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► To cite this version:

Joris Pensier, Denise Battaglini, Elias Baedorf-Kassis. Early mobilization in septic acute respiratory distress syndrome: the UNITE-COVID-II Study. *Anaesthesia Critical Care & Pain Medicine*, 2025, pp.101553. <10.1016/j.accpm.2025.101553>. <hal-05076434>

HAL Id: hal-05076434

<https://hal.science/hal-05076434v1>

Submitted on 3 Jul 2025

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Early mobilization in septic acute respiratory distress syndrome: the UNITE-COVID-II Study

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Keywords:

Mobilization; acute respiratory distress syndrome; intensive care unit.

Survivor of critical illness can experience post-intensive care syndrome, which encompasses long-lasting physical, cognitive, social, and psychological impairments [1]. Prolonged periods of mechanical ventilation may lead to ICU-acquired weakness (ICUAW), with up to 60% of acute respiratory distress syndrome (ARDS) patients being diagnosed with this condition. More than a third of these patients continue to be affected upon hospital discharge, making ARDS one of the conditions with the highest rates of ICUAW [2].

Early mobilization –within 72 hours of mechanical ventilation– has been widely advocated as a strategy to improve long-term outcomes by preventing ICUAW [3,4]. The UNITE-COVID-II cohort provides a large, real-world look at early mobilization in a model of severe critical illness combining sepsis and ARDS [5]. This international observational study spanned the second pandemic wave in comparison to the first [6]. Among the 6,243 patients across 45 countries, the study revealed that the proportion of patients receiving early mobilization rose from 27% during the first wave to 39% during the second wave. The analysis suggests that patients who received early mobilization had a lower 60-day mortality, with a significant odds ratio (OR) of 0.74 (95% confidence interval [CI] 0.64–0.86, $p<0.001$). They were also more likely to be discharged directly home (OR=1.34, 95%CI 1.17–1.54, $p<0.001$), rather than being sent to a rehabilitation facility. These real-world findings reinforce the potential benefits of early mobilization even among critically ill patients with COVID-19 ARDS [7]. They also suggest that the advantages of initiating early mobilization may extend to patients experiencing severe inflammation and prolonged mechanical ventilation. The partitioned respiratory mechanics observed in these patients align with those seen in other ARDS cases [8, 9], and there exists a similar relationship between ventilatory load and patient outcomes [10, 11]. Furthermore, unsupervised clustering methods have identified subphenotypes akin to those found in unselected ARDS and sepsis patients [12, 13]. Beyond the context of the pandemic, these findings on early mobilization may be applicable to a broader population of ARDS patients who exhibit similar respiratory and inflammatory profiles.

Nevertheless, the recent large multicenter TEAM trial failed to demonstrate a significant benefit of a standardized, active early mobilization protocol on 180-day mortality in critically ill ventilated patients [14]. Furthermore, the intervention group experienced a higher incidence of cardiovascular instability and episodes of oxygen desaturation. These adverse events have tempered enthusiasm for aggressive mobilization in unselected ventilated populations.

Meanwhile, the COVID-19 pandemic introduced an unprecedented population of ICU patients characterized by exaggerated immune-inflammatory responses and ARDS [7]. These severe patients experienced prolonged mechanical ventilation, persistent hypoxemia, and inflammatory organ injuries characterized by immunosuppression, lung fibrosis, and renal and neurological complications [7, 15]. In addition to impairing their respiratory function, many patients experienced reduced muscular strength and physical function because of the extended immobility brought on by mechanical ventilation, aiding in the development of ICUAW [4]. Thus, it was unclear whether early mobilization would prevent the onset of ICUAW in these ARDS patients without increasing the risk of cardiovascular and respiratory adverse events.

Results from the UNITE-COVID-II are in contrast with the TEAM trial [14]. To reconcile the positive associations observed in UNITE-COVID-II with the neutral and negative outcomes reported in TEAM, we must consider several key differences in study design, population characteristics, management of the control group, and intensity of the intervention (Figure 1.). Most importantly, in an observational study like UNITE-COVID-II, early mobilization may

simply be a marker for clinician assessment of stability. Thus, the association between early mobilization and outcomes in the UNITE-COVID-II study should not be interpreted as indicative of causality. The TEAM trial enrolled a broad ICU population comprising sepsis, medical, and surgical patients and specifically excluded the most severe patients (e.g., $FiO_2 > 60\%$ or norepinephrine > 0.2 mcg/kg/min) [14]. This resulted in a cohort with relatively low baseline severity (median APACHE II score of 18), a short ICU stay (median of 8 days), and a high number of ventilator-free days through 28 days (median of 21 days). In such a population, the risk of ICUAW is likely lower than that found in the UNITE-COVID-II cohort. In contrast, the UNITE-COVID-II cohort is characterized by inflammation, hypoxemic respiratory failure, and a high risk of debilitation [5]. Consequently, the potential benefits of early mobilization may be greater and more critical in preventing muscle wasting over weeks. Furthermore, RCTs have systematically underrepresented such cases. The observational data from UNITE-COVID-II help to fill this gap by examining a group largely left out due to stability criteria [3, 14, 16].

Figure 1. Early Mobilization in critically ill adults under mechanical ventilation: reconciling the recent evidence

ARDS: acute respiratory distress syndrome

**Early Mobilization in critically ill adults under mechanical ventilation:
Reconciling the recent evidence**

	TEAM randomized controlled trial	UNITE-COVID-II prospective observational cohort
Population	<ul style="list-style-type: none"> - Inclusion of patients with expected >24 hours of mechanical ventilation - Exclusion of unstable patients ($FiO_2 > 60\%$, norepinephrine > 0.2 mcg/kg/min) 	<ul style="list-style-type: none"> - COVID-19 patients of the first two waves - Model of sepsis-associated ARDS - Potentially unstable patients
Intervention	<ul style="list-style-type: none"> - Very early mobilization - High intensity (protocolized) 	<ul style="list-style-type: none"> - Early mobilization within 72 hours - Any active mobilization (not protocolized)
Control	<ul style="list-style-type: none"> - Early mobilization in 33% of the patients, according to guidelines 	<ul style="list-style-type: none"> - No active early mobilization
Result	<ul style="list-style-type: none"> - No difference of mortality - More frequent adverse events (arrhythmias, desaturation) 	<ul style="list-style-type: none"> - Lower 60-day mortality - More frequent direct home discharge

Furthermore, early mobilization can have varying interpretations depending on the definition applied. In the TEAM trial, 33% of the usual-care group and 68% of the intervention group received early mobilization as defined in UNITE-COVID-II. This suggests that the usual-care group of the trial already reflected an ICU environment with an adequate level of mobilization according to international guidelines [17]. Oppositely, most patients in the UNITECOVID- II cohort did not receive any active mobilization, in the global context of overwhelmed staff resources [18]. Notably, the increase in the proportion of patients receiving early mobilization within 72 hours of ICU admission between the first and second pandemic waves reflects how ICU teams across different countries reorganized their efforts to provide optimal care during a challenging period. Thus, the UNITE-COVID-II results may also serve as valuable guidance for future pandemics. Designing adaptative care pathways to ensure equal access to mobilization during the early phase of a pandemic may be key to building a resilient healthcare system [15,18].

The intervention in the TEAM trial involved a protocolized approach to very early, high-intensity mobilization, targeting the highest level of activity possible each day [14]. This often meant that patients, even those who had been sedated just hours before, were engaged in out-of-bed exercises as early as the second day. In contrast, within the real-world context of UNITE-COVID-II, ICU clinicians may intuitively delay early mobilization until a patient's respiratory and hemodynamic status is deemed stable enough to tolerate it. This observational design reflects the complexities of clinical judgment, which can introduce important unmeasured confounders. Even in an overall more stable population in the TEAM trial, some patients might have been pushed to mobilize at the edge of stability, precipitating arrhythmias, or desaturation. We could speculate that assessing the level of physiological stability required for early mobilization is more accurate when performed by clinicians who can evaluate individual patient conditions, rather than solely on rigid inclusion and exclusion criteria. Thus, initiating early mobilization at the appropriate time and dosage for each patient, as occurred organically in UNITE-COVID-II, could be advantageous. However, the inherent limitations of the study design preclude us from drawing definitive conclusions.

The UNITE-COVID-II study aligns with earlier RCTs, designed with a less intense intervention [3,16], where early mobilization has been found effective in reducing delirium incidence while improving functional outcomes [3,16]. It is difficult to draw firm conclusions on the impact of early mobilization on mortality ARDS patients, as RCTs were performed in a diverse ICU population, and no difference was found in meta-analyses [19]. In comparison, the UNITE-COVID-I study did not find a difference in mortality, underscoring the frailty of this finding considering the unmeasured confounders [6]. However, mortality might not be the best-suited endpoint to assess early mobilization, compared to other patient-centered outcomes such as quality of life and functional outcomes [19]. The UNITE-COVID-II results add a valuable piece to a population deemed too unstable to be included in these previous RCTs, especially as the latest guidelines were unable to identify clear thresholds for respiratory and hemodynamic stability [17]. Even among high-risk, hypoxemic sepsis-associated ARDS patients—arguably the most vulnerable population to ICUAW)—early mobilization might confer benefits when appropriately timed to patient stability. This broad study across 45 countries during the pandemic yielded a diverse and globally representative sample that is rarely achieved in RCTs, enhancing the applicability of the results.

Despite its contribution, the UNITE-COVID-II study has limitations that temper our interpretations. First, as an observational cohort, the decision to initiate early mobilization was at the clinicians' discretion. It is likely that patients who were showing better recovery were selected for early mobilization, compared to patients receiving neuromuscular blocking agents or deep sedation. Sedation levels, hemodynamic stability, APACHE or SOFA scores, and frailty indices were not recorded in this study, leading to residual confounding from multiple factors. Additionally, early mobilization was broadly defined as mobilization within 72 hours per local practice [5]. There was considerable variability in the types of activities performed: some patients might have only sat upright in bed or engaged in passive range-of-motion exercises, while others might only have stood or walked with assistance. The dosage and intensity of mobilization were not standardized, unlike in an RCT. This real-world variability makes the findings applicable to broad practice, but specific protocols cannot be directly derived from this study. Lastly, while discharge destination was recorded as a surrogate measure, the study did not follow patients beyond 60 days to assess objective functional measures or long-term outcomes [20].

In conclusion, the UNITE-COVID-II study offers a valuable perspective on early mobilization in the ICU, particularly for patients with sepsis and ARDS. In the wake of the literature uncertainty, this observational evidence serves as a reassuring counterpoint: it shows that even in a highly inflammatory and hypoxemic patient population, early mobilization EM is often feasible and might be associated with improved outcomes. Meanwhile, ICU practitioners can draw a practical conclusion that even during a pandemic surge straining resources, early mobilization should remain a key objective to enhance patient recovery.

Funding

None

Declaration of Interest

JP received funding from the Société Française d'Anesthésie- Réanimation, the Philippe Foundation, the Beth Israël Deaconess Medical Center (Boston, MA) and the University Hospital of Montpellier. DB has received honorarium for conference lectures from Estor. EBK has received research funding from the NIH, Draeger, and Hamilton Medical, and honorarium for conference lectures from Hamilton Medical.

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