and discharge from intensive care), aftercare and rehabilitation (e.g., rehabilitation, follow-up, and aftercare), interventions in general (e.g., therapy, management, and intervention), and postacute setting (e.g., postacute, outpatient, and after hospital). A team of experienced clinicians designed the search strategy in collaboration with a professional librarian. The search strategy was independently peer reviewed before being carried out. Additionally, we performed hand searching in 18 journals (published in 2012 before July 13th). Searches imposed no language restriction and included all studies published in peer-reviewed journals from January 1991 to June 2012.

Study Selection and Inclusion Criteria

Citations were checked for eligibility by two reviewers independently at the title, abstract, and full-text levels (**Fig. 1**). Disagreements between reviewers were resolved by discussion with a third reviewer. Interrater agreement for the selection process was assessed by kappa statistic calculation on full-text level.

We considered comparative intervention studies (27–29) targeting adult post-ICU patients. We included studies if they reported on one or more of the outcomes: patients' health-related quality of life (HRQOL), frequency or severity of symptoms of PICS, physical or functional status, need for care, patients' autonomy in activities of daily living, mortality, or hospital readmissions. We excluded interventions beginning in ICU and specific ICU-related treatments, like prolonged acute care or weaning, as well as disease-specific rehabilitations for myocardial infarction, stroke, amputation, etc.

Data Extraction and Quality Assessment

We designed and piloted our data extraction forms following guidelines (28–30). Data items concerned study setting, population, intervention, study design, statistical analyses, confounders, test instruments used, outcome data, and study limitations. Items were extracted and checked by two reviewers.

Two reviewers independently assessed risk of bias and overall quality of individual studies using the validated Effective Public Health Practice Project Quality assessment tool (31, 32). For each study, reviewers rated six components (selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts) leading to an overall methodological quality rating for each study of strong, moderate, or weak, with strong quality indicating a low risk of bias. Reviewers resolved rating disagreements through discussion.

Data Synthesis and Analysis

We assessed study designs according to the Cochrane Non-Randomized Studies Methods Group and Effective Practice and Organization of Care Group guidelines (29, 30). The interventions were categorized by healthcare setting post hoc into inpatient, outpatient, and mixed (30) and into eight subcategories based on the nature of interventions (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825). Due to heterogeneity of trials, no meta-analysis was possible, so we performed a narrative data synthesis.

RESULTS

Study Selection

We included 19 publications concerning 18 studies. We found 16 of the publications through databases and three by hand search (Fig. 1). Interrater agreement for inclusion after full-text review was excellent ($\kappa = 0.98$).

Study Characteristics, Risk of Bias, and Quality

Although nine studies claimed to be randomized controlled trials (RCT), after quality assessment only four trials (33–36) fulfilled randomization criteria for a valid RCT according to guidelines (37). The other five trials are regarded as controlled clinical trials (38–43). The nine remaining studies consisted of one non-RCT (44), one controlled before-and-after

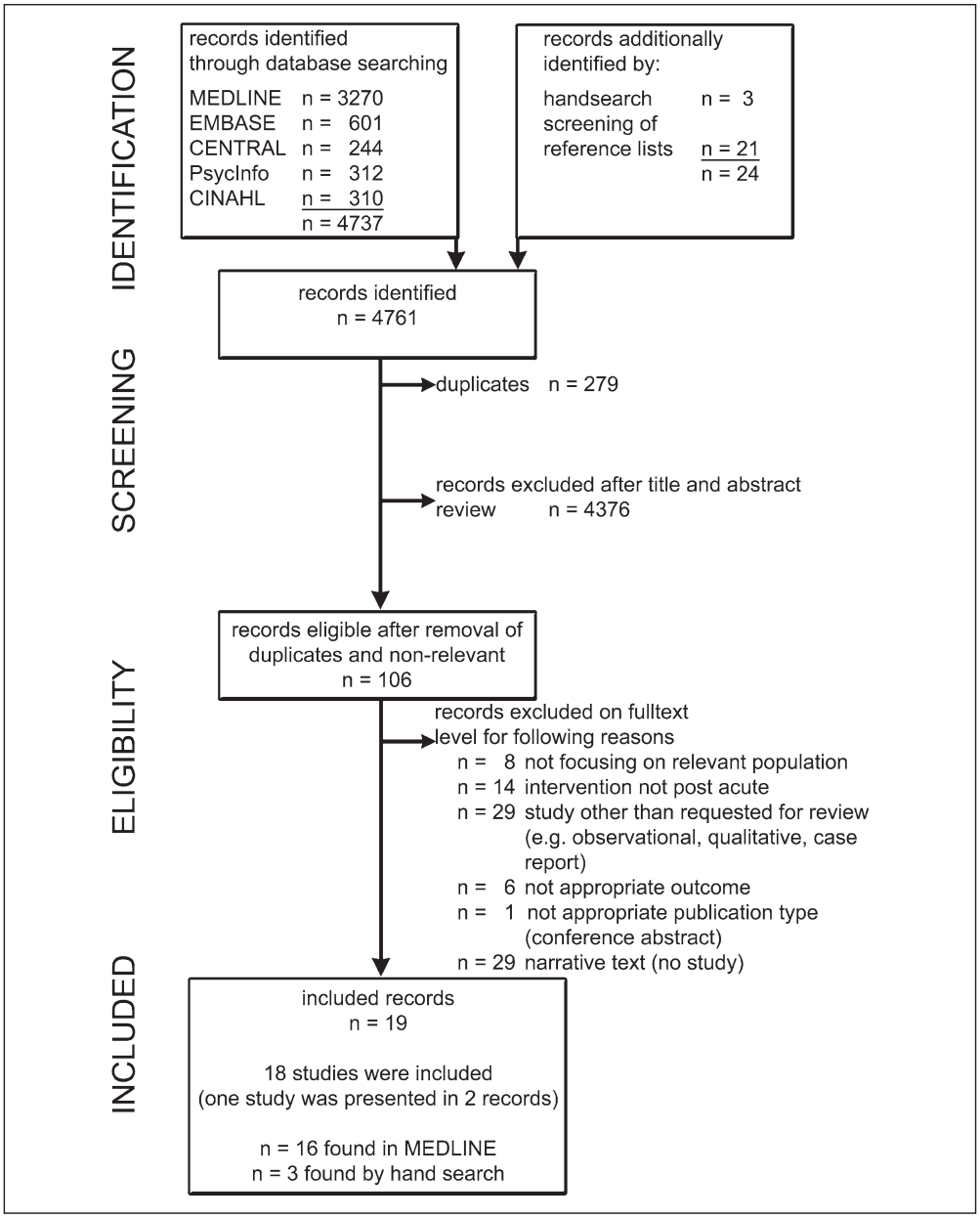

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study inclusion.

study (45), two historically controlled trials (46, 47), and five before-and-after studies (48–52). Five of the publications were labeled as pilot or feasibility studies (33, 40, 44, 48, 50).

We rated the methodological quality of five publications as "strong" (34–36, 42, 46), four as "moderate" (38, 39, 43, 47), and 10 as "weak" (33, 40, 41, 44, 45, 48–52). The most common shortcomings we found are in blinding, selection bias, attrition bias, and lack of adequate control for relevant sociodemographic and clinical characteristics of participants (detailed information in **Supplemental Digital Content Text 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825; and **Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825).

Most studies (n = 14) were conducted in Europe, three in the United States, and one in Australia. The majority of studies were single center (n = 13), with only five multicenter studies (34–36, 39, 50).

Participants

Studies included 2,510 patients, sample sizes ranging from 7 to 499, with an average of 139 participants. Fifteen studies tracked patients after critical illness in general, one after acute lung injury (50), and two studied patients with CIPNM (51, 52). One study exclusively recruited young men (44) and another only patients at least 75 years old (38).

Mechanical ventilation, ranging from 24 to 96 hours or with any length of time, was an inclusion criterion in seven studies (33, 34, 36, 39, 42, 43, 48, 50). Two studies additionally required a minimum length of stay in the ICU (34, 36). Length of stay in ICU, ranging from 24 (45) to 96 hours (46, 47, 49), alone was required in four studies. The remaining studies required neither a minimum stay in ICU nor mechanical ventilation.

Outcomes and Measures

Half of the studies did not differentiate between primary and secondary outcomes (33, 39, 42–45, 49–52). Eight studies assessed physical symptoms (33, 34, 39, 40, 48, 49, 51, 52) and 10 examined mental health symptoms, including symptoms of anxiety, depression, and PTSD (35, 36, 39, 41, 44, 46–50). Five studies reported on HRQOL (34, 35, 43, 45, 49), four on autonomy in daily activities (38, 40, 51, 52), and one on cognitive functioning (40). Few studies included need for care (38, 51), hospital readmission (42), mortality (42, 43), or nutrition (33).

Of all applied outcome test instruments, we found evidence of validation in (post)-ICU patients for the Short Form 36-item health survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Post-Traumatic Stress Scale, Post-Traumatic Stress Syndrome 14-Questions Inventory, Impact of Event Scale-Revised (IES-R), Electromyography, Medical Research Council scale, and Manual muscle testing (53–63) (for detailed information, see **Supplemental Table 3**, Supplemental Digital Content 1, http://

links.lww.com/CCM/A825; and for abbreviations of test instruments, see footnote of **Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A825).

Interventions

Supplemental Table 4 (Supplemental Digital Content 1, http://links.lww.com/CCM/A825) provides a description of each intervention and study characteristics. Interventions varied widely in many aspects, including healthcare setting, healthcare providers, study design, and measures used.

Effectiveness of Interventions According to Setting

Our analysis of intervention effectiveness focused on the eight controlled trials with low or moderate risk of bias (34–36, 38, 39, 42, 43, 46, 47) (**Table 1**).

Inpatient Interventions

After ICU discharge, treatment in a specifically designed geriatric ward was not more effective than treatment in a general ward (38). Patients in the geriatric ward scored higher on the Barthel Index than the control group after discharge (75.6 ± 28.4 vs 64.6 ± 26.9) and 6 months later (81.5 ± 30.4 vs 70.5 ± 33.4), but this was not statistically significant. Many patients needed care in specialized wards and were not approached for the study, reducing the relevance of the study for the most vulnerable patients.

Outpatient Interventions

In a multicenter trial rated as strong methodological quality, consultations in an ICU follow-up service did not improve HRQOL or mental health more than standard care within a year of ICU discharge (35). Standard effect sizes (95% CI) of the SF-36 Physical health Component Score (PCS) and Mental health Component Score (MCS) to measure HRQOL were −0.8 (−3.6 to 2.0) and −0.6 (−3.9 to 2.8) after 6 months and 1.1 (−1.9 to 4.2) and 0.4 (−3.0 to 3.7) after 12 months. Another trial of moderate quality (46) suggested that women who spent 4 days or more in the ICU may have benefited from an ICU follow-up service regarding symptoms of depression and PTSD, regardless of previous psychological problems. Fourteen months after ICU discharge, a significant difference for PTSD (IES 31 vs 20 points, $p < 0.01$) was found. For depression, the 75th percentile of the HADS was significantly lower (–4.9 points, $p < 0.05$), but no relevant difference in median HADS depression points and no effects on anxiety were seen.

Two studies on outpatient rehabilitation programs (34, 39) were found: A self-help rehabilitation manual, supplemental to routine care (39), showed a trend of improved physical

TABLE 1. Overview of Outcomes in Trials Considered for Evaluation of Effectiveness, Significance of Findings, and Study Quality

Author	Study Type	Physical Function	Anxiety	Depression	Posttraumatic Stress Disorder
Inpatient interventions					
Ward-based rehabilitation in acute hospital care					
Somme et al (38)	CCT	–	–	–	–
Outpatient interventions					
Consultation in an ICU follow-up clinic					
Cuthbertson et al (35)	RCT	–	No	No	No
Schandl et al (46)	HCT	–	No	Partly[a]	Yes[a]
Rehabilitation programs/complex aftercare programs					
Jones et al (39)	CCT	Yes	No	No	Partly
Elliott et al (34)	RCT	No	–	–	–
Mixed interventions					
Disease management support service					
Daly et al (42) and Douglas et al (43)	CCT	–	–	–	–
ICU diary (given to patient after ICU discharge)					
Jones et al (36)	RCT	–	–	–	Yes
Garrouste-Orgeas et al (47)	HCT	–	No	No	Yes

CCT = clinical controlled trial, No = no significant difference in outcomes, RCT = randomized controlled trial, HCT = historical controlled trial, Yes = significant difference in outcome between intervention and control group, Partly = significant findings only in some outcomes.

[a]For women and not for men.

Dashes indicate no outcome in the study.

function. SF-36 Physical Function (SF-36 PF) score of experimental patients improved more over time than that of control patients ($p = 0.06$ for repeated analysis of variance incorporating SF-36 PF premorbid, at 8 wk and 6 mo). For PTSD, fewer experimental patients than control patients scored over the cutoff in the IES at the 8-week follow-up, indicating fewer symptoms ($p = 0.026$; percentage of patients and effect measure is not reported). This finding did not repeat at 6 months. No significant difference in the HADS depression or anxiety was seen.

A home-based physical rehabilitation program, tested in a strong quality, multicenter trial, did not show an effect on physical function or HRQOL 6 months after hospital discharge (34). Effect sizes ([Intervention mean change – Control mean change]/pooled SD of change) for SF-36 PCS and MCS were –0.14 and 0.13 at 8 weeks and 0.03 and 0.10 at the 26-week follow-up.

Mixed Healthcare Setting Interventions

A nurse-based cross-sectoral program for patients with chronic critical illness incorporating case management was assessed in one trial and presented in two publications (42, 43). Although called disease management, this intervention only fulfils the criteria of a disease management support service (64). The intervention was not associated with changes in any predefined outcome other than duration of readmission. Mean stay for interventional patients was 11.4 days (± 10.6 SD) versus 16.7 days (± 13.0 SD) ($p = 0.03$) (42). Only a partly positive result for HRQOL was found (43) as more interventional patients improved in SF-8 PCS within 2 months after hospital discharge (36.3% vs 29.2%, $p = 0.02$; post hoc analysis). The authors hypothesize that chronic critical illness may have a natural trajectory of continued morbidity, unaffected by additional postacute care coordination services.

Another cross-sectoral intervention used in different healthcare settings is the ICU dairy. It is a written record of the course of a patient's illness and treatment while in the ICU. The patient is given the diary as a tool to help address symptoms of PICS after ICU discharge. Of the interventions in this review, ICU diaries show the best evidence for a positive effect on mental health outcomes. One strong quality international multicenter trial found fewer new cases of PTSD at the 3-month follow-up (prevalence, 5% vs 13%; $p = 0.02$) (36). Another trial of moderate quality showed fewer symptoms of PTSD after 12 months, with a significantly lower mean IES-R (21.0 [± 12.2 SD] vs 32.1 [± 15.4 SD], $p = 0.03$) and fewer interventional patients scoring above the cutoff (50% vs 69%) (47). For anxiety and depression, evaluated at the 3-month follow-up, no significant difference was seen.

Cognition	Health-Related Quality of Life	Autonomy	Need for Care	Readmission	Mortality	Study Quality
–	–	No	No	–	–	Moderate
–	No	–	–	–	–	Strong
–	–	–	–	–	–	Strong
–	–	–	–	–	–	Moderate
–	No	–	–	–	–	Strong
–	Partly	–	–	Partly[c]	No	Strong/ moderate
–	–	–	–	–	–	Strong
–	–	–	–	–	–	Moderate

DISCUSSION

This review identified 18 comparative studies on the effectiveness of rehabilitation interventions in post-ICU patients. Only eight controlled trials had low or medium risk of bias and were therefore considered for evaluation of effectiveness. They studied inpatient geriatric ward-based rehabilitation, outpatient rehabilitation, ICU follow-up clinics, a disease management support service, and ICU-diary interventions. Four of five studies that used PTSD as outcomes showed positive impact on PTSD. For none of the other outcomes did more than one trial find a positive impact.

The ICU diary showed the best evidence for effectiveness in this systematic review. It is a potentially effective, low cost, and highly acceptable intervention (65, 66). Documenting symptoms and ICU events in a diary may facilitate communication about threatening intensive care memories and may help to prevent PTSD (65, 67). However, for ICU staff, writing the ICU diary means more work, and they tend to view it as part of good patient care (68). Evidence on rehabilitation for post-ICU patients is still limited, as stated by the British National Institute for Health and Clinical Excellence's guideline (69). As the ICU diary is an innovative intervention, it is not yet mentioned in the National Institute for Health and Care Excellence guidelines.

To explore the heterogeneity in these complex interventions, we examined the intensity of interventions as experienced by the patient. Intensity was operationalized in terms of duration of interventions, frequency of patient contact with healthcare professionals, and number of intervention elements (30, 70, 71). We found that the intensity of inpatient and outpatient rehabilitation interventions is high but mostly of short duration. Aftercare in ICU follow-up clinics was less intense but lasted up to 12 months. The ICU diary was the least intense intervention, with at most one contact to discuss the diary and no further intervention elements.

Still, the ICU diary showed good evidence for reducing symptoms of PTSD. Focusing on mental health only, it achieved an effect on the targeted symptom of PICS. Most interventions with high intensity, like ICU follow-up clinics or complex rehabilitation, tried to affect more than one aspect of PICS. This produced heterogeneous results, only showing effectiveness in single outcomes, mostly just for PTSD.

The lack of overall effectiveness of post-ICU interventions on physical and mental health might be attributed to a delayed beginning of rehabilitation efforts. Introducing interventions only when cognitive and physical decline has already set in and has become difficult to reverse seems insufficient. Physical rehabilitation beginning immediately on ICU admission resulted in a decreased time to achieve improvements in activity and better functional outcomes at ICU and hospital discharge in comparison to delayed rehabilitation (72).

Bias Across Studies and Methodologic Challenges

Both the targeted population of post-ICU patients and the interventions found are complex. The lack of overall effects may obscure positive effects of specific components of the rehabilitation interventions. In addition, the wide range of outcomes and measures made comparisons and meta-analysis impossible. Most studies did not report effect sizes, complicating interpretation of results.

Generalizability of the studies was reduced by selection bias because of exclusion of specific patients, particularly the most vulnerable patients. For most of the interventions, patients needed a certain degree of mobility and cognitive functioning. But in fact, immediately after ICU discharge, independent walking is impossible for nearly three quarters of patients, whereas about one third show cognitive impairments (73). Thus, the findings may apply mostly to less severe post-ICU patients. Furthermore, the fitter patients are before, or shortly after, a critical illness, the more likely they are to recover (74–76).

Attrition bias is caused by high mortality and morbidity after ICU, which lead to high death and dropout rates in study populations (5, 19). This may lead to an overrepresentation of healthier subjects in both the control and intervention groups.

Usual care provided in the control group patients is heterogeneous, with some control groups receiving extensive rehabilitation interventions. Hence, standard care in control groups might already be as good as additional interventions to support patients in recovery. Only some investigators described standard care well. Maybe patients generally receive some sort of rehabilitation treatment or dedicated follow-up, but this mostly was not examined.

Implications for Research

This review shows a need for more research on evidence-based, effective rehabilitation interventions for post-ICU patients. Rather than focusing only on main effects in post-ICU patients, we suggest examining the effects in subgroups of patients in more detail. Interventions could be tailored to individual patient characteristics and needs. Until now, post-ICU patients do not have a recognized rehabilitation pathway, such as patients with stroke, myocardial infarction, or lung injury (7). Comprehensive research on rehabilitation interventions should help to establish a multidisciplinary, specialized rehabilitation for ICU survivors. Future research would benefit from a scientific description of the specific population of post-ICU patients, as was recently started with the introduction of the PICS concept. A systematic classification of post-ICU patients, and specific interventions, as well as a set of outcome measures, would improve comparability of studies.

Implications for Clinical Practice

The PICS concept is new and preliminary. Research on PICS started recently and evidence is still heterogeneous. PICS may help clinicians to handle a complex situation of several individual syndromes with complex etiology and interrelationships in post-ICU patients. Post-ICU patients may benefit from interventions like trauma-focused cognitive-behavioral therapy, specialized rehabilitation, and psychiatrist treatment,

but often they do not have access to those interventions. Reasons for this are a lack of awareness of their needs in aftercare and not qualifying for the interventions without having a certain diagnosis (like stroke, myocardial infarction, lung injury, etc.) (7, 69). Raising awareness for the special needs of ICU survivors by applying the PICS concept and treating it as an established group of diagnoses may pave the way to special interventions for post-ICU patients.

In clinical practice, the rehabilitation and aftercare process for patients with critical illness is still fragmented. Considering the evidence for safety and effectiveness of early rehabilitation beginning in the ICU (72, 77–79), a continuum of care, starting with early rehabilitation and lasting beyond ICU and hospital discharge, is desirable to improve short- and long-term outcomes for ICU survivors.

This review also supports the importance of outpatient care for post-ICU patients. This may call for effective primary care delivery in this domain. Primary care physicians may support the recovery of post-ICU patients when being more involved in the delivery of rehabilitation interventions.

Limitations of the Review

Indexing of studies in the new field of post-ICU patient care is still insufficient, so we may have missed relevant studies. Given the heterogeneity of patients, interventions, and outcomes, it was challenging to categorize and aggregate the data, so we may have misclassified studies. As we accepted only studies published in peer-reviewed journals, some publication bias is possible. However, this might be negligible since most published trials did not find overall positive effects. Language bias was minimized by the unrestricted initial search. Research on this topic has only developed recently. More trials on physical exercise are ongoing (80).

CONCLUSION

There is still a long way to go in rehabilitation of post-ICU patients. More research of appropriate methodological quality is needed. This review suggests that symptoms of PTSD may be reduced by simple interventions like ICU diaries. To encourage patients to read and use an ICU diary if provided and to discuss it with them seems worthwhile in everyday practice to prevent symptoms of PTSD.

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