

MATTERS ARISING

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Intubate patients with sepsis before midnight or do it when the time comes?

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Dear Editor,

The Rolling Stones say “*Time is on my side, yes it is!—Now you always say, that you want to be free...*”; indeed time is not always on patients’ and clinicians’ side in the ICU, and being free, especially from ventilation is of benefit if it can be avoided. However, it is the clinician who imposes ventilator treatment on the patient and chooses the time to do this.

The ever-recurring decision for every clinician is to act or not to act and when to act. The balance of benefit or harm of an intervention and the optimal timing of treatment is not always clear. Intervening or not and the timing are different questions but related especially in studies of the latter. In intensive care, the issue of timing of life-sustaining treatments such as renal replacement therapy (RRT) [1] and vasopressors in sepsis [2] have been investigated. There is also an ongoing debate regarding ventilation strategy, as early tracheal intubation exposes patients to procedural complications, ventilator-induced lung injury, or ventilator-acquired pneumonia, on the other hand, delayed intubation exposes them to self-induced

lung injury [3] or the emergency procedure in the context of more respiratory or hemodynamic instability that is associated with major adverse peri-intubation events can lead to more complications [4]. The timing of intubation has been studied in the general ICU population and COVID-19 patients in observational studies [5–7] and varies widely across countries and according to the physician in charge [8]. In sepsis, mechanical ventilation affects not only the lung but also other organs, making early intubation a double-edged sword: it may contribute to sustained oxygen delivery, but it may also contribute to circulatory instability due to sedatives and the effects of positive pressure ventilation.

In a paper recently published in this *Journal*, Kim et al. reported a cohort of 2440 patients with sepsis who received invasive mechanical ventilation in one of the 20 hospitals participating in the Korean Sepsis Alliance [9]. They found that the 2119 (87%) patients intubated on the first day of ICU admission had better outcomes, including lower ICU and hospital mortality, than those who received invasive ventilation later during their ICU stay. So, based on these results, should we intubate all patients admitted with sepsis upon arrival in the ICU? We argue that this study does not resolve the uncertainty. Although a valuable contribution to our knowledge on the timing of intubation in sepsis patients, there are some issues to mention that put these data into context.

To answer the question of timing of intubation Kim et al. used propensity score matching to minimize bias and render the two groups as similar as possible. This is not the first study exploring the timing of intubation using this method. For example, Mellado-Artigas et al. also using propensity score matching have reported that intubation of patients with septic shock within 8 h of

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after vasopressor start did not lead to decreased mortality [10]. Moreover, the majority of patients not intubated early were in fact never intubated and we think this is a crucial point.

Indeed, the exclusion of patients who were never intubated from the study by Kim et al. constitutes a major bias. When clinicians admit patients with sepsis and decide not to intubate immediately, their goal is certainly not to *delay* intubation, but to *avoid* intubation! The great majority of patients who are never intubated likely survive without important complications [11], but we are totally ignorant of the characteristics and outcomes of this valuable sub-group of patients in Kim et al.'s study (Fig. 1.). Hence, patients with delayed intubation in the study are assumably a subset of patients for whom the initial strategy of avoiding intubation failed and who worsened enough for the attending intensivists to change their minds and eventually decide to intubate. As the Mellado-Artigas et al. study suggests, comparing patients with early intubation to patients with a delayed intubation strategy i.e., combining patients who were never intubated and patients with delayed intubation would provide important insights that better match clinical practice.

Understanding how timing was assessed is also a central issue. Being a large nationwide study is a strength, providing data on a high number of patients but has also limitations as with a once-daily data collection use in the Kim et al. study, the dataset lacks granularity,

impairing precise biological and clinical assessments in patients who are usually unstable in the first days of their ICU stay and could deteriorate within a few hours. This lack of granularity is also critical at the time of the intubation: for patients with early intubation, the exact timing is not known since 'within the first calendar day of admission' as a definition is vague. Furthermore, there is uncertainty regarding if the patients' baseline characteristics were collected before or after intubation. On the other hand, patients with delayed intubation were likely to be in a more severe condition at the moment of intubation than they were at baseline. Collecting only one data point per day blinds the reader from trends and changes that might impact the decision of intubation and the ultimate outcomes.

Finally, the issue of residual confounding is important to take into consideration. The timing of intubation, earlier or later, is a question of clinical decision-making that is influenced by many factors that may be difficult to capture in a retrospective study. For example, staffing-related decision-making structures that can differ according to the health care systems can affect the timing of intubation and the outcomes, a reason why these results require external validation. Information regarding withholding or withdrawing decisions that can have a major impact on strategic decisions and mortality would have been important for a better understanding of the patients' profiles and management. However,

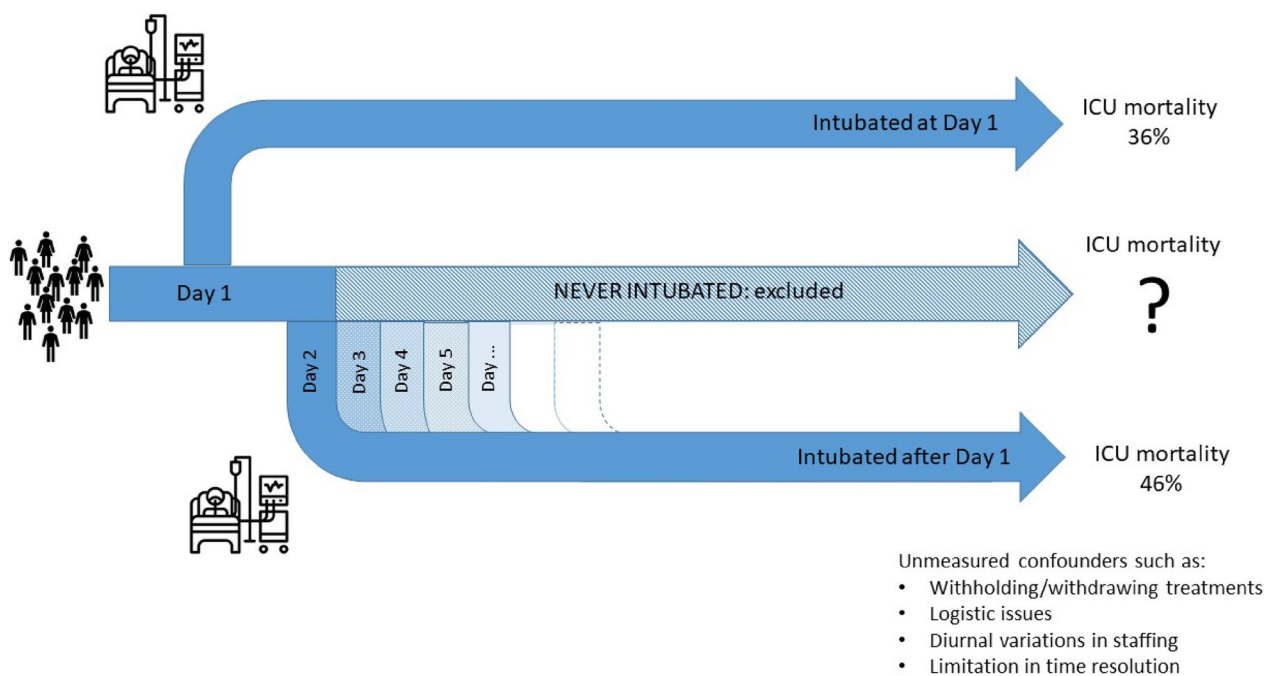


Fig. 1 Issues to consider for interpreting the Kim et al. study

many factors are highly subjective and are challenging to assess even in a study with a prospective design.

Altogether, despite the limitations developed above, this study provides interesting additional data on the timing of intubation in patients with sepsis who ultimately received invasive mechanical ventilation during their ICU stay. However, the study cannot provide a final answer to the burning clinical question: does the positive impact of avoiding intubation overcome the negative impact of delaying intubation in patients who finally receive invasive ventilation? Further studies, preferably RCTs in well-defined populations, combining patients who had delayed intubation with those who were never intubated are urgently needed.

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Declarations

Competing interests

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