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**TITLE:** THE EVOLUTION OF POST-INTENSIVE CARE SYNDROME

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In September of 2010, a stakeholders' conference was convened with a daunting, yet vital, overarching goal for the field of critical care medicine: improve the long-term outcomes of patients and their family members after discharge from intensive care (1). With the end in mind, the stakeholders began with a more proximal goal: "understand the long-term outcomes of intensive care patients and their families." To facilitate this goal, and simultaneously raise awareness, the term "post-intensive care syndrome" (PICS) was born. The term, which was designed to be applied to survivors and family members (PICS-F), encompasses the detrimental changes in cognition, mental health and physical function, which individuals face following critical care (1).

In the interim, the medical community has become more aware of PICS and our understanding has evolved. It is now well established that PICS and PICS-F are common (2-3), have a profound and lasting impact on patients, families, and society (2-6), and that sepsis plays a pivotal role in the relationship between critical illness and PICS (7). And yet, fundamental epidemiological questions remain unanswered conclusively. For example, what proportion of survivors experience PICS at 3- and 12-months? Can we predict who will develop PICS? And, amongst those who develop PICS, is co-occurrence across the physical and mental health domains the norm, or the exception?

In this issue of *Critical Care Medicine*, Marra and colleagues (8) provide the results from the largest epidemiological study of PICS conducted to date. In a prospective cohort study, the investigators examined the frequency and determinants of physical disability, depression, and cognition in critically ill survivors from 5 hospitals. In-person assessments were conducted at 3- and 12-months post-discharge. Cognition, depression, and disability were measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Beck Depression Inventory Second Edition (BDI-II), and Katz Activities of Daily Living (ADL), respectively. With a PICS focus on what is "new," rather than what is "worse," patients with pre-existing cognitive impairment and disability were excluded from participation.

By design, therefore, of 781 survivors, 250 (32%) were excluded due to pre-existing mild cognitive impairment and/or functional disability, and an additional 589 were excluded upstream given pre-existing severe cognitive impairment. Collectively, these details reveal the frequency with which significant impairments pre-date critical illness.

Further, providing a more comprehensive view of “survivorship,” among 531 eligible survivors, 66 died before 3 months and an additional 46 died between the 3- and 12-month assessments.

Armed with excellent cohort retention, the investigators confirmed estimates that the majority of survivors of critical illness incur PICS. Specifically, new PICS was present in 64% and 56% of survivors at 3 and 12 months, respectively. When new impairment was identified, it was most frequently confined to one domain, as only 19% and 6% of survivors had two or three problems, respectively, at 3 months. Notably, the infrequent nature of co-occurrence observed by Marra et al. contrasts with a small study conducted at 2 hospitals by Maley and colleagues (9). In the latter study, which was not limited to “new” PICS, 56% of survivors self-reported impairment in at least two PICS domains and one out of 3 reported impairment in all PICS domains (9). As 54% of survivors in the study by Maley et al. self-reported that function was worse in one or more domain, the collective data reveals that the vast majority of survivors of critical illness have neuropsychological or functional impairment, and many of these impairments are new or worse.

In the present study, the most common new impairment at 3- and 12-months was cognitive impairment (38% and 33%, respectively). Depression was present in approximately one-third of survivors at 3 and 12 months, while disability was present in 21% of survivors at 3-months and 21% at 12 months. In general, new impairment present at 3 months persisted (i.e., only 21% transitioned to being PICS-free), and those free of impairment at 3 months largely remained free of impairment at 12 months. Interestingly Marra et al found that two non-critical illness markers were associated with long term outcomes; severe frailty was associated with lower odds of being PICS-free, and more years of education was associated with a greater odds of being PICS-free at both three and 12 months.

Major strengths of this study include the adoption of an ADL outcome measure, in contrast to traditional physical outcome measures such as muscle strength, endurance measurements or a pulmonary function test. There is emerging evidence demonstrating that this type of approach to outcome measurement is more meaningful to survivors than standard physiologic measures, and that daily functional measures should be the focus of all long term trials within the critical care field (10). The large number of participants

involved, and retention rate achieved are additional key strengths of the presented work. The challenges with sustaining retention in long term studies are well documented and the authors should be congratulated for this.

An additional strength, worthy of our attention given its ability to illuminate a new path forward in survivorship, is the focus on social determinants of health. The identified relationship between greater degree of educational attainment and socioeconomic status and the ability to remain PICS-free is a novel path forward for survivorship. Evidence from across social science has demonstrated that strong educational foundations can help shape health outcomes. For example, education can foster supportive social connections, facilitate access to greater employment opportunities, help develop lifelong learning and problem solving and assist the individual to feel empowered and valued (11). These are important social determinants of health and wellbeing, and attributes that seem well aligned with optimal recovery from critical illness. Indeed, if we are to create a culture of resilience and post-traumatic growth in this population, these would appear to be important components of any rehabilitation program.

Unfortunately, the educational background of our patient population is not something a clinician can modify. Nevertheless, understanding how these important social determinants of health and wellbeing interact with recovery from critical care is crucial. As well as pre-existing social issues, new onset issues such as social isolation and financial problems may surface after a critical care stay. Further work around how we support individuals in each of these dimensions, will be an important step in creating safe and effective interventions in the future.

While the present study advances our understanding of PICS greatly, lingering questions remain. First, as mental health issues frequently co-exist, and post-traumatic stress disorder (PTSD) and anxiety were not assessed, mental health problems were likely underestimated in the present study. Future research is needed to unravel the complex interplay between mental and physical health, both as a risk factor for developing critical illness, and recovering from critical illness. Second, while the results support the hypothesis that heterogeneous subtypes of PICS exist, it is unclear whether this applies to the population of survivors with pre-existing impairments. Third, given the potential

salience of social determinants of health, future work designed to examine the bi-directional relationship between physical and neuropsychological impairments and loneliness and isolation is needed (12).

In conclusion, PICS was a concept which was created almost a decade ago. Since then, our understanding about the challenges patients face and how frequently they face them has matured. The article by Marra and colleagues confirms that PICS is the norm, and also lays down a foundation for a new direction to anticipate, and rehabilitate, PICS. This highly relevant study helps us comprehend how some of the different components of PICS interact, and which patients are most at risk for developing long term problems following critical care discharge. The field is more equipped than ever to look beyond recording and documenting the problems which patients face and test and implement strategies to mitigate and rehabilitate PICS. A novel direction to achieve these goals will require a firm grasp of how the social determinants of health, including issues such as social networks, health literacy and education, interact with recovery from critical illness (13). Furthermore, there must be a focus on how these issues effect the entire critical care journey; this includes the contextual factors which bring some patients to the ICU in the first place. It is only with this focus, that we will truly start to realize the improvements in patients' quality of life, which we are all so desperate to see.

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