



**HAL**  
open science

# The impact of aggressive and conservative propensity for initiation of neuromuscular blockade in mechanically ventilated patients with hypoxemic respiratory failure

Zach Shahn, Boris Jung, Daniel Talmor, Edward Kennedy, Li-Wei Lehman,  
Elias Baedorf-Kassis

## ► To cite this version:

Zach Shahn, Boris Jung, Daniel Talmor, Edward Kennedy, Li-Wei Lehman, et al.. The impact of aggressive and conservative propensity for initiation of neuromuscular blockade in mechanically ventilated patients with hypoxemic respiratory failure. *Journal of Critical Care*, 2024, 82, pp.154803. 10.1016/j.jcrc.2024.154803 . hal-04527833

**HAL Id: hal-04527833**

**<https://hal.science/hal-04527833>**

Submitted on 31 Mar 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **The impact of aggressive and conservative propensity for initiation of neuromuscular blockade in mechanically ventilated patients with hypoxemic respiratory failure**

Zach Shahn a,b, Boris Jung d,e,f, Daniel Talmor e, Edward H. Kennedy g, Li-wei H. Lehman a,c, Elias Baedorf-Kassis e,f,\*

*a MIT-IBM Watson AI Lab, Cambridge, MA, United States of America*

*b CUNY Graduate School of Public Health and Health Policy, New York City, NY, United States of America*

*c Institute for Medical Engineering & Science, Massachusetts Institute of Technology, Cambridge, MA, 02142, United States of America*

*d Medical Intensive Care Unit, Lapeyronie Teaching Hospital, Montpellier University, Montpellier, France*

*e Department of Anesthesia, Pain and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, United States of America*

*f Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, United States of America*

*g Department of Statistics & Data Science, Carnegie Mellon University, Pittsburgh, PA 15213, United States of America*

## ***Keywords:***

Neuromuscular blockade NMB Paralysis Mechanical ventilation Incremental interventions

## **\* Corresponding author at:**

Department of Anesthesia, Pain and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, United States of America

## ***E-mail address:***

enbaedor@bidmc.harvard.edu (E. Baedorf-Kassis).

## ABSTRACT

### ***Introduction:***

Neuromuscular blockade (NMB) in ventilated patients may cause benefit or harm. We applied “incremental interventions” to determine the impact of altering NMB initiation aggressiveness.

### ***Methods:***

Retrospective cohort study of ventilated patients with PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 150 mmHg and PEEP ≥ 8cmH<sub>2</sub>O from the Medical Information Mart of Intensive Care IV database (MIMIC-IV version 1.0) estimating the effect of incremental interventions on in-hospital mortality and ventilator-free days, modifying hourly propensity for NMB initiation to be aggressive or conservative relative to usual care, adjusting for confounding with inverse probability weighting.

### ***Results:***

5221 patients were included (13.3% initiated on NMB). Incremental interventions estimated a strong effect on NMB usage: 5-fold higher hourly odds of initiation increased usage to 36.5% (CI = [34.3%,38.7%]) and 5-fold lower odds decreased usage to 3.8% (CI = [3.3%,4.3%]). Aggressive and conservative strategies demonstrated a U-shaped mortality relationship. 5-fold higher or lower propensity increased in-hospital mortality by 2.6% (0.95 CI = [1.5%,3.7%]) or 1.3% (0.95 CI = [0.1%,2.5%]) respectively. In secondary analysis of a healthier patient cohort, results were similar, however conservative strategies also improved ventilator-free days.

### ***Interpretation:***

Aggressive or conservative initiation of NMB may worsen mortality. In healthier populations, marginally conservative NMB initiation strategies may lead to increased ventilator free days with minimal impact on mortality.

## 1. Introduction

Neuromuscular blockade (NMB) is commonly used in patients with acute respiratory failure [1,2], particularly in patients with acute respiratory distress syndrome (ARDS) [3], a disease that carries a profound morbidity and mortality [4] and became a leading cause of death worldwide during the COVID pandemic [5]. NMB has been suggested to provide benefit through several mechanisms. Removal of spontaneous breathing activity from the patient allows full control during mechanical ventilation, which could reduce the risk for self-inflicted lung injury [6, 7], while removal of dyssynchrony and expiratory muscle activity may reduce lung derecruitment and overdistension [8,9]. Additionally, NMB use has been associated with improved mechanics, decreased inflammatory markers, decreased oxygen consumption, and decreased hemodynamic complications [8, 10, 11]. Conversely, the use of NMB may result in direct and indirect harm. NMB may cause skeletal and respiratory muscle injury and weakness [12], it may lead to further atelectasis and derecruitment [13], and it may lead to higher sedation requirements and prolonged duration of mechanical ventilation [14], which have independently been found to worsen patient outcomes.

Several randomized trials have investigated the potential risks and benefits of NMB with mixed results. Two small single center trials suggested NMB initiation improved mortality, inflammatory biomarkers, mechanics, and oxygenation [10, 15]. The larger subsequent single center ACURASYS trial found improved 90-day mortality in patients with moderate-severe ARDS (- 9.1%, 0.95 CI = [- 18.9%, 0.7%]) [16]. In the large follow up multi-center ROSE trial, this mortality benefit was no longer found, with similar outcomes between the NMB and control groups (-0.3%, 0.95 CI = [- 6.4%, 5.9%]) [17]. Patients were also less active and had more adverse cardiovascular events in the NMB arm, providing some suggestive evidence that the net effects of NMB initiation may be harmful in the absence of mortality benefits.

It is unclear how these mixed findings should be incorporated into practice. The wide confidence intervals from both large studies overlap considerably, and both are consistent with null effects. The control arm of the ACURASYS trial entailed never initiating NMB within 48 h after baseline, and the NMB treatment arm protocols of both studies called for early initiation of NMB immediately after randomization. However, under usual care, clinicians may be unlikely to either immediately initiate NMB or avoid initiation at all costs, but rather monitor their patients and make the decision to initiate based on clinician-specific aspects of evolving time-varying patient state (for example, dyssynchrony level, presence of spontaneous breathing, or severity of illness). Such a monitoring clinician might interpret the (highly uncertain) mortality results from the ACURASYS trial as reflecting harms of *never* initiating NMB as much as benefits of always initiating. While the ROSE trial did provide “usual care” in its control arm (modified to include light sedation targets), its confidence interval included a broad range of plausible effect sizes (beneficial or harmful), and it only

provided weak evidence against universal immediate initiation. It did not provide any direct evidence that strategies more conservative than usual care would be beneficial.

The question remains whether, on average, clinicians should be more aggressive in NMB initiation decisions than they currently are (even if perhaps not as aggressive as in the experimental arms of the ROSE and ACURASYS trials), or whether they should on average be more conservative (even if perhaps not as conservative as in the control arm of the ACURASYS trial). In this paper, we address these questions by applying a recently developed method for estimating effects of so-called *incremental interventions* [18, 19]. This approach has been applied to clinical care in several studies [20, 21], including our own application to mechanically ventilated patients in the ICU [22]. An incremental intervention multiplies the odds of initiating NMB in each patient at each time relative to usual care by some factor. An incremental intervention by a factor  $> 1$  shifts usual care to be more aggressive, and an incremental intervention by a factor  $< 1$  shifts usual care to be more conservative. Thus, incremental effect estimates address our questions of interest. A shift by a factor of infinity corresponds to the experimental arms of the ROSE and ACURASYS trials, where everyone initiates NMB, and a shift by a factor of 0 corresponds to the control arm of ACURASYS, where no one initiates NMB. We consider shifts by factors between 0.2 and 5, which reflect more realistic alterations to usual care, in which clinicians continue to exercise their judgement.

While incremental interventions are not directly actionable in that they do not indicate exactly when to initiate NMB, incremental effect estimates can be highly suggestive about how care should change and inform the design of future randomized trials whose results would be actionable. If incremental interventions making NMB initiation less likely than under usual care (given patient history) are estimated to be beneficial, this implies that on average physicians would do better to be more hesitant to initiate. Such findings would also imply that further randomized trials testing specific initiation strategies might identify initiation rules that are both beneficial and directly actionable. If usual care is found to be near optimal in the class of incremental interventions, this suggests that improvements in care will need to come from treatment rules encouraging treatment in particular situations as opposed to broad encouragement or discouragement to treat.

## 2. Methods

### 2.1. Cohort construction

We performed a retrospective cohort study of mechanically ventilated patients from the Medical Information Mart for Intensive Care IV database (MIMIC-IV version 1.0), publicly available at PhysioNet. The database contains records from 64,975 hospital admissions

between 2008 and 2019 to Beth Israel Deaconess Medical Center, a tertiary academic medical center in Boston, MA, USA. Institutional review boards at BIDMC (2001-P-001699/14) and Massachusetts Institute of Technology (0403000206) have approved use of MIMIC-IV for research and granted waiver of informed consent.

Inclusion criteria for our primary analysis were that patients were invasively mechanically ventilated with no prior NMB initiation, had PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq 150$ , and PEEP  $\geq 8$ . These inclusion criteria were chosen to be similar to the ACURASYS and ROSE trials. We also conducted a secondary analysis in patients that were healthier at baseline with inclusion criteria for this secondary cohort that patients were mechanically ventilated with no prior NMB initiation (with no restrictions based on PaO<sub>2</sub>/FiO<sub>2</sub> ratio or PEEP.) Patients were entered into each cohort at the first time that inclusion criteria were met, and the follow-up period over which treatment strategies of interest were to be applied lasted until extubation from the index intubation. Outcomes were obtained over the full hospital stay.

For each patient in our cohort, we extracted baseline variables, including: age, sex, weight, first care unit, admission type, select Elixhauser comorbidities, and a baseline frailty score. We also extracted time-stamped, time-varying variables over the course of follow-up, including: vital signs (heart rate, respiratory rate, arterial pressure, temperature, spO<sub>2</sub>), lab values (pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, AADO<sub>2</sub>), fluid volume, vasopressor dose, sedative dose, sedation level, SOFA score, and both set and observed ventilator readings (PEEP, standardized tidal volume, peak inspiratory pressure, mean airway pressure, PaO<sub>2</sub>-FiO<sub>2</sub> ratio, inspiratory time, driving pressure, compliance). The full list of confounders we adjusted for is in our treatment model summary in the supplementary materials (Supplemental Table 1).

## ***2.2. Outcomes***

We considered in-hospital mortality as the primary endpoint for the analysis with ventilator-free days as a secondary endpoint. Ventilator free days were defined as the number of the 30 days following baseline (i.e. first time at which the inclusion criteria were met) that a patient was alive and not invasively ventilated.

## ***2.3. Statistical analysis***

We estimated effects of incremental interventions adjusting for time-varying confounding via inverse probability weighting using our prior established methodology [22]. At a given time  $t$ , we let  $h_t$  denote a patient's covariate and treatment history through  $t$ . We let  $\pi_t(h_t)$  denote the probability under usual care of initiating NMB at time  $t$  conditional on history  $h_t$  and no

previous NMB initiations prior to  $t$ . We estimated counterfactual expected population outcomes under interventions that multiply the conditional odds

$$\frac{\pi_t(h_t)}{1-\pi_t(h_t)}$$

of NMB initiation at each hour by a factor of  $\delta$  for  $\delta$  in a range of values between 0.2 and 5. Interventions corresponding to values of  $\delta$  that are  $<1$  prolong the average time until NMB initiation and lead to fewer total NMB initiations, and values of  $\delta >1$  shorten the average time to NMB initiation and lead to more total NMB initiations. Because these interventions are based on propensity for initiations that would never occur in practice (i.e., if someone has zero chance of NMB initiation, their chances will remain zero regardless of the value of  $\delta$ ). Similarly, if a patient is extremely unlikely to be initiated on NMB at a given time under usual care, under the intervention corresponding to  $\delta = 5$  their odds of NMB initiation at that time would be five times as high, but they would still be highly unlikely to initiate NMB. For outcome  $Y$ , we estimated the expected value of  $Y$  under an intervention multiplying NMB initiation odds by  $\delta$  adjusting for time-varying confounding via inverse probability weighting as

$$\hat{E}[Y(\delta)] = \frac{1}{n} \sum_i \left( \prod_t \frac{\delta A_{it} + 1 - A_{it}}{\delta \hat{\pi}_t(h_{it}) + 1 - \hat{\pi}_t(h_{it})} \right) Y_i$$

In the above formula,  $\hat{\pi}_t(h_{it})$  is the estimated conditional probability of NMB initiation at time  $t$  under usual care, which we obtain from a pooled logistic regression model using the most recent value of each covariate mentioned in the cohort construction section as predictors. If our probability of NMB initiation model is well specified and the covariates we included in that model contain the drivers of NMB initiation decisions that are also associated with outcomes of interest, then our effect estimates are unbiased. We estimated confidence intervals via bootstrap. A summary of our probability of treatment model as well as R code for our analysis can be found in Supplementary Materials.

## 2. Results

Our primary cohort contained 5221 patients. Under usual care, 13.3% of patients in the cohort initiated NMB at some point during follow-up, mean ventilator free days was 16.6 (sd = 11.8), and in-hospital mortality rate was 34.5%. Baseline cohort characteristics are summarized in Table 1.

Incremental interventions were estimated to have strong monotonic effects on NMB usage, as expected (Fig. 1). Under an incremental intervention multiplying odds of NMB initiation by  $\delta = 5$  at each hour, we estimated that the proportion of patients initiating NMBs at any point during follow-up would increase to 36.5% (CI = [34.3%, 38.7%]). Under an incremental

intervention multiplying odds of NMB initiation by  $\delta = 1/5$  at each hour, we estimated that the proportion of patients initiating NMB at some point during follow-up would decrease to 3.8% (CI = [3.3%, 4.3%]). Changing propensity for NMB initiation ranging from aggressive ( $\delta = 5$ ) to conservative ( $\delta = 1/5$ ) for a given patient has minimal impact on the odds of NMB initiation in patients with low baseline propensity (Fig. 2 left), and a much larger impact on the odds of NMB initiation in patients with higher baseline propensity (Fig. 2 right).

The relationship between NMB initiation aggressiveness and in-hospital mortality was U-shaped (Fig. 3). Both strategies that were more aggressive than usual care and strategies that were significantly more conservative than usual care were estimated to increase mortality relative to usual care. An intervention of  $\delta = 5$  was estimated to increase mortality by 2.6% (0.95 CI = [1.5%, 3.7%]), and an intervention of  $\delta = 1/5$  was estimated to increase mortality by 1.3% (0.95 CI = [0.1%, 2.5%]). The usual care strategy ( $\delta = 1$ ) was estimated to be near optimal for mortality among the class of incremental interventions.

More aggressive NMB initiation strategies were also estimated to monotonically decrease ventilator free days (Fig. 4), though this relationship was not statistically significant.

In our secondary cohort ( $n = 24,019$ ) including healthier patients (no PaO<sub>2</sub>/FiO<sub>2</sub> ratio or PEEP eligibility criteria meant to approximate ARDS), results were qualitatively similar (see the Supplemental table 2 for baseline information on this cohort). While NMB initiation was rarer both under usual care (4.4%) and under incremental interventions (14.5% (CI = [13.9%, 15.1%]) for  $\delta = 5$ ), a similar U-shaped curve described the estimated relationship between aggressiveness of the incremental intervention and in-hospital mortality rate (see Fig. 4). An intervention of  $\delta = 5$  was estimated to increase mortality by 1.2% (0.95 CI = [0.8%, 1.6%]), and an intervention of  $\delta = 1/5$  was estimated to increase mortality by 0.5% (0.95 CI = [0.3%, 0.6%]). However, conservative strategies in the range  $35 \leq \delta \leq 1$  were estimated to have very little impact on mortality. There was a stronger and statistically significant monotonic relationship between aggressiveness and ventilator free days. Under an intervention of  $\delta = 5$ , mean ventilator free days were estimated to decrease by 0.18 days (0.95 CI = [0.11, 0.25]). Under an intervention of  $\delta = 1/5$ , mean ventilator free days were estimated to increase by 0.10 days (0.95 CI = [0.07, 0.12]).



**Table 1**  
 Baseline characteristics of primary cohort (invasively mechanically ventilated with no prior NMB initiation, had PaO<sub>2</sub>/FiO<sub>2</sub> ratio ≤ 150, and PEEP ≥ 8), n = 5221.

	Mean (SD)
Age	62.8 (15.3)
Male	0.62
Weight (Kg)	92 (29)
Elixhauser SID30	23.3 (15.5)
In-hospital mortality rate	0.35
SOFA (24 h)	
Total	6.9 (3.6)
Liver	0.4 (0.9)
Cardiovascular	1.9 (1.4)
CNS	0.4 (1.0)
Coagulation	0.6 (1.0)
Respiration	2.3 (1.3)
Renal	0.8 (1.2)
Baseline Illness	
Congestive Heart Failure	0.19
Valvular Heart Disease	0.1
Peripheral Vascular	0.08
Hypertension	0.33
Paralysis	0.02
Chronic Pulmonary	0.19
Diabetes Uncomplicated	0.13
Diabetes Complicated	0.04
Liver Disease	0.13
Obesity	0.1
Alcohol Abuse	0.07
Drug Abuse	0.04
Depression	0.09
Metastatic Cancer	0.02
Solid Tumor	0.03
Rheumatoid Arthritis	0.03
Coagulopathy	0.17
Sepsis	0.74
Baseline hours after admission	25.4 (48.1)
Sedation Level	
Unarousable	0.18
Deep	0.13
Moderate	0.21
Light	0.12
Restless	0.03
Agitated	0
Sedatives	
Opioid	0.55
Ketamine	0
Dexmetomidine	0.03
Benzodiazepines	0.25
propofol	0.55
Vasopressors	0.53
Total fluids (L)	1.7 (1.8)
Dysynchrony	2.2 (2.5)
Ventilator Parameters	
PEEP set	8.7 (3.3)
Tidal volume set	448.4 (82.6)
Respiratory rate	20.9 (5.5)
Minute volume	9.9 (3.0)
Vent Mechanics	
Compliance	37.4 (16.7)
Driving pressure	13.1 (4.0)
Plateau pressure	22.0 (5.3)
Mean airway pressure	13.5 (4.2)
Peak inspiratory pressure	26 (7.1)
Gas Exchange	
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	132.4 (82.9)
SpO <sub>2</sub>	96.1 (4.4)
FiO <sub>2</sub>	63.9 (24.6)
Vitals	
Mean blood pressure	76.2 (14.1)
Heart rate	89.9 (18.1)

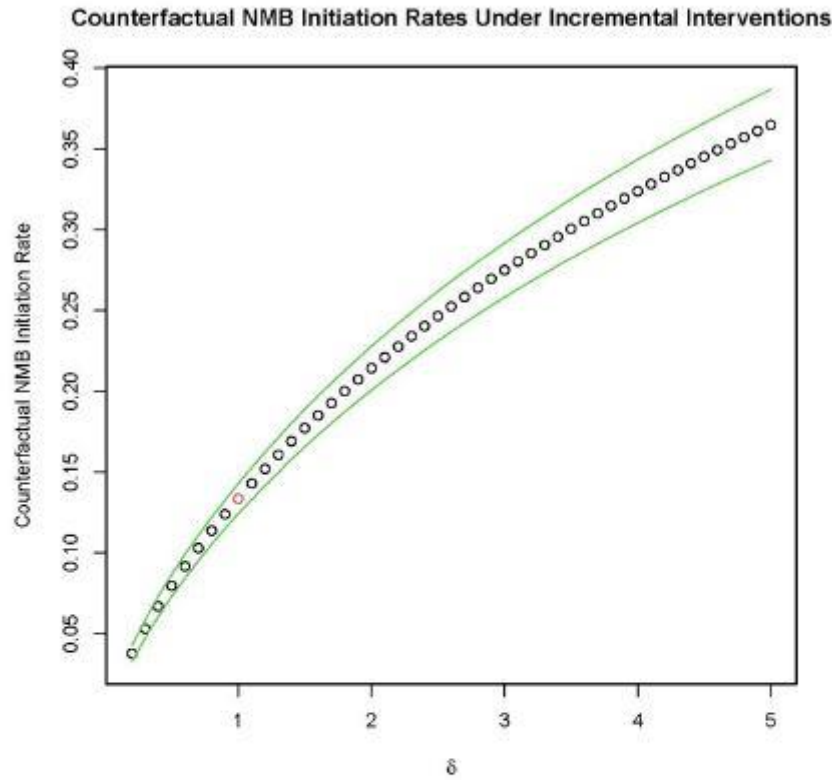


Fig. 1. Data from the primary cohort included patients who were invasively mechanically ventilated with no prior NMB initiation, had PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq 150$ , and PEEP  $\geq 8$  (n = 5221). Estimated neuromuscular blockade (NMB) initiation rate (and bootstrap confidence intervals) under a range of incremental interventions making liberation strategies more or less aggressive relative to usual care ranging from aggressive ( $\delta = 5$ ) to conservative ( $\delta = \frac{1}{5}$ ). The propensity at  $\delta = 1$  indicates usual care. To the left of these lines are more conservative initiation strategies and to the right are more aggressive initiation strategies. The figure demonstrates that incremental interventions do indeed have a large overall impact on the initiation rate of NMB within the population.

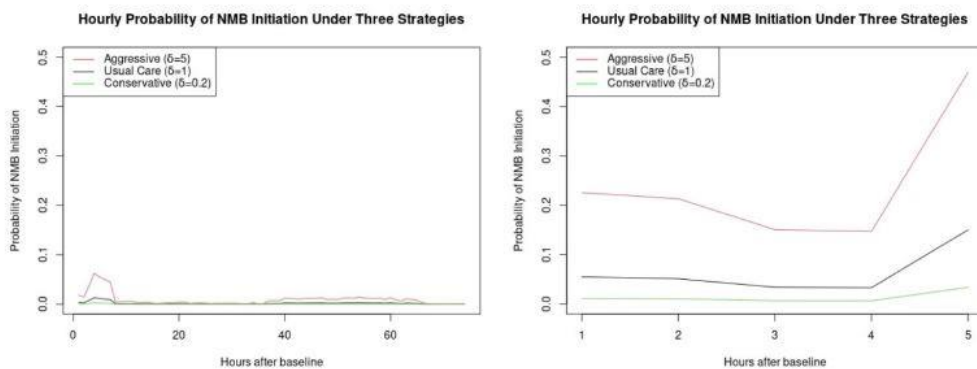


Fig. 2. Hourly probability of NMB initiation under usual care, an aggressive incremental intervention ( $\delta = 5$ ), and a conservative incremental intervention ( $\delta = \frac{1}{5}$ ) for two representative patients—one with low hourly probability of NMB initiation in the usual care group (Left), and one with high hourly probability of NMB initiation (Right). Unsurprisingly, the patient with high probability of NMB initiation was initiated on NMB sooner, and the impact of changing propensity was much higher than in the patient with low odds for NMB initiation under usual care. Each patient's estimated hourly probability of NMB initiation under usual care fluctuates with time varying covariates, and the probabilities of initiation under incremental interventions fluctuate along with the usual care probabilities. In the patient with higher probabilities of initiation under usual care, the impact of the incremental interventions on probability of initiation on an absolute scale is much larger than in the patient with low probabilities of initiation.

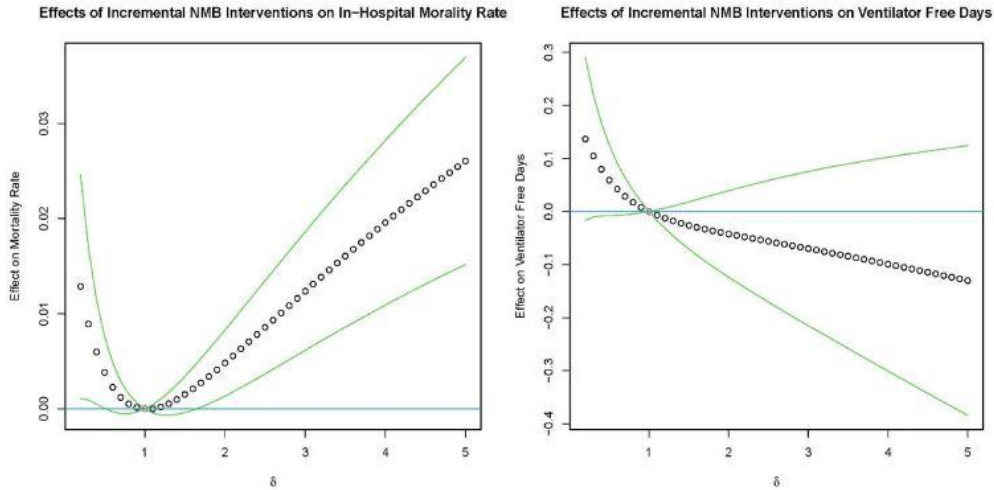


Fig. 3. Estimated effects of *incremental interventions* on patient outcomes (mortality on the left and ventilator-free days on the right) relative to usual care in the primary cohort (patients who were invasively mechanically ventilated with no prior NMB initiation, had PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq 150$ , and PEEP  $\geq 8$ ) (n = 5221). The aggressiveness of the incremental interventions is indexed by  $\delta$ , which is the factor by which an incremental intervention multiplies hourly odds of NMB initiation under usual care. Values of  $\delta > 1$  indicate strategies that are more aggressive than usual care. We considered values of  $\delta$  corresponding to interventions multiplying hourly odds of NMB initiation under usual care by up to 5. Values of  $\delta < 1$  indicate strategies are more conservative than usual care. We considered values of  $\delta$  corresponding to interventions multiplying hourly odds of NMB initiation under usual care by as little as 1/5.  $\delta = 1$  corresponds to usual care. We estimated effects for a range of  $\delta$  values, adjusting for time-varying confounding via inverse probability weighting. The effect on mortality with changing propensity for NMB initiation appears U-shaped, with both very aggressive and conservative strategies for NMB initiation resulting in worsened mortality. The effects of NMB initiation on ventilator free days were unclear as confidence intervals were wide and included both beneficial and harmful effects of aggressive and conservative strategies. The intervals are very narrow at  $\delta = 1$  since this value corresponds to the mean outcome under usual care, which can be very efficiently estimated under essentially no assumptions.

## 4. Discussion

### 4.1. Interpretation of results

There has been much debate and discussion as to the relative risks and benefits of using NMB in patients with acute respiratory failure after the initial ACURASYS study [16] and the follow-up ROSE study [17]. The findings from our primary analysis provide interesting context for the trial evidence. Our study suggests that both very aggressive and conservative use of NMB increase mortality relative to usual care. We could view the experimental arms of both the ACURASYS and ROSE trials, in which NMB was initiated immediately, as the extreme of aggressive strategies (i.e.  $\delta = \infty$ ). The confidence interval from the ROSE trial, which had slightly modified usual care (similar to  $\delta = 1$ ) as its control arm, was consistent with harmful effects of aggressive strategies of the magnitude we estimated. The ACURASYS control arm in contrast could be interpreted as the extreme conservative strategy, tantamount to  $\delta = 0$ . Our findings suggest that crude strategies of the form ‘always initiate NMB immediately’ or ‘always avoid initiating NMB as long as possible’ will be inferior to usual care. Clinicians’ more nuanced decision making around NMB initiation appears beneficial compared to these crude approaches. Thus, future trials should evaluate treatment rules for NMB initiation in patients with ARDS that are more responsive to patient state.

Our secondary analysis in a healthier cohort produced potentially more actionable results. Taken together, our results imply that somewhat more conservative NMB initiation strategies would present a favorable tradeoff between mortality on one hand and ventilator free days on

the other in a cohort of patients which includes healthier patients. For example, setting  $\delta = 3/5$  (which represents a somewhat more conservative propensity for initiation compared with usual care), ventilator free days are expected to increase on average by 0.046 (0.95 CI = [0.03, 0.06]) in the full cohort. This may initially appear to be a marginal increase, but that is because only 4.4% of the entire cohort initiates NMB under usual care. Under the intervention  $\delta = 3/5$ , the expected proportion of patients initiating NMB declines by about 1.6%. Assuming that the vast majority of the impact of the intervention will be

realized in patients who do not initiate NMB under the intervention but would under usual care (as opposed to patients in whom NMB initiation is merely delayed) we can roughly estimate that the average increase in coma free days among patients who do not initiate NMB because of the intervention is  $0.046 / 0.016 = 2.9$  ventilator free days. Thus, the estimated benefits from setting  $\delta$  to  $3/5$  (the approximate minimum value corresponding to the most conservative strategy before which mortality begins to increase relative to usual care) are highly clinically significant among the patients who might be spared NMB initiation as a result of the intervention.

#### ***4.2. Discussion of incremental propensity score intervention effects***

An important consideration when interpreting our results is that incremental interventions describe natural shifts from usual care (to be more or less aggressive), rather than treatment rules indicating exactly when to initiate NMB. The basic oxygenation rules used in the ROSE and ACURASYS trials were deterministic and actionable treatment rules but, we argued, did not improve on usual care. Other factors that contribute to the NMB initiation decision include ventilator settings, type and timing of lung injury, presence of spontaneous breathing and dyssynchrony, level of sedation, and sedative choice. However, a realistic prescriptive and deterministic treatment rule incorporating these factors would be complex, difficult to properly specify, and followed exactly by very few patients in our cohort. This latter point in particular makes stable estimation of realistic actionable strategies difficult. Incremental interventions avoid analytic challenges associated with complex deterministic treatment rules, and, as an additional benefit, their effects are concentrated in patients with reasonable clinical equipoise regarding the treatment of interest under usual care. While not directly actionable, estimates of effects of incremental interventions can still be highly suggestive about how care should change and inform the design of future actionable interventions, as illustrated by our results in this study.

#### ***4.3. Limitations***

A potential limitation of this analysis, as with any observational study attempting to estimate causal effects, is the potential presence of unobserved confounders. Examples of missing confounders could be ‘appearance’ or ‘behavior’. Clinicians might base their NMB initiation decisions on aspects of patient appearance or behavior that are not captured by proxy in the medical record and are associated with outcomes. However, we believe that the set of baseline and time-varying confounders we adjusted for contained most relevant information about patient state that might influence NMB initiation decisions and be associated with outcomes of interest. (The full list of confounders in our probability of treatment model summary in the

supplementary materials can help the reader judge this claim.) We would not typically expect to see the U-shaped mortality results we obtained in the presence of severe confounding. If our results were mostly driven by sicker patients (in ways not captured by the data) being initiated on NMB more often, we would have expected to see that conservative strategies were *beneficial*. That we did not estimate a monotonic relationship between NMB initiation aggressiveness and mortality is therefore somewhat reassuring.

Another limitation is that our results must be interpreted relative to usual care at BIDMC, the center from which our data were collected. Our results do not necessarily extend to other centers. If usual care does not outperform very conservative or aggressive strategies at other centers, then perhaps usual care at BIDMC should be studied more closely as a model for other centers to emulate.

An additional limitation, mentioned previously, is that the incremental interventions we studied do not correspond directly to protocols that could easily be implemented in a trial. In our primary ARDS cohort, usual care performed quite well, and our results do not point toward prescriptive treatment strategies that might improve upon it. Rather, our contribution is to provide evidence that any such strategies will likely need to be nuanced and take into account patient state. Finally, these data do not include any patients with COVID, so while these findings might be able to be extrapolated into the COVID – ARDS population, this needs to be confirmed in future studies.

### **CRedit authorship contribution statement**

**Zach Shahn:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

**Boris Jung:** Investigation, Methodology, Writing – original draft, Writing – review & editing.

**Daniel Talmor:** Conceptualization, Writing – original draft, Writing – review & editing.

**Edward H. Kennedy:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

**Li-wei H. Lehman:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

**Elias Baedorf-Kassis:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

### **Declaration of competing interest**

Funding was also provided by the MIT-IBM Watson AI Lab. LL was in part funded by NIH grants R01 EB017205 and 1U01TR003528-01A1. EBK and DT having received lecturing fees for educational talks from Hamilton Medical Inc. ZS was primarily employed by IBM Research during some of the work.

## Acknowledgements

Authors contributions: ZS, LL, BJ, EK, DT and EBK conceptualized the study. ZS and LL extracted data and/or performed analysis on the data. ZS and EBK primarily wrote the manuscript with critical review and editing by all authors. ZS serves as the guarantor of the paper.

## References

- [1] Bourenne J, Hraiech S, Roch A, Gainnier M, Papazian L, Forel J-M. Sedation and neuromuscular blocking agents in acute respiratory distress syndrome. *Ann Trans Med* 2017;5:291. <https://doi.org/10.21037/atm.2017.07.19>.
- [2] deBacker J, Hart N, Fan E. Neuromuscular blockade in the 21st century management of the critically ill patient. *CHEST* 2017;151:697–706. <https://doi.org/10.1016/j.chest.2016.10.040>.
- [3] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33. <https://doi.org/10.1001/jama.2012.5669>.
- [4] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315:788–800. <https://doi.org/10.1001/jama.2016.0291>.
- [5] Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *Lancet* 2022;399:1513–36. [https://doi.org/10.1016/S0140-6736\(21\)02796-3](https://doi.org/10.1016/S0140-6736(21)02796-3).
- [6] Yoshida T, Uchiyama A, Fujino Y. The role of spontaneous effort during mechanical ventilation: normal lung versus injured lung. *J Intensive Care* 2015;3:18. <https://doi.org/10.1186/s40560-015-0083-6>.
- [7] Yoshida T, Roldan R, Beraldo MA, Torsani V, Gomes S, De Santis RR, et al. Spontaneous effort during mechanical ventilation: maximal injury with less positive end-expiratory pressure\*. *Crit Care Med* 2016;44:e678. <https://doi.org/10.1097/CCM.0000000000001649>.
- [8] Guervilly C, Bisbal M, Forel JM, Mechat M, Lehingue S, Bourenne J, et al. Effects of neuromuscular blockers on transpulmonary pressures in moderate to severe acute respiratory distress syndrome. *Intensive Care Med* 2017;43:408–18. <https://doi.org/10.1007/s00134-016-4653-4>.

- [9] Baedorf Kassis E, Loring SH, Talmor D. Lung volumes and transpulmonary pressure are decreased with expiratory effort and restored with passive breathing in ARDS: a reapplication of the traditional Campbell diagram. *Intensive Care Med* 2018;44: 534–6. <https://doi.org/10.1007/s00134-018-5105-0>.
- [10] Forel J-M, Roch A, Marin V, Michelet P, Demory D, Blache J-L, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome\*. *Crit Care Med* 2006;34:2749. <https://doi.org/10.1097/01.CCM.0000239435.87433.0D>.
- [11] Sottile PD, Albers D, Moss MM. Neuromuscular blockade is associated with the attenuation of biomarkers of epithelial and endothelial injury in patients with moderate-to-severe acute respiratory distress syndrome. *Crit Care* 2018;22:63. <https://doi.org/10.1186/s13054-018-1974-4>.
- [12] Moerer O, Baller C, Hinz J, Buscher H, Crozier TA. Neuromuscular effects of rapacuronium on the diaphragm and skeletal muscles in anaesthetized patients using cervical magnetic stimulation for stimulating the phrenic nerves. *Eur J Anaesthesiol* 2002;19:883–7.
- [13] Pellegrini M, Hedenstierna G, Roneus A, Segelsjö M, Larsson A, Perchiazzi G. The diaphragm acts as a brake during expiration to prevent lung collapse. *Am J Respir Crit Care Med* 2017;195:1608–16. <https://doi.org/10.1164/rccm.201605-0992OC>.
- [14] Wongtangman K, Grabitz SD, Hammer M, Wachtendorf LJ, Xu X, Schaefer MS, et al. Optimal sedation in patients who receive neuromuscular blocking agent infusions for treatment of acute respiratory distress syndrome-a retrospective cohort study from a New England health care network. *Crit Care Med* 2021;49: 1137–48. <https://doi.org/10.1097/CCM.0000000000004951>.
- [15] Gainnier M, Roch A, Forel J-M, Thirion X, Arnal J-M, Donati S, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome\*. *Crit Care Med* 2004;32:113. <https://doi.org/10.1097/01.CCM.0000104114.72614.BC>.
- [16] Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;363:1107–16. <https://doi.org/10.1056/NEJMoa1005372>.
- [17] National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;380:1997–2008. <https://doi.org/10.1056/NEJMoa1901686>.

[18] Kennedy E. Nonparametric causal effects based on incremental propensity score interventions. *J Am Stat Assoc* 2019;114:645–56.

[19] Bonvini M, McClean A, Branson Z, Kennedy EH. Incremental causal effects: An introduction and review. 2021.

[20] Naimi AI, Rudolph JE, Kennedy EH, Cartus A, Kirkpatrick SI, Haas DM, et al. Incremental propensity score effects for time-fixed exposures. *Epidemiology* 2021; 32:202–8. <https://doi.org/10.1097/EDE.0000000000001315>.

[21] Rudolph JE, Kim K, Kennedy EH, Naimi AI. Estimation of the time-varying incremental effect of low-dose aspirin on incidence of pregnancy. *Epidemiology* 2023;34:38. <https://doi.org/10.1097/EDE.0000000000001545>.

[22] Shahn Z, Choudhri A, Jung B, Talmor D, Lehman LH, Baedorf-Kassis E. Effects of aggressive and conservative strategies for mechanical ventilation liberation. *J Crit Care* 2023;76:154275. <https://doi.org/10.1016/j.jcrc.2023.154275>.