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The Post - ICU Patient

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The Post-ICU Patient

Management of long-term impairments after critical illness

Survivors of critical illness and their caregivers frequently face long-term impairments of cognition, mental health, mobility and beyond, which demand for a patient-centred transition management and well-coordinated, outpatient post-ICU care.

Introduction

In recent years, the post-ICU sequelae of survivors of critical illness have become a focus of attention in research and patient care. This is the result of progress made in critical care throughout the last decades, which led to vast increases in survival rates and, therefore, growth of the cohort of post-ICU patients (Iwashyna et al. 2012; Zimmerman et al. 2013). Early investigations outlined that post-ICU patients are burdened with multifaceted consequences of critical illness summarised under the term post-intensive care syndrome (PICS). Notably, patients often perceive such functional impairments that potentially result from treatment as extremely relevant (Fried et al. 2002; Needham et al. 2012). The aim of this narrative review is to provide an overview over the established and further extended PICS domains and outpatient management of post-ICU patients.

Cognition

Studies in different patient populations and settings have established the association of critical illness and long-term cognitive impairments (**Figure 1**) (Adhikari et al. 2009; Hopkins et al. 2005; Iwashyna et al. 2010; Jackson et al. 2011; Jackson et al. 2003; Marra et al. 2018; Mitchell et al. 2018; Pandharipande et al. 2013; Wolters et al. 2013). Across studies, cognitive impairments were found in 4% to 62% of patients with follow-up periods from 2 to 156 months (Wolters et al. 2013). However, there has been no consensus on categorisation of cognitive impairments and tools of assessment, which partially explains the variations.

Upon ICU discharge, the frequency of cognitive impairments is high, and after an initial improvement (Hopkins et al. 2005), impairments persist for years. They pertain to almost all domains of cognition, including memory, verbal fluency, attention and executive function (Wolters et al. 2013). Additionally, ICU survivors face a 60% increase in relative risk to suffer from dementia three years after discharge (Guerra et al. 2015). Presence and duration of delirium is a risk factor for long-term cognitive impairment (Girard et al. 2010; Goldberg et al. 2020), but the underlying pathophysiology is widely unknown. Few studies have considered pre-ICU cognitive functions. Two population-based, prospective cohort studies found a decline in cognitive functions in ICU survivors when compared to their pre-ICU status (Ehlenbach et al. 2010; Iwashyna et al. 2010), and in a cross-sectional study, 37% of ICU patients showed pre-existing cognitive impairments (Pisani et al. 2003).

Considering the connection between delirium and cognitive impairment (Goldberg et al. 2020), preventing delirium seems rational. Regular screening for delirium (Luetz et al. 2014), implementation of bundles such as the ABCDEF bundle (Barnes-Daly et al. 2017; Marra et al. 2017), the preference for non-benzodiazepine sedatives if sedation is necessary (Pandharipande et al. 2007; Pandharipande et al. 2010), and modifications of the patient environment can

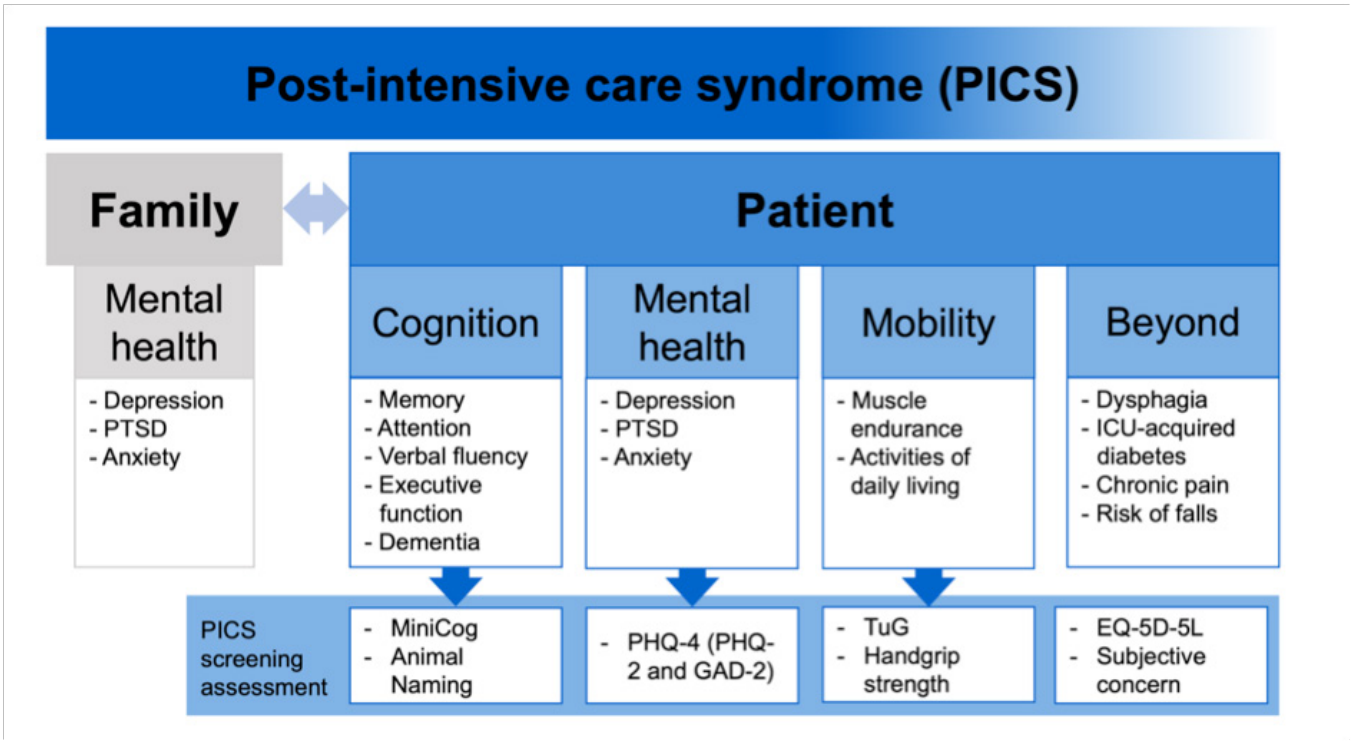

Figure 1. Domains of long-term impairments in post-ICU patients and caregivers (modified and extended from Needham et al. (2012)) and instruments used for ambulatory PICS screening after ICU treatment as proposed by Spies et al. (2020). EQ-5D-5L and items for the patients' subjective concern about functional impairments are used to assess health-related quality of life.
Abbreviations: PICS=Post-intensive care syndrome; PTSD=Post-traumatic stress disorder; ICU=Intensive care unit; PHQ=Patient health questionnaire; GAD=Generalised anxiety disorder scale; TuG=Timed up-and-go; EQ-5D-5L= European quality of life 5 dimensions 5 level.

reduce delirium (Litton et al. 2016; Luetz et al. 2019). Unlike a no-sedation strategy (Olsen et al. 2020; Strøm et al. 2010), no or light sedation has been shown to prevent delirium (Hager et al. 2013; Pandharipande et al. 2007). This is also the subject of current guidelines (Barr et al. 2013; Taskforce DAS et al. 2015).

As a brief screening for cognitive impairments, Spies et al. (2020) proposed to use the MiniCog (Borson et al. 2003) and Animal Naming test (Sager et al. 2006). If the patient is above threshold, the Trail Making test (Reitan 1958) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 2012) provide in-depth assessment. Data on treatment of already manifest cognitive impairment is limited. Two pilot studies showed promising results of cognitive rehabilitation (Jackson et al. 2012; Wilson et al. 2018), while another study using a combined cognitive-physical rehabilitation did not detect an effect on executive functions (Brummel et al. 2012). In the future, larger trials need to investigate the potential of cognitive rehabilitation and have to consider pre-existing cognitive impairments. Studies also need to investigate if delirium prevention improves cognitive outcomes – an association still to be established.

Mental Health

Mental health impairments after critical illness pertain to depression, anxiety, and post-traumatic stress disorder (PTSD) (Marra et al. 2018). Symptoms of depression are present in about 30% of post-ICU patients, persisting even five years after discharge (Bienvenu et al. 2018; Davydow et al. 2009; Rabiee et al. 2016), but studies did not consistently use the same assessment tools, definitions and time frames (Rabiee et al. 2016). With regards to anxiety, 32% to 40% of patients show symptoms within the first year after discharge (Nikayin et al. 2016). Just like depression, anxiety symptoms remain relatively stable (Bienvenu et al. 2018; Hopkins et al. 2005). For PTSD, prevalence varied from 4% to 62% across studies, with a pooled prevalence of 17% to 44% in the year after ICU discharge (Parker et al. 2015). After eight years, PTSD prevalence was still 24% (Kapfhammer et al. 2004). Notably, a large number of patients show overlapping symptoms (Huang et al. 2016; Marra et al. 2018). For instance, Wolters et al. (2016) found that 63% percent with any mental health symptoms showed symptoms of anxiety, depression and PTSD. Analogous to cognitive impairments, very few studies assessed pre-existing psychiatric symptoms, but results indicate

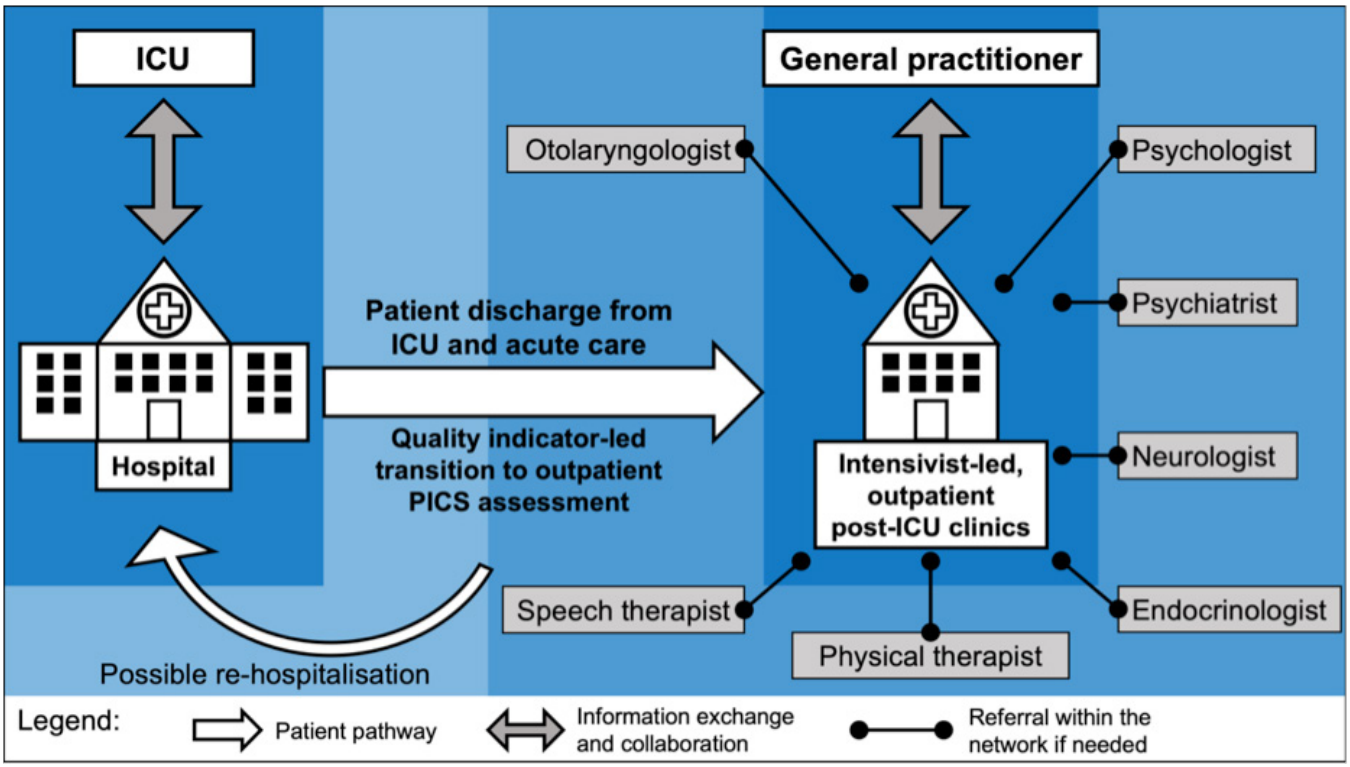

Figure 2. Management of the post-ICU patient. After a quality indicator-led discharge and transition to ambulatory care, patients are regularly assessed for PICS-related symptoms in post-ICU clinics, which work in close collaboration with the general practitioner and rely on a network of specialists for referrals. Abbreviations: PICS=Post-intensive care syndrome; ICU=Intensive care unit.

that prevalence is high (Davydow et al. 2009; Rabiee et al. 2016). For instance, 6.2% of mechanically ventilated ICU patients had a psychiatric diagnosis and about 50% received a prescription for psychoactive medication in the five years preceding their ICU stay, significantly more than in the general population. ICU treatment increased the risk for a psychiatric diagnosis and psychoactive medication prescription, with hypnotics and antidepressants being most commonly prescribed (Wunsch et al. 2014).

Risk factors associated with mental health impairments are nightmares and extreme fear in the ICU (Parker et al. 2015; Rattray et al. 2005; Samuelson et al. 2007), lack of recollection of ICU experience (Rattray et al. 2005), and delusional memories from the ICU (Jones et al. 2001; Nikayin et al. 2016). Further, pre-ICU psychiatric morbidity (Wade et al. 2012; Weinert and Meller 2006), stress during ICU treatment (Wade et al. 2012), and psychiatric symptoms at hospital discharge were associated with post-ICU depression, anxiety and PTSD (Davydow et al. 2009; Nikayin et al. 2016; Rabiee et al. 2016; Rattray et al. 2005). Interestingly, neither age, severity of illness, or sex were identified as risk factors. Likewise, delirium, was not associated with PTSD or depression in the ICU context (Girard et al. 2007; Jackson et al. 2014; Wolters et al. 2016), even though post-operative delirium was found to be a risk factor for PTSD (Drews et al. 2015). It has been shown that mental health problems significantly diminished health-related quality of life (Davydow et al. 2009; Parker et al. 2015).

As a screening tool for mental health impairments, the Patient Health Questionnaire-4 was proposed, followed by the more detailed Patient Health Questionnaire-8 for depression, Generalised Anxiety Disorder Scale-7 for anxiety (Kroenke et al. 2010), and Impact of Event Scale-revised for PTSD (Spies et al. 2020; Weiss 2007). For treatment, ICU diaries reduced PTSD symptoms in one large randomised controlled trial and one prospective, non-randomised study (Garrouste-Orgeas et al. 2012; Jones et al. 2010), and anxiety and depression symptoms in another small randomised controlled trial (Knowles and Tarrier 2009), whereas a recent, large randomised controlled trial published in JAMA did not detect an effect of ICU diaries on PTSD, anxiety or depression (Garrouste-Orgeas et al. 2019). Provision of a self-help manual reduced PTSD symptoms but not depression or anxiety symptoms (Jones et al. 2003), and the benefit of post-ICU follow-ups remains inconclusive (Cuthbertson et al. 2009; Schandl et al. 2012). Interestingly, physical rehabilitation has been shown to

reduce anxiety and depression (Jones et al. 2015; McWilliams et al. 2009), whereas a recent review concluded that early physical therapy does not reduce anxiety or depression (Fuke et al. 2018). Clearly, there is a demand for randomised controlled trials that rigorously compare different approaches such as self-help manuals and post-ICU follow-ups to provide evidence on strategies to reduce mental health impairments after critical illness.

Mobility and Physical Impairments

Physical impairments manifest early during the ICU stay as intensive care unit-acquired weakness (ICUAW), which is a muscular weakness defined by a Medical Research Council (MRC) score < 48 that occurs during critical illness in absence of any other plausible aetiology (Fan et al. 2014a). It has consistently been shown that muscle weakness during the ICU has a direct impact on the treatment success, like liberation from mechanical ventilation and discharge from the ICU as well as hospital (Hermans et al. 2014). Furthermore, muscle weakness at discharge from the ICU is a predictor for long-term mortality, physical function and health-related quality of life up until five years after discharge (Hermans et al. 2014; Van Aerde et al. 2020). Interestingly, Van Aerde et al. (2020) observed a dose-response relationship between muscle strength at ICU discharge and 5-year mortality. Furthermore, the optimal cut-off for predicting 5-year mortality and morbidity is a MRC score ≤ 55, which is above the diagnostic cut-off of 48 for ICUAW.

For screening of physical impairments, Spies et al. (2020) recommended to use handgrip strength (Roberts et al. 2011) and the Timed Up-and-Go (Podsiadlo and Richardson 1991), followed by the more elaborate Short Physical Performance Battery (Pavasini et al. 2016) and 2-Minute Walk Test (Brooks et al. 2006). Long-term follow up studies have shown that muscle strength measured with the MRC score fully recovers one year after ICU discharge, while muscle endurance measured via 6-minute walk test remains at 75% of predicted values (Fan et al. 2014b; Herridge et al. 2011; Wollersheim et al. 2019). This suggests that the physical impairments extend beyond muscle strength and that muscle endurance or regenerability might be a more relevant parameter during long-term evaluation. The term introduced by Van Aerde et al. (2020) "ICU-acquired neuromuscular complications" might therefore be more appropriate than the commonly used ICUAW, as weakness appears to be only one aspect of the spectrum of physical impairments. Just like cognitive and mental impairments, there is little evidence on pre-existing physical impairments, even though worse functional physical status right before hospital admission was associated with increased ICU mortality (Zampieri et al. 2017).

> **"current recommended management encompasses the early, goal-directed therapy of the critical illness itself in conjunction with early protocol-based mobilisation, to improve physical function, reduce duration of a possible delirium, counteract muscle atrophy and shorten time on mechanical ventilation and in the ICU"**

Current recommended management encompasses the early, goal-directed therapy of the critical illness itself in conjunction with early (within 72 hours after ICU admission) protocol-based mobilisation to improve physical function, reduce duration of a possible delirium, counteract muscle atrophy and shorten time on mechanical ventilation and in the ICU (Bein et al. 2015; Ding et al. 2019; Schaller et al. 2016; Schweickert et al. 2009; Wollersheim et al. 2019).

Other Functional Impairments

PICS was initially defined around physical function, cognition and mental health. Yet, additional post-ICU sequelae have been discovered outside the classical PICS domains. Dysphagia, for instance, is commonly observed after endotracheal intubation and has an incidence of up to 62% depending on the study cohort and length of intubation (Skoretz et al. 2010). It is an independent risk factor for 28- and 90-day mortality (Schefold et al. 2017), but Brodsky et al. (2017) were able to show that 100% of ARDS survivors discharged with dysphagia had recovered until five years after discharge.

Critical illness-associated hyperglycaemia is common and affects mortality (Plummer et al. 2014). The hyperglycaemia during acute treatment has been thoroughly investigated, while progression to a permanent dysregulation of the glucose homeostasis was neglected (NICE-SUGAR Study Investigators et al. 2009; Van den Berghe et al. 2006; Van den Berghe et al. 2001). A recent meta-analysis has shown that critical illness-associated hyperglycaemia increases the risk of developing diabetes with an odds ratio of 3.5 (Ali Abdelhamid et al. 2016). Systematic screening for ICU-acquired diabetes after discharge for early diagnosis and prevention of long-term consequences might therefore be warranted (Preiser and de Longueville 2017).

ICU patients regularly receive analgesic therapy as pain frequently occurs in critically ill patients. Interestingly, pain is also among the top three symptoms reported four months after ICU discharge, which has led to systematic investigations

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showing that chronic, ICU-related pain has a major impact on patients' daily life (Baumbach et al. 2016; Choi et al. 2014).

Another organ system that has received increased attention is the skeletal system, which is affected immensely by immobilisation during and after the ICU stay (Leblanc et al. 1990). ICU survivors experience an increased bone resorption, leading to decreased bone mineral density (Orford et al. 2016). The combination with frequently observed falls in post-ICU patients cumulates to an increased risk for fractures and imposes a major detriment on recovery (Parry et al. 2020).

Family and Caregivers

The family's role for the ICU patient is twofold, whereby family is used as a surrogate for all people the patient wishes to be included in his or her care (Brown et al. 2015). Firstly, the family is a treatment resource in a concept termed "patient-family-engagement" (PFE), which was defined by Braun et al. (2015) as "[...] an active partnership between health professionals and patients and families working at every level of the healthcare system to improve health and the quality, safety, and delivery of healthcare." Secondly, the family bears a huge burden during the ICU treatment, which can manifest in anxiety as well as depression and can lead to subsequent symptoms of PTSD (Azoulay et al. 2005; Pochard et al. 2001). Additionally, in the post-ICU care, family members regularly work as unpaid caregivers, which can cause depressive symptoms (Cameron et al. 2016). Notably, symptoms in family members are positively correlated to the degree of impairments in the post-ICU patient himself (Choi et al. 2014).

Family support interventions can reduce the ICU length of stay, most likely by facilitating the shared-decision-making process of futile interventions since no impact on mortality could be detected (Lee et al. 2019; White et al. 2018). Even though families were more satisfied with the communication with the ICU team, no benefit for their mental health was detected (Carson et al. 2016; Shelton et al. 2010; White et al. 2018). Nevertheless, the implementation of structured family support is weakly recommended in current guidelines (Davidson et al. 2017). An additional measure to include the family in the ICU treatment is a flexible or extended visitation policy, since evidence indicates towards reduced anxiety and depression in family members as well as reduced anxiety and delirium in patients (Nassar Junior et al. 2018; Rosa et al. 2019; Rosa et al. 2017). On the contrary, extended visiting hours might increase the risk of ICU staff burnout (Nassar Junior et al. 2018).

Post-ICU Care Trajectories and PICS Management

With a growing cohort of ICU survivors (Kaukonen et al. 2014; Pronovost et al. 2004), more patients require transition management from inpatient to outpatient care. Post-ICU rehabilitation should be organised to mitigate functional disabilities, enable social participation and foster return to work. These demands are hardly met, as shown in a study of 103 mechanically ventilated ICU patients followed for one year post discharge and characterisation of their care pathways and quality of life (Unroe et al. 2010). Patients experienced multiple transitions of care locations, and 67% were re-hospitalised at least once. Simultaneously, each patient accrued more than $300,000 of health care costs (Unroe et al. 2010), with re-hospitalisations being an expensive element of post-ICU care (Kress and Herridge 2012). Only 9% were independently functioning and 27% were considered having a good quality of life (Unroe et al. 2010). Several studies showed approximately 50% of previously employed survivors of critical illness were unemployed one year after discharge (Hopkins et al. 2005; Myhren et al. 2010; Norman et al. 2016), leading to a 60% loss of income (Kamdar et al. 2017). The economic consequences for the society have not been thoroughly quantified yet but are likely to be substantial. Devoid of structured post-ICU follow-up, ICU discharge has been described as "ejection" instead of smooth "transition" (Sevin and Jackson 2019).

In light of complex impairments and fragmented patient trajectories, attention should be given to coordinated and evidence-based transitions from inpatient to outpatient care. Description of ideal patient pathways and implementation of intersectoral quality indicators, as defined for mechanically-ventilated patients in Germany (Kastrup et al. 2017), can help streamline the process. In more detail, these quality indicators comprise the handover to the outpatient care physician, individualised needs assessments, and transfer conferences with stakeholders from inpatient and outpatient care (i.e. transfer manager, physician, and respiratory therapist).

After transitioning to an outpatient setting, post-ICU clinics can serve as a hub to guide patients and ensure that their health concerns are addressed (**Figure 2**). These clinics should be staffed with intensivists, regularly assess patients for long-term impairments (Spies et al. 2020), and work in close communication with the patients' general practitioners to exchange information. Drawing on a network of specialists such as psychotherapists and physical therapists, post-ICU clinics can develop care plans tailored to the patients' individual needs to pave the tedious road to recovery. With continuity in post-ICU care, costly hospital re-admissions might be avoidable, PICS symptoms alleviated and return to work more likely. A similar concept was implemented at Vanderbilt ICU Recovery Center, but evaluation of effectiveness is still pending (Sevin et al. 2018). Another post-ICU programme in the UK, which included functional assessments and referrals, did not show an effect on quality of life or mental health outcomes after twelve months (Cuth-

bertson et al. 2009). Yet, post-ICU care was led by nurses, even though, as noted by Sevin and Jackson (2019), intensivists might be more sensitive to ICU-specific problems such as ICUAW. A Cochrane review on post-ICU follow-up services concluded that there are large variations in the design of interventions and insufficient evidence to draw conclusions at this point (Schofield-Robinson et al. 2018). Taken together, large-scale randomised-controlled trials need to rigorously assess the potential of intensivist-led, outpatient post-ICU clinics to guide patient care after critical illness.

Conclusions

Over the last two decades, functional outcomes of critical illness have gained a centre stage of intensive care research, due to the growing cohort of ICU survivors and, thus, more patients with impairments. Clinical research does not merely focus on survival, but also how the patient manages to recover in the subsequent months and years. Despite a broad consensus that a fragmented care process imposes risks on patients, evidence on effective interventions to counter impairments is scarce, and post-ICU care trajectories are an area of future improvement. In collaboration with patients' general practitioners, post-ICU clinics might function as integrative hubs, which are embedded in a broad referral network of specialists. These institutions can harmonise inpatient-to-outpatient transitions and streamline post-ICU care processes to ensure optimal patient recovery.

Conflict of Interest

All authors declare no conflicts of interest for the submitted work. For grants, personal fees, non-financial support and patents outside the submitted work, International Committee of Medical Journal Editors (ICMJE) disclosure forms are available upon request. ■

Abbreviations

ICU - Intensive care unit
PICS - Post-intensive care syndrome
RBANS - Repeatable Battery for the Assessment of Neuropsychological Status
PTSD - Post-traumatic stress disorder
ICUAW - Intensive care unit-acquired weakness
MRC - Medical Research Council
PFE - Patient-family-engagement

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