Long-Term Outcomes after Delirium in the ICU: Addressing Gaps in Our Knowledge

Delirium occurs in up to 50% of all critically ill adults (1). This common ICU phenomenon is associated with a substantial burden to patients and families and has serious ICU and post-ICU sequelae (1). Mortality is an important concern among ICU survivors and their families (2). The relationship between ICU delirium and post-ICU mortality is unclear (3). Cohort studies evaluating the association between delirium and mortality over 1 to 12 months of follow up have discordant results (1, 3, 4). Among these studies, there is important variability in ICU patient populations, methods of delirium detection and evaluation (e.g. incidence vs. prevalence, duration, severity), and how potential confounding has been considered.

In this issue of the *Journal*, Fiest and colleagues (pp. 412–420) make an important contribution via their population-based study evaluating the association of ICU delirium and mortality over up to 2.5 years of follow up in 12,137 adults consecutively admitted >24 hours to any of the 14 medical-surgical ICUs in the province of Alberta, Canada (population: 4.4 million) (5). This study also explored the association between ICU delirium and subsequent hospital readmissions and emergency department visits, including mortality as a competing risk. Using five province-wide databases, the authors evaluated comprehensive data, including patient demographics, ICU clinical variables, mortality, hospitalizations, and emergency department visits. Using propensity scoring, the "ICU delirium" and "no ICU delirium" patient cohorts were matched on five baseline variables and four ICU variables. The statistical methods considered time dependence of the outcome measures with delirium, patient clustering within ICUs, and different methods of evaluating delirium (e.g., duration and severity).

Among the 5,936 propensity-matched critically ill adults who survived to hospital discharge, the incidence of delirium in the ICU was associated with greater mortality (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.08–1.92) up to 30 days after hospital discharge (5). Beyond 90 days after hospital discharge, a significant association was not found (HR, 1.09; 95% CI, 0.91–1.16). During the 2.5-year study period, delirium occurrence was associated with an increased risk for emergency department visits, hospital readmissions, or death after the index hospitalization (HR, 1.12; 95% CI, 1.07–1.17).

These results are an important building block in better understanding the long-term outcomes of ICU delirium and in reflecting on clinical care in the ICU (5). The survivorship experience is a critical concern for ICU patients and families (6). The incidence and duration of ICU delirium may be a potentially modifiable risk factor for post–intensive care syndrome (6). Notably, a longer duration of delirium in the ICU is independently associated with worse global cognition at the 3- and 12-month follow up (7). Although not evaluated in the paper by Fiest and colleagues (5), multicomponent ICU quality-improvement interventions (e.g., the ABCDEF bundle), supported by the Pain, Agitation/Sedation, Delirium, Immobility, and Sleep clinical practice guidelines (3), are associated with reductions in ICU delirium, hospital mortality, and ICU readmissions (8). However, the impact of such interventions on long-term mortality and patient outcomes requires more evaluation.

To further build on the analysis by Fiest and colleagues (5), future studies should evaluate interrelationships between ICU sedation status (including coma), sedative choice, and delirium occurrence and their effect on post-ICU mortality and patient outcomes. Herein, we provide some recommendations for future research in this area. First, explicit consideration of a sedative-induced coma is important given its association with mortality and given that coma is a competing risk in evaluating delirium in the ICU (3, 4, 9). Second, an evaluation of specific classes of medications in the ICU (e.g., benzodiazepines, propofol, dexmedetomidine, and opioids) is important to better understand associations of delirium with post-ICU mortality and patient outcomes (3, 10, 11). Third, given that critically ill adults are frequently discharged on psychoactive medications, further exploration of associations of post-ICU medications and patient mortality and outcomes is recommended (12). Fourth, given that preexisting frailty and cognitive function are important predictors of ICU delirium and associated with increased mortality and deleterious post-ICU patient outcomes (13, 14), these baseline variables are important to evaluate in future research. Finally, given that post-ICU exposures (e.g., rehabilitation services and hospital readmissions) and variability in patient recovery trajectories impact survivors' post-ICU outcomes, their consideration is warranted. Figure 1 proposes key baseline, ICU, and post-ICU risk factors and research considerations for delirium and long-term outcome studies.

In conclusion, via this new population-based retrospective study (5), important progress has been made in better understanding the association of delirium with post-ICU mortality and healthcare resource use. To continue advancing the field, future prospective studies should embrace a recent Core Outcome Set for ICU delirium research that recommends inclusion of seven outcomes: delirium occurrence (prevalence or incidence), delirium severity, time to delirium resolution, health-related quality of life, emotional distress, cognition, and mortality (15). Future prospective studies also should consider addressing key knowledge gaps via evaluating established delirium risk factors, post-ICU mortality, and patient-important outcomes while taking into account the complexities of competing risks in assessing delirium and long-term outcomes. ■

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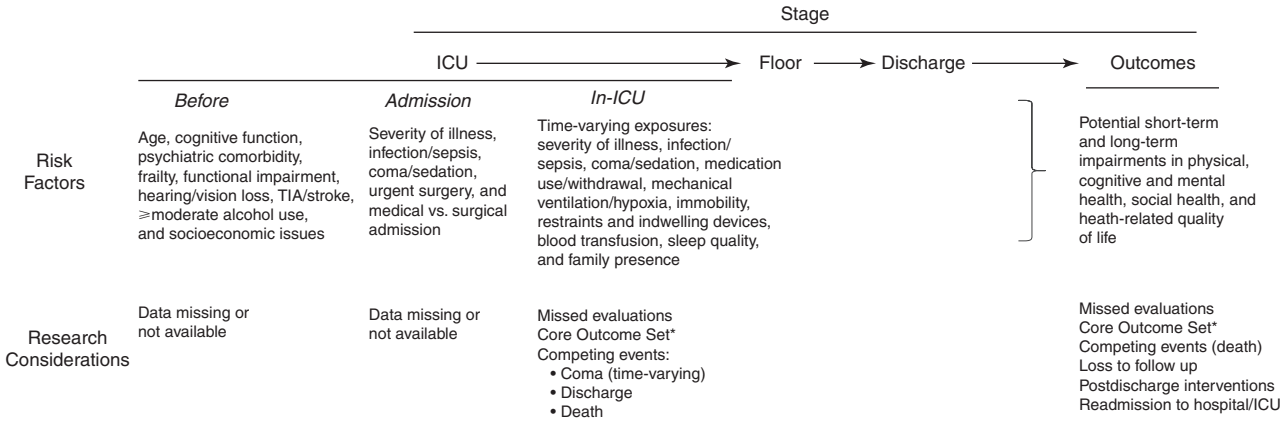

Figure 1. Risk factors and research considerations for delirium and long-term outcomes studies. Various risk factors and research considerations may influence reported associations between in-hospital incidence, duration, and/or severity and postdischarge outcomes. Readmission to the ICU or hospital may further negatively impact delirium and long-term patient outcomes. *Two separate Core Outcome Sets exist for research on delirium in the ICU and on long-term outcomes after acute respiratory failure (15, 16). Please also see https://www.improvelto.com/. TIA = transient ischemic attack.

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The CypA-netics of Ventilator-induced Lung Injury

For patients with acute respiratory distress syndrome (ARDS), mechanical ventilation is often an obligatory life-saving intervention. Mechanical ventilation itself may, however, evoke ventilator-induced lung injury (VILI) (1). In spite of lung-protective ventilation strategies with, for example, low V_T having been implemented into clinical practice (2), ventilated areas of ARDS lungs may still encounter injurious transparenchymal forces because of a marked reduction in aerated lung size ("baby lung"). The absence of a definite safety threshold for VILI therefore necessitates further efforts to minimize VILI, even more so as the requirement for mechanical power to ensure adequate ventilation increases the sicker the patient is. To solve this obvious dilemma, personalized ventilation and novel therapeutic strategies based on point-of-care monitoring of the mechanical forces acting on the lung tissue and better insight into the mechanotransduction pathways that convert these forces into injurious cellular responses are required. To this end, a body of work has identified various inflammatory and barrier-disruptive mediators as potential biomarkers and therapeutic targets in VILI. Yet, this knowledge has so far not translated into improved patient care or novel treatment approaches.

In this issue of the *Journal*, Koh and colleagues (pp. 421–430) report findings from animal experiments and patient sample analyses that suggest secreted extracellular CypA (cyclophilin A) as a biomarker and mediator of VILI (3). Originally, Handschumacher and colleagues had identified CypA as a ubiquitously expressed cytosolic protein that intracellularly binds cyclosporin A, thereby mediating its immunosuppressive activity (4). Subsequently, CypA was shown to also serve as an extracellular signaling molecule that can be secreted by endothelial and epithelial cells, monocytes, or macrophages in response to, for example, oxidative stress or LPS and then acts as a proinflammatory cytokine in acute and chronic inflammatory diseases, including rheumatoid arthritis, coronary artery disease, or sepsis (5). CypA is considered to exert its proinflammatory effects by activation of the transmembrane protein CD147, a member of the immunoglobulin superfamily expressed by many cell types, including epithelial cells, endothelial cells, and leukocytes. Of late, CypA was also identified as an endogenous ligand for another immunoglobulin superfamily receptor and a triggering receptor expressed on TREM-2 (myeloid cells-2), to which it binds with an even higher affinity to elicit both pro- and antiinflammatory responses (6). Yet, despite abundant evidence for CypA's involvement in inflammatory processes, its role in acute lung injury and specifically VILI has so far not been addressed.

In their present study, Koh and colleagues show CypA levels to be 5- to 6-fold elevated in the BAL fluid (BALF) of patients with ARDS as compared with healthy volunteers and similarly in mice ventilated with excessive V_T of 35–40 ml/kg body weight as compared with mice undergoing lung-protective ventilation. In overventilated mice, flow cytometric analyses detected a concomitant decrease in intracellular CypA in alveolar epithelial cells but not in alveolar macrophages, whereas cyclic stretch of primary human alveolar epithelial cells *in vitro* resulted in CypA secretion into the supernatant. *In vivo*, CypA blockade by MM-284, a nonimmunosuppressive cyclosporin A derivative that inhibits CypA extracellular signaling, improved survival and classic parameters of lung injury in overventilated mice, including lung function and oxygenation, and reduced alveolocapillary barrier dysfunction and epithelial injury. *Ex vivo* stimulation with recombinant CypA induced inflammatory responses in human monocyte-derived macrophages, including IL-6 secretion, yet not in primary alveolar epithelial cells. These data thus suggest a scenario in which overventilation causes CypA secretion from stretched alveolar epithelial cells, which in turn activates alveolar macrophages, triggering proinflammatory responses that will ultimately drive alveolocapillary barrier failure and impaired lung function and oxygenation (Figure 1). Although this concept is coherent, the exact cellular sources of CypA in VILI, its auto- or paracrine target cells, and the individual receptors mediating these effects (e.g., CD147 vs. TREM2) remain to be validated *in vivo* by cell-specific conditional knockout models and/or single-cell transcriptomic analyses.

May CypA hence present a promising therapeutic target to reduce lung injury and improve survival in patients with ARDS? The following aspects should be considered. First, although MM-284 attenuated lung injury in overventilated lungs of naïve mice, evidence that CypA blockade similarly reduces VILI in lungs preinjured by, for example, pneumonia or sepsis is presently lacking. The plethora of inflammatory pathways triggered in such critical inflammatory conditions may simply outweigh the benefits of CypA blockade in VILI. On the other hand, therapeutic effects of CypA blockade in ARDS may not be restricted to VILI but may also target inflammatory pathways of ARDS and its underlying diseases. Although this might point toward a broader therapeutic potential of CypA blockade, it also raises the question of the perfect timing for this intervention. In their preclinical study, Koh and

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