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Title: Functional Outcomes following critical illness: Epidemiology, current management strategies and the future priorities

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Abstract

Intensive care unit (ICU) survivorship has gained significant attention over the course of the COVID-19 pandemic. In this review we summarize the contemporary literature in relation to the epidemiology and management of post-ICU problems.

Survivors of critical illness can have complex physical, social, emotional and cognitive needs in the months following hospital discharge. Emerging evidence has shown that pre-ICU characteristics such as educational attainment, alongside in-ICU factors such as delirium, may contribute to worsening outcomes. Evidence regarding the impact of post-ICU recovery services is evolving, but models such as post-ICU clinics and peer support programs are gaining rapid momentum. Future research should focus on modifiable risk factors and how identification and treatment of these can improve outcomes. Furthermore, rigorous evaluation of post-acute critical care recovery services is necessary.

Keywords: post intensive care syndrome; long-term outcomes; critical illness; recovery.

Introduction

Patients who have survived critical illness may experience physical, cognitive and emotional problems in the months following discharge (1-3). These problems, which have been termed Post Intensive Care Syndrome (PICS), can have wide ranging implications for the individual, the healthcare system and society as a whole (4).

In this review, we focus on the epidemiology of these problems and potential interventions which may mitigate them. We will specifically draw on learning from a recent expert consensus conference. Future directions for clinical practice and research will be explored.

Post-Intensive Care Syndrome Epidemiology

Long-term impairments after critical illness are common and often enduring. In a seminal epidemiological study of 406 intensive care unit (ICU) survivors, one or more long-term impairments were present at 3- and 12-months in 64% and 56% of survivors, respectively (5). At 12 months, new physical, cognitive, and mental health impairments (i.e., depression) were found in 21%, 33%, and 31% of survivors, respectively (5). Co-occurring problems were present in 25% of survivors at 3 months (e.g., cognitive and physical problems) and in 21% of survivors at 12 months (5).

In a recent multicenter observational cohort study, new, long-term physical, cognitive, and/or mental health impairments were present in 58% of medical ICU patients, 64% of patients after an urgent surgical ICU admission, and 43% of patients after an elective

surgical ICU admission (6). When separated into specific functional domains, the story was more nuanced. Cognitive decline was experienced across all three groups. However, physical and mental health function was dependent on the type of ICU admission, as elective surgical patients experienced improvements, whereas urgent surgical and medical patients experienced declines (6).

When viewed together, these studies reveal several important facts. First, they confirm that new, long-term impairments are common after critical illness. Second, these impairments may affect physical, cognitive, and/or mental health functioning; one-quarter of survivors will have developed 2 or more impairments by 3 months, and often, impairments endure (5). Third, the likelihood of developing new impairments depends on whether the ICU admission was for a medical, urgent surgical, or elective surgical reason (6). These findings can be used to inform, prepare and educate patients and family during the recovery process.

These long-term functional impairments often result in an inability to return to employment, compounding their effects. In a systematic review of 42 studies, 67% and 44% of ICU survivors had not returned to work 3 and 12 months after critical illness, respectively (7). Loss of employment incurs financial cost, further contributing to the long-term stress experienced by survivors of critical illness, as well as their families. In contrast, return to employment was associated with improved health-related quality of life and fewer depressive symptoms, highlighting the importance of designing recovery programs which facilitate a return to employment (7).

Risk Factors

Using existing, as well as novel systematic reviews to inform their recommendations, the recent international consensus conference on prediction and identification of long-term impairments after critical illness, identified risk factors for long-term impairments in order to facilitate timely identification of these problems (8). The experts concluded that existing tools are inadequate to reliably predict PICS problems and future additional work is necessary to improve our ability to do so. Yet, prediction of post-ICU problems and the responsibility to provide anticipatory guidance to ICU survivors is a task ICU clinicians should incorporate into clinical practice (9).

Pre-existing physical, cognitive, or mental health problems were each put forth as established risk factors that could be used to identify patients at high-risk of developing long-term impairments after critical illness (8). Memories of frightening experiences in the ICU was identified as a risk factor for long-term mental health problems, highlighting the importance of inquiring about such memories post-discharge, and using this information to screen for anxiety, depression, and/or post-traumatic stress disorder. Risk factors for long-term cognitive impairment included delirium, hypoxemia, acute respiratory distress syndrome (ARDS), sepsis, and shock. As the relationship between duration of delirium and long-term cognitive impairment has been identified in multiple studies, reviewing the medical record for this risk factor post-discharge is recommended (10-11). Finally, after critical illness, patients with early symptoms of anxiety, depression, or post-traumatic stress disorder (PTSD) are at high risk to continue to suffer from these problems.

At the time of the consensus conference, there was uniform agreement that social determinants of health could be key factors for post-ICU long-term impairments, and that “these have not been adequately researched but should be” (8). Related to this assumption, recent work by Geense et al found that higher education level was protective against the development of long-term impairments, confirming prior work by Marra et al (5-6). Whether higher education level reflects cognitive and/or psychological resiliency, more effective coping skills, and/or more robust social support remains unclear and warrants further investigation. Likewise, it was acknowledged that religiosity and spirituality are factors that may mitigate long-term impairments, although these potentially protective factors also require further inquiry.

Screening and identification

With the aim of identifying and rehabilitating impairments in a timely fashion, the consensus conference recommended that patients with any of the aforementioned risk factors be screened for PICS problems two to four weeks after discharge and that serial assessments for PICS problems should occur with important health and/or life changes (8). The initial post-discharge assessment should be informed by recommended functional reconciliation assessments, completed as part of ICU admission and discharge, to ensure post-acute care services are aligned with patients’ new functional impairments (Figure 1). The recommended screening tools are provided in Table 1.

The importance and value of screening patients for potential problems following critical illness was highlighted in a recent multi-centre study (12). This European cohort study

demonstrated that undertaking routine screening for problems such as PTSD was useful in detecting ongoing symptoms of PTSD at three months following hospital discharge (12).

Interventions

Opportunities to intervene in the development of PICS and improve functional outcomes, fall into two main categories: prevention of PICS through improved ICU care and interventions to ameliorate PICS or its impacts once established.

Improving in ICU care via the ABCDEF bundle

The ABCDEF bundle, also known as the A2F bundle, is a multicomponent ICU intervention focused on assessing, preventing, and managing symptoms rather than diseases (13). ABCDEF stands for **A**ssess, prevent, and manage pain; **B**oth spontaneous awakening and breathing trials; **C**hoice of Analgesia and Sedation; **D**elirium assess, prevent, and manage; **E**arly Mobility and Exercise; **F**amily engagement/empowerment (14). The goal of the bundle is to optimize wakefulness, cognitive engagement, and physical activity in critically ill patients. Certain characteristics of critical care itself may contribute to PICS, for example, the use of benzodiazepines has been associated with PTSD after critical illness (15). Thus, targeting modifiable risk factors in the ICU may diminish the incidence and impact of PICS. Implementation of the complete A2F bundle is associated with decreased hospital mortality, mechanical ventilation, coma, delirium, use of restraints, ICU readmission, and discharge to a facility other than home, with a significant dose response curve being observed between more of the bundle being performed and improvements in each of these clinical outcomes (13-14). Several of these

outcomes have been associated with PICS, most linearly delirium, which is the strongest independent predictor of cognitive impairment after critical illness (11).

Models of support following discharge

Several models of post-ICU care have been explored, including telephone follow up, peer support programmes and post-ICU clinics, with the goal of enhancing recovery and treating or ameliorating the problems of PICS (16-19).

Of these, multidisciplinary post-ICU clinics have been perhaps the most difficult interventions to study. These clinics are often comprised of multiple and heterogeneous interventions, targeting a variety of patient populations in geographically diverse settings and health care systems, and assessed using disparate outcomes (20). Although several studies show promise, no post-ICU care model has been definitively shown to improve patient outcomes after critical illness (20). And yet, perceived clinical need for such services has resulted in widespread interest in such care, and an increasing number of multidisciplinary post-ICU clinics have been established worldwide over the past 10 years (21). Although such clinics can take many forms, a recent large qualitative study of survivors of critical illness, their caregivers, and the clinicians seeking to create post-ICU programs, collated the characteristics of post-ICU programs desired by their users (22). These included care coordination, provision of educational materials, advice for managing physiological disturbances and symptoms, information about adaptation, peer support, interventions tailored to caregivers, and socioeconomic guidance. Medication management by pharmacists, screening for anxiety, depression, PTSD, and cognitive

dysfunction, physical and respiratory function assessments, and case management services are common features of these clinics; peer support, debriefing of an ICU diary, and ICU visits may also be offered (22-23).

Peer support programmes have also gained popularity from the critical care community in the last decade (24). A recent international study described patient perceived benefits of peer support, offered via support groups, online forums or integrated into routine care across the recovery arc (25). Benefits identified included reduced anxiety, increased external validation of progress, and improved interactions with the health service. However, similar to post-ICU clinics, proof of effectiveness of this type of intervention is lacking and more work is urgently required in this area of innovation (26).

Beyond this evidence, barriers to the implementation and sustenance of post-ICU programs remain. Recent multi-center work identified a number of these barriers, including insufficient funding for post hospital care programs, lack of space, difficulty identifying appropriate patients, and patient and family attendance (27). Awareness and understanding of PICS and post ICU recovery is also not widespread, even amongst clinicians caring for critically ill patients and those recovering from critical illness (28). As such, an understanding of how post-ICU care can be delivered in a reliable and consistent manner is needed.

Wider benefits of understanding long-term functional outcomes

In addition to patient reported outcomes, a number of potential benefits of post-ICU care interventions have been identified and require further exploration. Early data suggest possible system benefits from multidisciplinary post-ICU follow up including decreased hospital readmissions, identification of unmet needs and reduced costs (29-31).

Follow-up services may also serve as platforms from which clinicians and researchers can learn about the natural history and sequelae of new diseases such as COVID-19 (32-33). This process can have clear benefits for the individual, healthcare system and society as whole. For example, understanding specific alignments which patients have in the recovery phase could help alter practice and drive quality improvement in the critical care environment. This was demonstrated in recent work which highlighted a high prevalence of Meralgia Paraesthetica in patients with COVID-19, thought to be related to proning techniques (34). This learning could potentially lead to improvements to care, which can be undertaken in a timely fashion.

The challenges which the ICU workforce face have been highlighted throughout the pandemic. Multi-centre work from France has shown that ICU staff are at a high risk of developing emotional issues such as anxiety, depression and burnout (35). Work undertaken by the Society of Critical Care Medicine's THRIVE initiative demonstrated that longitudinal feedback improved staff satisfaction at work, as well as potentially improving patient care in the ICU (36). Those involved in the study also described the follow-up process as a mechanism by which clinician burnout could be avoided. This feedback can

be obtained via ICU follow-up programmes of care and via ongoing contact with patients and families. This novel mechanism is still developing, and more research is required around its relationship with clinician burnout syndrome (37).

Future Directions

The field of post-ICU care is rapidly evolving and growing; the COVID-19 pandemic has brought the often-stark challenges of ICU survivors into public consciousness, pushing a number of new post-ICU clinics into being and providing a model for the now widespread post COVID clinic (38). With this significant expansion, more work is urgently required to understand: 1) the risk factors for the development of post-ICU problems and 2) evaluation of complex interventions across the patient journey.

1. Risk factors for the development of post-ICU problems

As highlighted previously, the integration of routine screening and rigorous evaluation of this approach is needed in order to better risk stratify patients for potential intervention. Recent work has also highlighted that patient reported outcome measures should be closely aligned with biological and molecular screening. Using in-ICU biomarkers, Brummel and colleagues reported an association with C-reactive protein and Matrix metalloproteinase-9 and greater disability in basic and instrumental activities of daily living at three- and 12-months post discharge (39). Future studies which pair longitudinal measurement of inflammation and related molecular pathways, throughout the course of critical illness, are therefore warranted.

2. Evaluation of complex interventions across the patient journey

Post-ICU follow-up clinics and services not only need thoughtful evaluation; thoughtful implementation is also required. This review has highlighted that patients have a multitude of issues following hospital discharge, which span both health and social care boundaries. Further, in a recent multi-center cohort, researchers from the UK demonstrated a tangible and significant link between emotional and social health during recovery from critical illness (40). Therefore, it is clear, for those recovering from critical illness, health is made up of more than the delivery of healthcare. Supportive measures which include integrated social care provision are needed (41). This is especially true in a post- COVID-19 world, where socio-economic problems will proliferate across the population due to high rates of unemployment, exacerbating identified healthcare disparities. An integrated approach to supporting all aspects of health and wellbeing has been adopted in small pockets internationally and has proven feasible and acceptable by patients (42). However, additional evaluation is needed.

Conclusion

Patients can face complex problems following critical illness, which often occur as symptom clusters which are interrelated. This review has identified that factors inherent to critical illness itself, as well as pre-existing problems can contribute to worsening outcomes, just as certain factors such as prior level of education appear to be protective. Complex interventions such as post- ICU clinics and peer support groups, have been widely implemented internationally, however, further evaluation of how these services impact patient and service outcomes is warranted. Further, services which provide integrated health and social care require further investigation.

Keypoints:

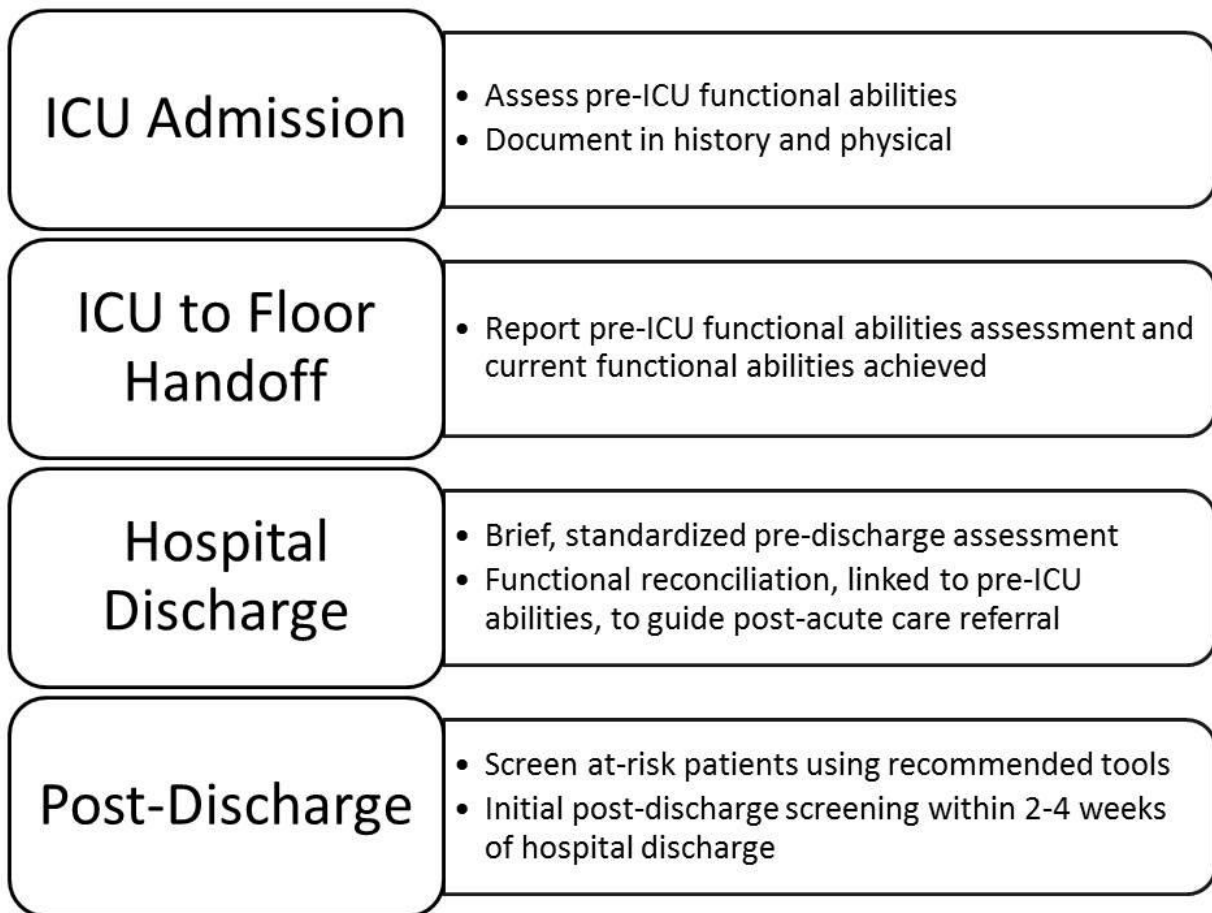
- Survivors of critical illness can face complex health and social challenges in the months and years following discharge.
- Pre-ICU and in-ICU factors may contribute to worsening outcomes, which may be detected, and potentially modified through the use of routine screening.
- Post-ICU clinics and peer support forums have gained increasing interest, especially in the context of the COVID-19 pandemic. Further evaluation of these models of care are required.

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Conflicts of Interest: None

Figure. Recommended longitudinal approach to screen and identify long-term impairments after critical illness. ICU=intensive care unit.



Original Source: Mikkelsen, ME. Still, M. Anderson, BJ. et al. (2020) Society of Critical Care Medicine's international consensus conference on prediction and identification of long-term impairments after critical illness. *Crit Care Med*;48(11):1670-1679.

Table. Recommended screening instruments to assess for physical, cognitive, and mental health problems after critical illness.

Domain	Screening Instrument	Scoring
Physical	6-minute walk (43) and/or EuroQol-5D-5L (44)	The 6-minute walk test is resulted as a percent predicted value; mobility responses range from no problems walking, to slight, moderate, or severe problems walking and unable to walk.
Cognition	Montreal Cognitive Assessment (MoCA) (45) or MoCA-blind	A score of 18-25, 10-17, and less than 10 is used to identify mild, moderate, or severe impairment, respectively.
Anxiety	Hospital Anxiety and Depression Scale (46)	A score of 8 or greater on the anxiety or depression subscale is used to identify symptoms of clinically significant anxiety or depression.
Depression	Hospital Anxiety and Depression Scale (46)	A score of 8 or greater on the anxiety or depression subscale is used to identify symptoms of clinically significant anxiety or depression.
Post-traumatic stress disorder	Impact of event scale-revised (IES-R) (47) or IES-6 (48)	An average score of 1.6 or greater for the IES-R or 1.75 or greater for the IES-6 is used to identify PTSD symptoms.

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