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Delayed intubation and increased hospital mortality in critically ill patients: a dose-response analysis of a multicentre retrospective cohort

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Abstract

Background.

Whether delaying invasive mechanical ventilation in favour of a trial of non-invasive support harms critically ill patients remains contested, a debate sharpened by the COVID-19 pandemic. Most evidence anchors intubation timing to illness onset in selected syndromes. We examined the association between time from intensive care unit (ICU) admission to first charted invasive ventilation and hospital mortality.

Methods.

Multicentre retrospective cohort study using the eICU Collaborative Research Database v2.0 (208 US hospitals, 2014–2015). Of 29,098 mechanically ventilated adults in their first ICU stay, 4,398 had a plausible charted ventilation-onset timestamp (− 72 h to + 14 days) and known discharge status. Patients were classified as pre-ICU intubation (< − 1 h), immediate (− 1 to + 2 h, reference), early delay (2–24 h) or delayed (> 24 h). The primary outcome was hospital mortality. Multivariable logistic models with hospital-clustered robust standard errors adjusted for demographics, illness severity, Glasgow Coma Scale, sepsis, comorbidities, organ support and hospital characteristics. Sensitivity analyses included multiple imputation, exclusion of deaths within 48 h and modified Poisson estimation of adjusted risk ratios; prespecified strata were sepsis, Sequential Organ Failure Assessment (SOFA) score and age.

Results.

Crude hospital mortality was 22.4% (pre-ICU), 25.6% (immediate), 44.1% (early delay) and 34.9% (delayed). Despite the delayed group being least severely ill (median SOFA 4 vs 6–8), delay was associated with graded adjusted mortality: early delay odds ratio (OR) 2.16 (95% confidence interval 1.22–3.83) and delayed OR 2.48 (1.53–4.04) versus immediate intubation (P for trend < 0.001). Pre-ICU intubation was associated with lower mortality (OR 0.48, 0.38–0.61). Estimates were robust to all sensitivity analyses (delayed OR 2.31–2.87; adjusted risk ratio 1.61, 1.17–2.20) and broadly consistent across prespecified strata. Among survivors, delayed intubation was associated with longer ICU (ratio 2.75, 2.17–3.48) and hospital (ratio 1.98, 1.66–2.36) stays.

Conclusions.

Intubation delayed beyond ICU admission was associated with a graded, dose–response increase in adjusted hospital mortality despite lower baseline severity and biases favouring the delayed group. The findings support protocolised, time-limited non-invasive trials with early escalation and identify pre-ICU

controlled intubation as a distinct, lower-risk pathway. Prospective validation with respiratory parameters at the decision point is warranted.

Background

Invasive mechanical ventilation saves lives at the price of ventilator-induced lung injury,[1,2] and modern respiratory critical care increasingly offers an alternative: a trial of non-invasive support (high-flow nasal oxygen or non-invasive ventilation), reserving intubation for those who fail.[3–5] That trial is not free. Beyond delay itself, it can impose the injurious load of prolonged vigorous spontaneous breathing.[6,7] In the acute respiratory distress syndrome (ARDS),[8] observational cohorts have linked later intubation to higher mortality,[9,10] and failure of high-flow therapy with delayed escalation appears particularly hazardous.[11] Yet the COVID-19 experience showed how unsettled the field remains: meta-analyses of that literature found no overall mortality difference between early and late intubation, despite strong opinions on both sides.[12] Most existing evidence anchors timing to illness onset within selected syndromes, mixes pre-ICU with post-admission intubations, and rarely quantifies how risk changes with each additional increment of delay.

Three design gaps persist. First, timing anchored to ICU admission — an objective, uniformly recorded landmark — is seldom used, yet it is the timescale on which ICU clinicians actually make the escalate-or-wait decision. Second, patients intubated before ICU arrival (in the field, emergency department or operating room) are usually pooled with at-admission intubations, although they plausibly represent a distinct, controlled-intubation pathway. Third, two biases run in opposite directions and are rarely addressed together: confounding by indication (patients deemed salvageable and initially stable are offered non-invasive trials) and immortal time bias (delayed patients must survive long enough to be intubated)[13] both favour the delayed group, so any observed harm of delay is likely underestimated. Target-trial-emulation frameworks make such biases explicit by fixing time zero at the escalation decision, and they define the evidentiary standard towards which observational work on this question should aim.[14]

We therefore analysed a multicentre cohort of mechanically ventilated adults from 86 US hospitals with charted ventilation-onset timestamps. We classified the full continuum of timing relative to ICU admission, from pre-ICU intubation through immediate, early-delayed and delayed intubation, and quantified the association of delay with hospital mortality and length of stay, with explicit attention to the direction of the competing biases.

Methods

Data source, ethics and reporting

We used the eICU Collaborative Research Database v2.0, a multicentre database of 208 US hospitals in 2014–2015;[15] patient-level data were extracted through the mimicdb.com research platform, which provides credentialed access to the eICU-CRD under its data use agreement. The original database was approved by the institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), with waiver of informed consent because the data are de-identified; this secondary analysis was exempt from additional ethics review. Reporting follows the STROBE statement.[16]

Study population

Adults aged 18–100 years admitted to an ICU for the first time during the index hospitalisation and receiving invasive mechanical ventilation were screened (n = 29,098). The analytic cohort comprised the 4,454 patients (15.3%) with a charted ventilation-onset timestamp, after excluding implausible timestamps outside − 72 h to + 14 days (n = 25) and missing hospital discharge status (n = 31), leaving 4,398 patients treated in 86 hospitals (Fig. 1). To characterise selection into the timestamped subcohort, we compared included patients with the 24,700 ventilated patients without a usable timestamp (Supplementary Table e1).

Exposure: ventilation-onset timing

Time from ICU admission to the first charted invasive ventilation record (negative values denote intubation begun before ICU arrival) was categorised a priori: pre-ICU intubation (< − 1 h), immediate (− 1 to + 2 h; reference), early delay (2–24 h) and delayed (> 24 h). The immediate window accommodates charting latency around admission; the 24-h boundary separates same-day escalation from prolonged non-invasive trials.

Outcomes

The primary outcome was all-cause hospital mortality. Secondary outcomes were ICU and hospital length of stay (LOS) among hospital survivors.

Covariates

Pre-specified confounders comprised age, sex, race, body mass index (WHO categories), SOFA score,[17] Glasgow Coma Scale, admission diagnosis of sepsis,[18] comorbidities (congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, hypertension), vasopressor, diuretic and continuous renal replacement therapy use, ICU type, and hospital characteristics (bed capacity, census region, teaching status). An APACHE IV-adjusted[19] model was fitted as a sensitivity analysis. Missing data were as follows: SOFA 645 patients (14.7%), Glasgow Coma Scale 1,100 (25.0%), APACHE

IV 855 (19.4%), body mass index 95 (2.2%), race 23 (0.5%), hospital bed capacity 260 (5.9%) and census region 129 (2.9%).

Statistical analysis

Multivariable logistic regression estimated adjusted odds ratios (ORs) for hospital death by timing category versus immediate intubation, with hospital-clustered robust standard errors. Missing continuous covariates were median-imputed and missing categorical covariates mode-imputed in the primary analysis. Because hospital mortality was common (24.1%), odds ratios overstate risk ratios; we therefore also fitted a modified Poisson model with the same covariate set and clustered errors to obtain adjusted risk ratios. Dose–response was assessed with an ordinal term coded 0 (immediate), 1 (early delay) and 2 (delayed), fitted together with the pre-ICU indicator. Sensitivity analyses comprised a complete-case model; multiple imputation by chained equations (m = 10) of continuous and binary covariates with pooled cluster-robust estimates; APACHE IV adjustment in place of SOFA; exclusion of deaths within 48 h of admission (probing immortal time and early-death confounding); and capping delay at 7 days (probing outlier influence). Pre-specified strata were sepsis, SOFA (≤ 6 vs > 6, cohort median) and age (< 65 vs ≥ 65 years); within sparse strata, perfectly separating or near-empty dummy levels (< 5 patients) were omitted from the corresponding model. LOS among survivors was compared using log-linear models (ratio of geometric means; the two survivors with a zero-day ICU stay were assigned half of the smallest observed positive stay). To gauge robustness to unmeasured confounding, E-values were computed from the adjusted risk ratios.[20] Model parsimony was assessed with the events-per-variable (EPV) ratio; because some subgroup models had EPV < 10, Firth penalised logistic regression was fitted as a sensitivity analysis for the primary model and the affected strata. Balance between the timestamped and non-timestamped ventilated populations was summarised with standardised mean differences (SMDs), with |SMD| >0.1 considered meaningful. Analyses used Python 3.12 (statsmodels); two-sided P < 0.05 was considered significant.

Results

Cohort and timing distribution

Of 4,398 ventilated patients with charted ventilation-onset times (Fig. 1), 2,763 (62.8%) were intubated before ICU arrival (median − 5.9 h), 1,458 (33.2%) immediately around admission, 68 (1.5%) after an early delay of 2–24 h (median 12.6 h) and 109 (2.5%) after a delay beyond 24 h (median 65.6 h) (Fig. 2A). The groups differed markedly at baseline (Table 1). Pre-ICU patients had the lowest Glasgow Coma Scale scores (median 11), consistent with field or emergency-department intubation for depressed consciousness. Delayed patients were the least severely ill (median SOFA 4, APACHE IV 58, GCS 15), with the lowest vasopressor use (19.3%) but the most chronic cardiopulmonary comorbidity. Early-delay patients were the sickest (median SOFA 8) and most often septic (39.7%). Compared with ventilated patients lacking timestamps, the analytic cohort was slightly younger and modestly sicker, with higher

vasopressor use and crude mortality; standardised mean differences exceeded 0.1 only for age, SOFA, hypertension, vasopressor and diuretic use, and both length-of-stay measures (Supplementary Table e1).

Table 1

Characteristics and crude outcomes of 4,398 ventilated patients by ventilation-onset timing relative to ICU admission. Continuous data are median [IQR]; categorical data are %. CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; GCS, Glasgow Coma Scale. Missing data (whole cohort): SOFA 14.7%, GCS 25.0%, APACHE IV 19.4%, BMI 2.2%, race 0.5%.

Variable	**Pre-ICU < − 1 h (n = 2,763)**	**Immediate − 1 to + 2 h (n = 1,458)**	**Early delay 2–24 h (n = 68)**	**Delayed > 24 h (n = 109)**
Time to ventilation, hours	−5.9	0.0	12.6	65.6
Age, years	62.0 [51.0, 73.0]	63.0 [52.0, 74.0]	63.0 [51.0, 71.2]	63.0 [54.0, 72.0]
Female sex, %	43.3	45.1	32.4	45.9
BMI, kg/m²	27.6 [23.4, 33.3]	27.6 [23.5, 33.2]	27.4 [22.8, 33.2]	27.0 [23.5, 33.6]
Caucasian, %	71.8	73.3	76.5	78.0
SOFA score	7.0 [4.0, 9.0]	6.0 [4.0, 9.0]	8.0 [6.0, 11.0]	4.0 [2.0, 7.0]
APACHE IV score	76.0 [54.0, 99.0]	69.0 [51.0, 93.0]	79.0 [62.0, 96.0]	58.0 [40.0, 74.0]
GCS	11.0 [9.0, 15.0]	15.0 [11.0, 15.0]	15.0 [12.0, 15.0]	15.0 [14.0, 15.0]
Sepsis, %	19.1	19.6	39.7	31.2
CHF, %	10.5	10.2	11.8	15.6
CKD, %	16.2	16.0	17.6	15.6
COPD, %	20.6	18.2	23.5	22.0
Diabetes, %	12.0	13.3	16.2	18.3
Hypertension, %	58.5	58.3	60.3	66.1
Vasopressor use, %	30.0	39.4	36.8	19.3
Diuretic use, %	29.0	39.4	22.1	39.4
CRRT, %	2.4	5.2	1.5	8.3
ICU LOS, days	3.7 [1.9, 7.8]	4.9 [2.3, 11.1]	5.1 [2.6, 8.6]	11.3 [7.2, 17.9]
Hospital LOS, days	8.1 [4.3, 14.7]	10.4 [5.9, 18.5]	9.3 [3.9, 16.7]	16.8 [11.0, 28.2]
Hospital mortality, %	22.4	25.6	44.1	34.9

Crude outcomes

Crude hospital mortality was 22.4% (pre-ICU), 25.6% (immediate), 44.1% (early delay) and 34.9% (delayed) (Fig. 2B). Median ICU stay among all patients rose from 3.7 days (pre-ICU) to 11.3 days (delayed), and median hospital stay from 8.1 to 16.8 days.

Adjusted mortality: the graded hazard of delay

After adjustment (Table 2, Figs. 2C and 3), delay was associated with a graded increase in hospital mortality versus immediate intubation: early delay OR 2.16 (95% CI 1.22–3.83; P = 0.008) and delayed OR 2.48 (1.53–4.04; P < 0.001), with a significant ordinal trend (OR 1.64 per delay step, 1.29–2.08; P for trend < 0.001). This gradient emerged despite the delayed group being the least severely ill at baseline. In contrast, pre-ICU intubation was associated with 52% lower adjusted odds of death (OR 0.48, 0.38–0.61; P < 0.001). The modified Poisson model gave concordant adjusted risk ratios (early delay RR 1.53, 1.10–2.13; delayed RR 1.61, 1.17–2.20; pre-ICU RR 0.62, 0.52–0.74). On the risk-ratio scale, the E-value for the delayed group was 2.60 for the point estimate and 1.62 for the confidence limit, meaning an unmeasured confounder associated with both delay and death by risk ratios of at least 1.6 each, beyond the measured covariates, would be required to explain away the association; corresponding E-values for early delay were 2.43 (point estimate) and 1.43 (confidence limit).

Table 2

Adjusted estimates for hospital death by ventilation-onset timing (reference: immediate intubation − 1 to + 2 h). Primary model: logistic regression adjusted for age, sex, race, BMI category, SOFA, GCS, sepsis, comorbidities, vasopressor/diuretic/CRRT use, ICU type and hospital characteristics, with hospital-clustered robust SEs; median imputation for continuous and mode imputation for categorical covariates. Trend test: ordinal term across immediate → early delay → delayed (pre-ICU indicator retained). RR: modified Poisson model. MI: multiple imputation by chained equations (m = 10). Firth: penalised logistic regression addressing sparse-data (separation) bias.

Analysis	Pre-ICU (< − 1 h)	Early delay (2–24 h)	Delayed (> 24 h)
Primary model (n = 4,398)	0.48 (0.38–0.61)	2.16 (1.22–3.83)	2.48 (1.53–4.04)
Complete-case (n = 2,949)	0.46 (0.30–0.70)	2.30 (1.15–4.60)	2.57 (1.41–4.71)
Multiple imputation (m = 10)	0.55 (0.41–0.74)	2.28 (1.30–4.01)	2.44 (1.50–3.98)
APACHE IV-adjusted	0.44 (0.34–0.58)	2.16 (1.28–3.63)	2.49 (1.55–4.00)
Excluding deaths ≤ 48 h (n = 4,054)	0.47 (0.35–0.62)	1.68 (1.05–2.68)	2.87 (1.74–4.74)
Delay capped at 7 days (n = 4,383)	0.48 (0.38–0.61)	2.16 (1.21–3.85)	2.31 (1.37–3.91)
Adjusted risk ratio (modified Poisson)	0.62 (0.52–0.74)	1.53 (1.10–2.13)	1.61 (1.17–2.20)
Firth penalised logistic	0.49 (0.40–0.58)	2.14 (1.23–3.75)	2.47 (1.56–3.90)
Ordinal trend (per delay step)	—	—	1.64 (1.29–2.08); P < 0.001

Estimates were robust across all sensitivity analyses (Table 2): complete-case (delayed OR 2.57, 1.41–4.71), multiple imputation (2.44, 1.50–3.98), APACHE IV adjustment (2.49, 1.55–4.00), and capping delay at 7 days (2.31, 1.37–3.91). Most informatively, excluding deaths within 48 h strengthened the delayed estimate (OR 2.87, 1.74–4.74), arguing against the explanation that rapidly deteriorating patients dying before they could be intubated late drive the association. Stratum-specific estimates were directionally consistent (Fig. 3): the delay hazard was significant in non-septic patients (OR 3.71, 2.22–6.19), in patients with SOFA ≤ 6 (2.47, 1.36–4.46), and in both age strata (< 65 years: 3.69, 1.84–7.42; ≥65 years: 1.98, 1.05–3.71); in septic patients, early delay carried the largest estimate (OR 2.53, 1.21–5.29). The primary model had 27 events per variable, but the sepsis and SOFA ≤ 6 strata fell below 10; Firth penalised regression reproduced the primary estimates almost exactly (early delay OR 2.14, 1.23–3.75; delayed OR 2.47, 1.56–3.90; pre-ICU OR 0.49, 0.40–0.58) and left all subgroup conclusions unchanged, indicating that sparse-stratum separation did not materially inflate the estimates.

Length of stay among survivors

Among 3,337 survivors (Table 3), delayed intubation was associated with 2.8-fold longer adjusted ICU stays (ratio 2.75, 2.17–3.48; P < 0.001) and 2.0-fold longer hospital stays (ratio 1.98, 1.66–2.36). Pre-ICU intubation showed a non-significant tendency towards shorter stays (ICU ratio 0.84, 0.69–1.02; hospital ratio 0.91, 0.78–1.05).

Table 3
Stratum-specific adjusted odds ratios (95% CI) for hospital death (reference: immediate) and adjusted length-of-stay ratios among 3,337 hospital survivors (log-linear models). SOFA > 6 = above cohort median. Within sparse strata, perfectly separating or near-empty dummy levels (< 5 patients) were omitted from the corresponding model. Events per variable were below 10 in the sepsis (8.7) and SOFA ≤ 6 (7.3) strata; Firth penalised refits of these strata yielded essentially unchanged estimates (sepsis: early delay OR 2.41 vs 2.53, delayed 0.98 vs 0.97; SOFA ≤ 6: early delay 2.10 vs 2.09, delayed 2.43 vs 2.47). Length-of-stay ratios are conditional on survival and should be read as associational; death acts as a competing event that truncates stay.

Stratum / outcome	Pre-ICU (< − 1 h)	Early delay (2–24 h)	Delayed (> 24 h)
Sepsis (n = 874)	0.61 (0.38–0.98)	2.53 (1.21–5.29)	0.97 (0.35–2.74)
No sepsis (n = 3,524)	0.44 (0.34–0.57)	1.73 (0.79–3.77)	3.71 (2.22–6.19)
SOFA > 6 (n = 1,807)	0.51 (0.38–0.67)	1.75 (0.79–3.89)	1.51 (0.50–4.53)
SOFA ≤ 6 (n = 1,946)	0.48 (0.29–0.80)	2.09 (0.65–6.70)	2.47 (1.36–4.46)
Age < 65 years (n = 2,388)	0.51 (0.34–0.78)	2.73 (1.13–6.63)	3.69 (1.84–7.42)
Age ≥ 65 years (n = 2,010)	0.52 (0.40–0.68)	1.75 (0.63–4.88)	1.98 (1.05–3.71)
ICU LOS, survivors (ratio)	0.84 (0.69–1.02)	1.25 (0.83–1.88)	2.75 (2.17–3.48)
Hospital LOS, survivors (ratio)	0.91 (0.78–1.05)	1.05 (0.71–1.55)	1.98 (1.66–2.36)

Discussion

In an unselected multicentre cohort of ventilated critically ill adults, intubation delayed beyond ICU admission was associated with a graded, roughly 2- to 2.5-fold increase in adjusted hospital mortality, despite delayed patients being the least severely ill at baseline, and with markedly prolonged stays among survivors. Two features distinguish this analysis. First, anchoring timing to ICU admission across the full continuum isolated pre-ICU (controlled) intubation as a distinct lower-risk pathway (OR 0.48). Second, an explicit reading of the bias structure — confounding by indication and immortal time both favouring the delayed group — suggests our harm estimates are conservative, an interpretation supported by the strengthened estimate after early deaths were removed.

Comparison with previous work

Our findings align with and extend the syndrome-specific literature. In the ICON audit, delayed intubation after ICU admission was associated with worse outcomes,*9* and in ARDS cohorts later intubation tracked higher mortality.*10* Failure of high-flow nasal oxygen with delayed escalation was likewise

hazardous in a Korean ICU cohort.*11* The COVID-19 literature, by contrast, found no consistent mortality signal for intubation timing;*12* the heterogeneity of that literature may itself reflect the competing case-mix and immortal-time forces we examine here, since timing anchored to disease onset behaves very differently from timing anchored to the escalation decision. We add three elements: a dose–response within one unselected cohort (immediate → 2–24 h → >24 h; trend OR 1.64 per step); the demonstration that the hazard survives removal of early deaths, arguing against the "rapid deteriorator" explanation; and the contrast with pre-ICU intubation, whose lower adjusted mortality plausibly reflects controlled, protocolised airway management en route to (often surgical) critical care rather than a failed watchful-waiting trial.

Several mechanisms could link delay to harm. Prolonged spontaneous breathing in failing lungs can amplify patient-self-inflicted lung injury and regional pendelluft,*6,7* postpone the institution of lung-protective low-tidal-volume ventilation and sedation-controlled synchrony,*21,22* and defer correction of hypoxaemia and work-of-breathing–driven catabolism; in ARDS, driving pressure during spontaneous or assisted breathing is a key mediator of outcome that escalation to controlled ventilation can modulate.*23* The especially large early-delay estimate in septic patients is compatible with the narrow physiological reserve of sepsis, in which hours of unmanaged respiratory failure may compound organ dysfunction.*18,24* Current sepsis guidelines already emphasise prompt source control and organ support, and our data suggest respiratory escalation timing deserves the same urgency.*25*

Clinical implications

The results support protocolised limits on non-invasive trials: objective failure criteria and pre-agreed maximum trial durations before definitive airway control, particularly in sepsis, where guidelines already mandate hourly reassessment of resuscitation and support targets.*25* For ICU nursing practice, the data argue for structured, protocol-driven reassessment during any non-invasive trial — serial documentation of oxygenation, respiratory rate and work of breathing at defined intervals, with explicit escalation triggers communicated to the medical team — so that physiological deterioration is detected and acted on before the window for controlled intubation closes. They also caution against reading lower baseline severity in delayed-intubation patients as reassurance — this apparently stable group carried the highest adjusted risk. Finally, the pre-ICU contrast suggests that the manner of intubation (controlled versus rescue) may matter as much as its timing, a hypothesis testable in datasets capturing pre-hospital and emergency-department airway pathways. Randomised evidence on non-invasive strategies in COVID-19 respiratory failure showed that helmet non-invasive ventilation, compared with high-flow oxygen, reduced intubation rates without a clear mortality difference,*26* reinforcing that the duration and failure criteria of the non-invasive trial — not the device per se — may be the modifiable factor.

Strengths and limitations

Strengths include the multicentre unselected ventilated population, the full-continuum timing classification anchored to an objective landmark, hospital-clustered inference, a sensitivity programme addressing missing data (complete-case and multiple imputation), early-death confounding and outlier

delay, corroboration in risk-ratio space, and explicit reasoning about the conservative direction of the two dominant biases.

Several limitations temper interpretation. First and most important, ventilation-onset timestamps were available for only 15.3% of ventilated patients. Charting practice likely varies by hospital and pathway; although included patients were broadly comparable to excluded ones (Supplementary Table e1) and estimates were stable across analyses, selection into the timestamped subcohort could limit generalisability. Second, the delayed groups were small (68 and 109 patients), yielding wide confidence intervals even though effects were large, significant and graded; Firth penalised regression, which corrects small-sample and separation bias, reproduced the primary estimates almost exactly, mitigating — though not eliminating — this concern. Third, we lacked the indication for intubation, the type and settings of preceding non-invasive support, respiratory parameters (oxygenation, respiratory rate, work of breathing) at the decision point, and do-not-intubate preferences; residual confounding by indication is therefore probable, even if its expected direction favours the delayed group. Fourth, although multiple imputation supported the primary estimates, covariate missingness was substantial for Glasgow Coma Scale and severity scores. Fifth, timing was anchored to ICU admission, not illness onset, and pre-ICU trajectory data were unavailable. Sixth, discharge status was the only mortality horizon; longer-term and functional outcomes are unknown. Seventh, length-of-stay analyses were restricted to survivors; because death is a competing event that truncates stay and its probability differed by timing group, these ratios are susceptible to survivorship (depletion-of-susceptibles) bias and should be interpreted as associational rather than causal. Finally, the observational design precludes causal claims; our estimates should motivate, rather than replace, randomised or target-trial-emulation*14* evidence on trial-of-non-invasive duration.

Conclusions

Among mechanically ventilated critically ill patients, intubation delayed beyond ICU admission was associated with a graded, dose–response increase in hospital mortality and markedly longer stays, despite lower baseline illness severity and bias structures that favour the delayed group. Pre-ICU, controlled intubation defined a distinct lower-risk pathway. These findings support time-limited, criteria-guided trials of non-invasive support with early escalation when failure criteria are met, and call for prospective studies capturing the respiratory trajectory at the intubation decision point.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CI, confidence interval; CRRT, continuous renal replacement therapy; EPV, events per variable; GCS, Glasgow Coma Scale; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; RR, risk ratio; SMD, standardised mean difference; SOFA, Sequential Organ Failure Assessment; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WHO, World Health Organization.

Declarations

Ethics approval and consent to participate. The eICU Collaborative Research Database is a de-identified dataset; its original collection was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center with waiver of informed consent. This secondary analysis of de-identified data was exempt from additional institutional review. This study was conducted in accordance with the Declaration of Helsinki.

Clinical trial number. Not applicable.

Consent for publication. Not applicable.

Availability of data and materials. The data that support the findings of this study are available from PhysioNet (the eICU Collaborative Research Database v2.0; https://eicu-crd.mit.edu/), but restrictions apply to the availability of these data, which are accessible only to credentialed researchers who have completed the required training and signed the data use agreement. Patient-level data for this analysis were extracted through the mimicdb.com research platform under the authors' credentialed access. The analysis code (Python 3.12, statsmodels) reproducing all tables and figures is available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. RY, FZ and SL contributed equally to this work. RY, YL and QO conceived and designed the study. FZ and SL curated and extracted the data. XC, MD and QW performed the statistical analysis and interpreted the results. RY drafted the manuscript. FZ, SL, XC, MD and QW critically revised the manuscript for important intellectual content. YL and QO supervised the study, take responsibility for the integrity of the work as a whole and are the guarantors. All authors read and approved the final manuscript.

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Figures

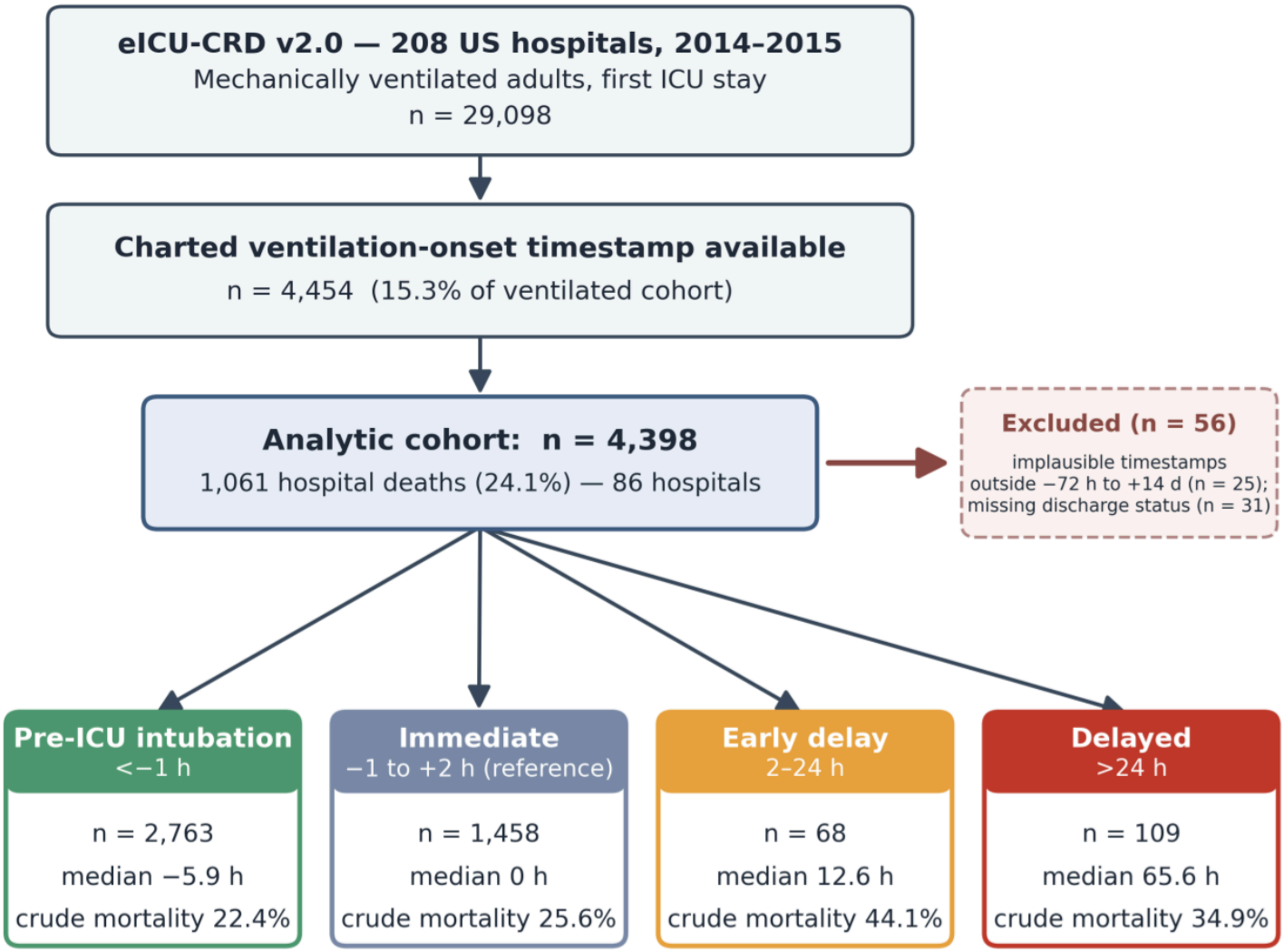


Figure 1

Study flow diagram. Derivation of the analytic cohort of 4,398 ventilated patients with charted ventilation-onset timestamps, and classification into four parallel timing groups relative to ICU admission with crude hospital mortality.

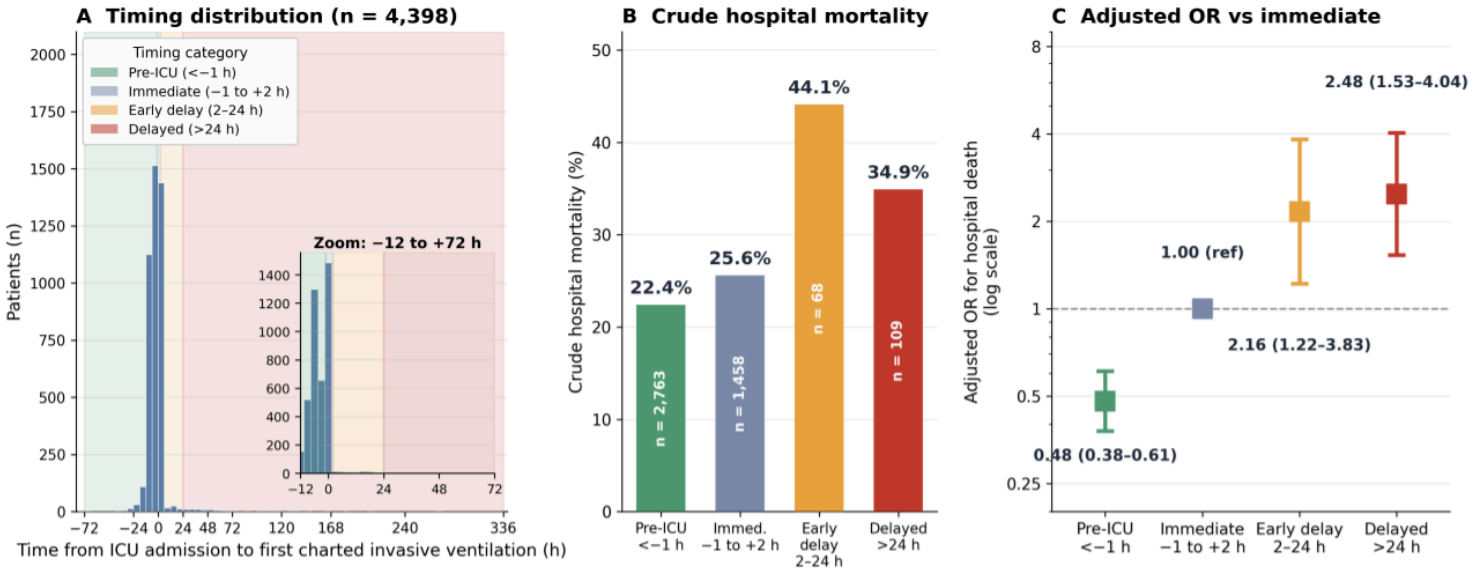


Figure 2

Ventilation-onset timing and hospital mortality. (A) Distribution of time from ICU admission to first charted invasive ventilation (negative values: intubation before ICU arrival); shaded bands mark the four timing categories, with a zoomed inset (−12 to +72 h). (B) Crude hospital mortality by timing category. (C) Adjusted odds ratios versus immediate intubation (95% CI, log scale) from the primary model.

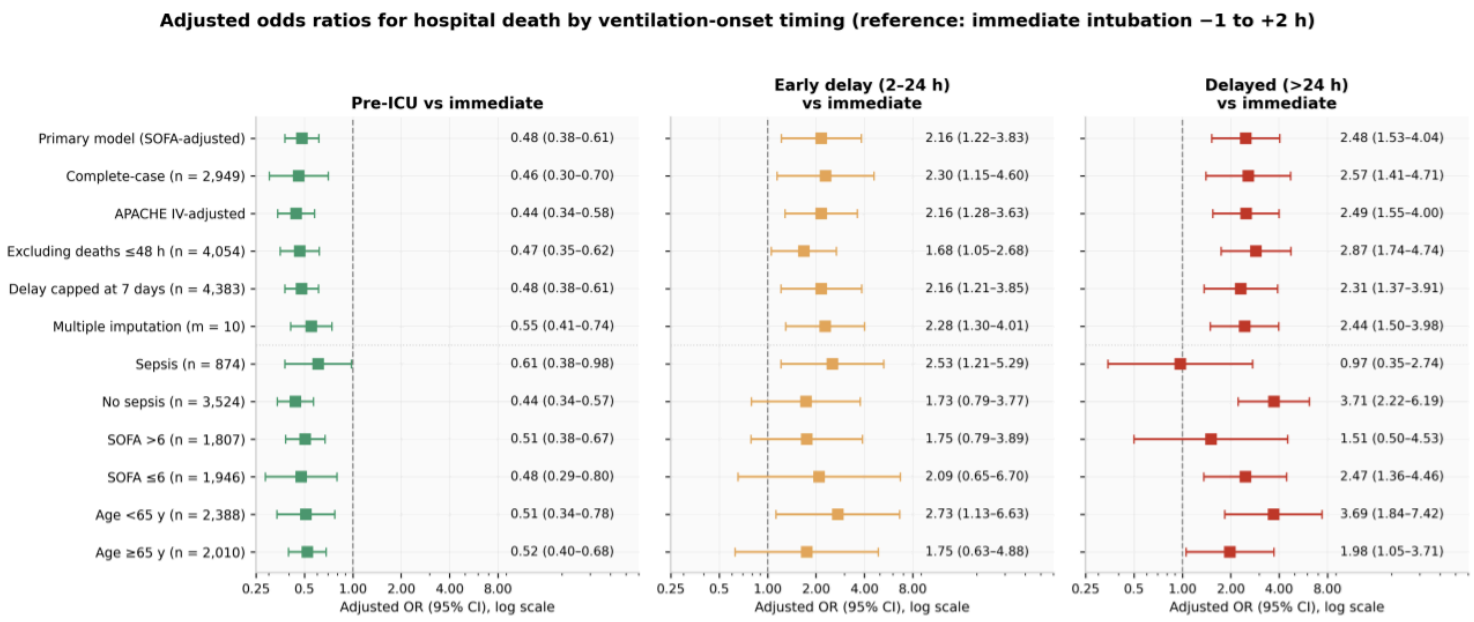


Figure 3

Forest plots of adjusted odds ratios for hospital death by ventilation-onset timing (reference: immediate intubation) across sensitivity analyses (above the dotted line) and pre-specified subgroups (below): pre-ICU (left), early delay 2–24 h (centre) and delayed >24 h (right). Log scale.