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Effects of aggressive and conservative strategies for mechanical ventilation liberation

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ABSTRACT

Background:

The optimal approach for transitioning from strict lung protective ventilation to support modes of ventilation when patients determine their own respiratory rate and tidal volume remains unclear. While aggressive liberation from lung protective settings could expedite extubation and prevent harm from prolonged ventilation and sedation, conservative liberation could prevent lung injury from spontaneous breathing.

Research question:

Should physicians take a more aggressive or conservative approach to liberation?

Methods:

Retrospective cohort study of mechanically ventilated patients from the Medical Information Mart for Intensive Care IV database (MIMIC-IV version 1.0) estimating effects of incremental interventions modifying the propensity for liberation to be more aggressive or conservative relative to usual care, with adjustment for confounding via inverse probability weighting. Outcomes included in-hospital mortality, ventilator free days, and ICU free days. Analysis was performed on the entire cohort as well as subgroups differentiated by PaO₂/FiO₂ ratio, and SOFA.

Results:

7433 patients were included. Strategies multiplying the odds of a first liberation relative to usual care at each hour had a large impact on time to first liberation attempt (43 h under usual care, 24 h (0.95 CI = [23,25]) with an aggressive strategy doubling liberation odds, and 74 h (0.95 CI = [69,78]) under a conservative strategy halving liberation odds). In the full cohort, we estimated aggressive liberation increased ICU-free days by 0.9 days (0.95 CI = [0.8,1.0]) and ventilator free days by 0.82 days (0.95 CI = [0.67,0.97]), but had minimal effect on mortality (only a 0.3% (0.95 CI = [□ 0.2%,0.8%]) difference between minimum and maximum rates). With baseline SOFA ≥ 12 ($n = 1355$), aggressive liberation moderately increased mortality (58.5% [0.95 CI = (55.7%, 61.2%)]) compared with conservative liberation (55.1% [0.95 CI = (51.6%,58.6%)]).

Interpretation:

Aggressive liberation may improve ventilator free and ICU free days with little impact on mortality in patients with SOFA score < 12. Trials are needed.

1. Introduction

Lung protective mechanical ventilation strategies have become the standard of care to prevent lung injury and improve morbidity and mortality in patients requiring mechanical ventilation [1-3]. While lung protective mechanical ventilation is of critical importance, the goal for all ventilated patients is successful extubation and removal of mechanical support. The final steps in weaning from the ventilator to determine readiness for extubation have been extensively investigated with data from multiple studies to guide clinical decision making [4-6], however we know very little about the initial liberation toward extubation when patients transition from lung protective ventilation to a support mode of ventilation. After this transition from tightly controlled settings, patients determine their own respiratory rate and tidal volumes with the ventilator providing support with each breath to augment the inspiratory effort. It remains unclear when it is safe to liberate patients from the rigid parameters of protective ventilation, with potential risks and benefits of both maintenance of lung protection and liberation.

Lung protective ventilation strategies require the strict application of low tidal volumes and non-injurious pressures [7,8], which may cause patient discomfort. Assuring tolerance of these settings often requires high levels of sedation and/or paralytics [9] with the use of these potentially causing delayed weaning, prolonged duration of mechanical ventilation, increased critical illness myopathy, increased delirium, and worsened mortality [10-14]. Furthermore, prolonged intubation may lead to complications such as ventilator associated pneumonias and the need for tracheostomy [10]. To limit these harms it may be beneficial to expedite weaning from strict lung protective ventilation parameters to allow for lower sedation requirements. However, it is also possible that allowing patients to breathe spontaneously before they have adequately recovered from their critical illness may result in worsened injury or further impact patient hemodynamics [15-17]. While spontaneous breathing may be beneficial in less sick patients with improved ventilation/perfusion matching and more physiologic breathing [18], this may not be the case for sicker patients with potentially injurious pressure and volume subsequently leading to worsened lung injury – what has been described as patient self-induced lung injury (P-SILI) [19-23].

In this paper, we take an important first step toward assessing the tradeoffs involved in liberation timing. Using a recently developed technique, we estimate the effects of so-called *incremental interventions* [24] that shift the probability (or, more precisely, multiply the odds) of liberation given patient history at each time relative to usual care. If a patient were very unlikely to be liberated at a given time under usual care due to their clinical characteristics (i.e. they remain severely ill or have a reason to not be weaned such as brain injury), incremental interventions (because they are multiplicative) would not markedly increase or decrease the *absolute* likelihood of liberation. If, on the other hand, there is considerable variation in whether a patient with a given history would be liberated under usual care, then incremental interventions would result in a much larger shift in absolute

probability of liberation. In other words, incremental interventions mostly impact those patients in whom there is significant variation in care under usual care, a desirable property.

Note that incremental interventions are not directly actionable, as they do not specify exactly in which scenarios clinicians should liberate. While it would be ideal to identify actionable interventions that improve on usual care, we study incremental interventions because they sidestep analytic barriers to reliably estimating effects of actionable treatment rules in a complicated decision making setting. To be realistic, an actionable liberation strategy would need to be complex, basing decisions on a large number of variables including and not limited to ventilator settings, type and timing of lung injury, level of sedation, and sedative choice. In observational datasets, very few patients would follow any such complex strategy precisely, making it difficult to reliably estimate its effects. In contrast, simplified rules that might be followed by a larger number of patients would (due to their insufficient complexity) likely call for liberations in scenarios in which the probability of liberation under usual care is close to 0, which is called a “positivity violation” and can make estimation of causal effects highly unstable. Incremental interventions avoid these analytic challenges [24], making them well suited for this study.

In addition to being tractable, incremental intervention effects can also be highly suggestive about how care should change and inform the design of future randomized trials whose results would be actionable. For example, if aggressive incremental interventions making liberation more likely than under usual care (given patient history) are estimated to be beneficial, this would imply that on average physicians would do better to look for earlier opportunities to liberate. But most importantly, such results would suggest a need for randomized trials testing actionable protocols for aggressive liberation.

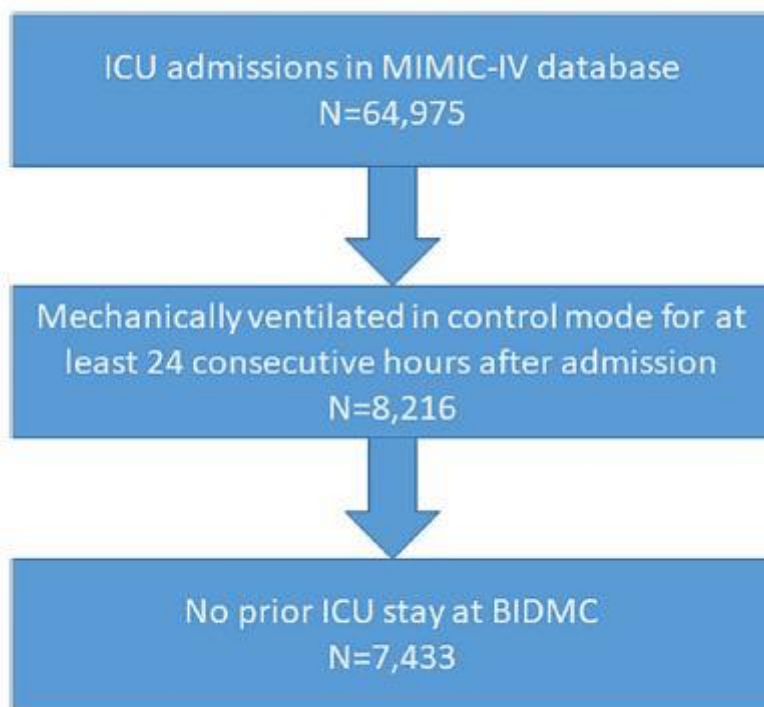


Fig. 1. Flow chart depicting cohort construction.

Distributions of Probability of Liberation Over Patient-Hours

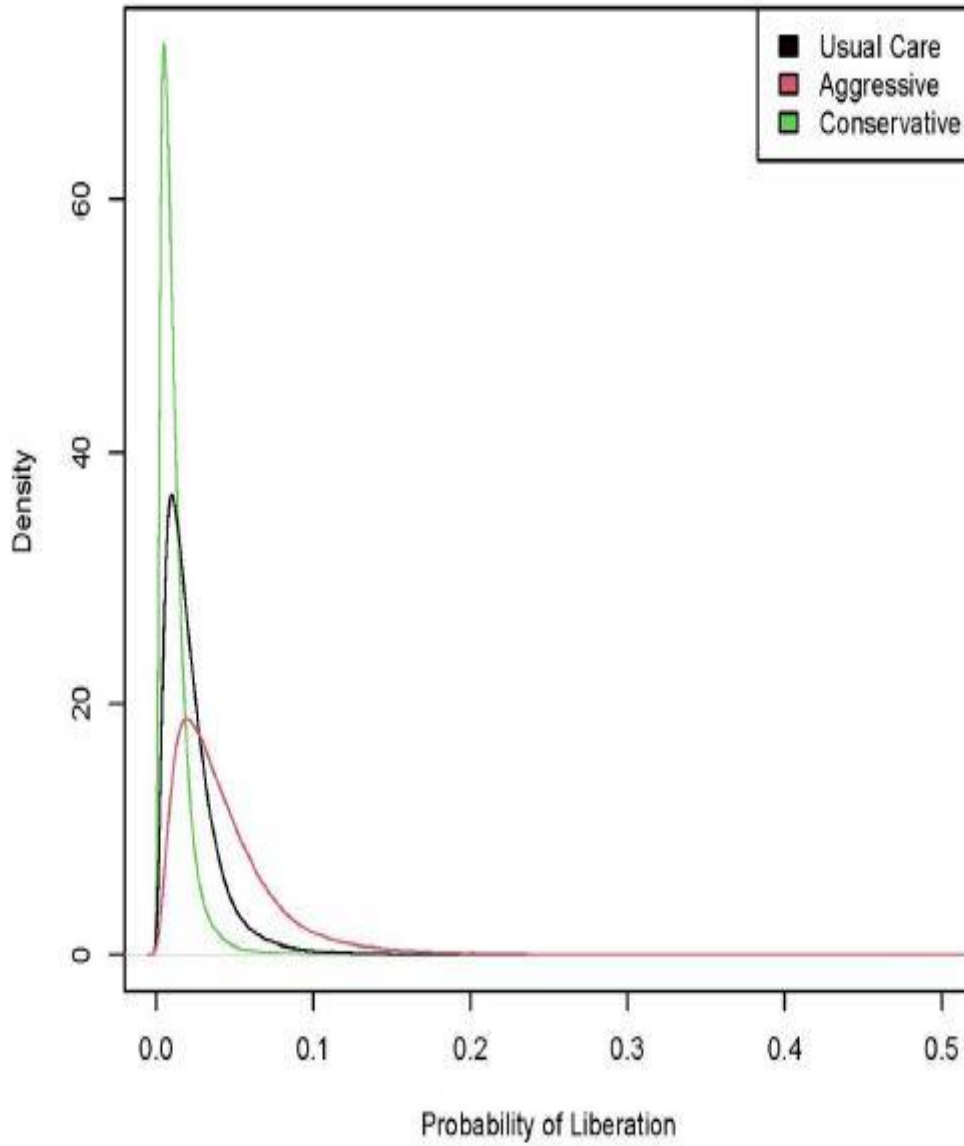


Fig. 2. Distributions over all patient-hours in the cohort of estimated probabilities of liberation under three treatment regimes—usual care, “aggressive” (corresponding to an incremental intervention with $\delta = 2$), and “conservative” (corresponding to an incremental intervention with $\delta = 12$).

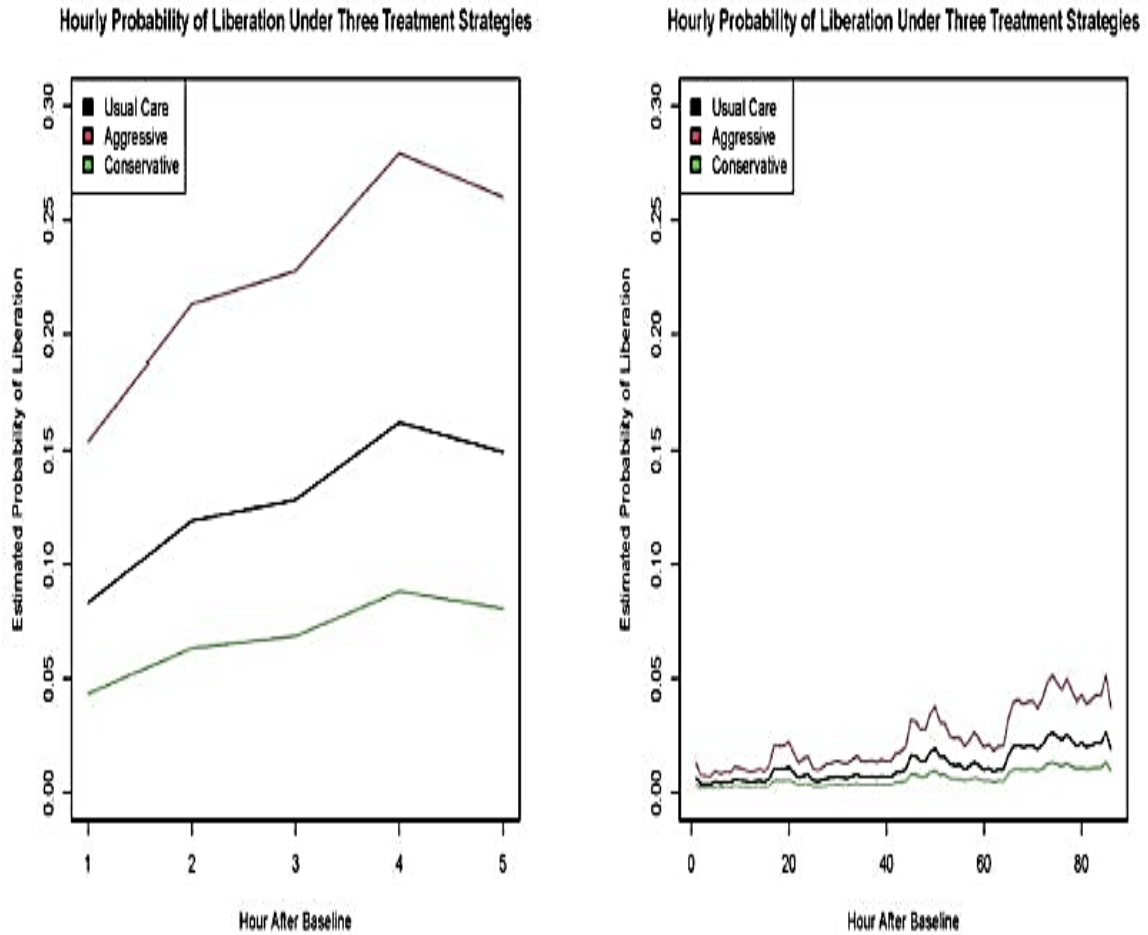


Fig. 3. Hourly probability of liberation under usual care, an aggressive incremental intervention ($\delta = 2$), and a conservative incremental intervention ($\delta = 12$) for two representative patients—one with high hourly probability of liberation (Left), and one with low hourly probability of liberation (Right). Unsurprisingly, the patient with high probability of liberation was liberated sooner (after 5 h) than the patient with lower hourly probability of liberation (86 h). Each patient's estimated hourly probability of liberation under usual care fluctuates with time varying covariates, and the probabilities of liberation under incremental interventions fluctuate along with the usual care probabilities. In the patient with higher probabilities of liberation under usual care, the impact of the incremental interventions on probability of liberation on an absolute scale is much larger than in the patient with low probabilities of liberation.

Table 1

Baseline (after 24 consecutive hours of control mode ventilation) characteristics of the cohort.

Variable measured at baseline	Mean (sd) or %
Age (years)	63 (17)
Male	58%
First Care Unit	
Cardiac Vascular ICU	12%
Coronary Care Unit	11%
Medical ICU	42%
Surgical ICU	16%
Neuro SICU	3%
Sequential Organ Failure Assessment (24 h)	7.6 (4.2)
Positive End Expiratory Pressure (cm H ₂ O)	7.7 (3.6)
Tidal Volume (mL)	445 (77)
Respiratory Rate (breaths per minute)	20.2 (5.6)
Peak Inspiratory Pressure (cm H ₂ O)	24.0 (7.5)
Plateau Pressure (cm H ₂ O)	19.9 (5.4)
Mean Airway Pressure (cm H ₂ O)	12.1 (4.4)
Minute Volume (L x bpm)	9.2 (2.8)
PaO ₂ /FiO ₂ Ratio	244 (133)
PO ₂ (mm Hg)	113 (58)
PCO ₂ (mm Hg)	41 (9)
AADO ₂ (mm Hg)	187 (113)
pH	7.4 (0.1)
Total CO ₂ (mEq/L)	25.0 (5.7)
FiO ₂ (mm Hg)	49.0 (14.7)
Lactate (mmol/L)	2.2 (2.2)
Creatinine (mg/dL)	1.7 (1.5)
Systolic Blood Pressure	115 (20)
Diastolic Blood Pressure	59 (13)
Mean Blood Pressure	76 (14)
SpO ₂	97.3 (4.0)
Heart Rate	85 (19)

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 Beth Israel Deaconess Medical Center (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 were that patients needed to be mechanically ventilated in a control mode for 24 consecutive hours after ICU admission without a liberation attempt. Liberation attempts were defined as switches from controlled modes of ventilation to support modes of ventilation. We excluded patients with records of previous ICU admission at BIDMC. Patients were entered into the cohort at the first time that inclusion criteria were met (Fig. 1). Control modes are listed in the supplementary materials.

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, spO₂), lab values (PH, PO₂, PCO₂, AADO₂), fluid volume, vasopressor dose, sedation level, SOFA score, and both set and observed ventilator readings (PEEP, standardized tidal volume, peak inspiratory pressure, mean airway pressure, PaO₂-FiO₂ ratio, inspiratory time, driving pressure, compliance). Our constructed dataset contained a row for each post-baseline patient-hour when there had not been a prior liberation attempt. At each patient-hour, we input the most recent measurement of each covariate listed above and included an indicator for whether an initial liberation attempt occurred in that patient-hour. Missingness was rare (<5% of person times were missing for every covariate we adjusted for), and we imputed missing values with cohort medians.

2.2. Outcomes

We considered in-hospital mortality as the primary endpoint for the analysis. Additional secondary endpoints included ICU-free days, and ventilator-free days as outcomes. ICU free days were defined as the number of the 30 days following baseline (i.e. after 24 consecutive hours ventilated in control mode) that a patient was alive and not in an ICU at BIDMC. If a patient died out of hospital or was admitted to an ICU at another hospital during this time, this was not captured in our data. Ventilator-free days were defined analogously as the number of the 30 days following baseline that a patients was alive and not invasively ventilated. Additional subgroup analysis was also performed in patients with SOFA \geq 12, SOFA \leq 5,

PaO₂-FiO₂ ratio ≤ 150, and PaO₂-FiO₂ ratio ≥ 300 at baseline. The subgroup analyses simply entailed conducting the analyses described below in these subgroups.

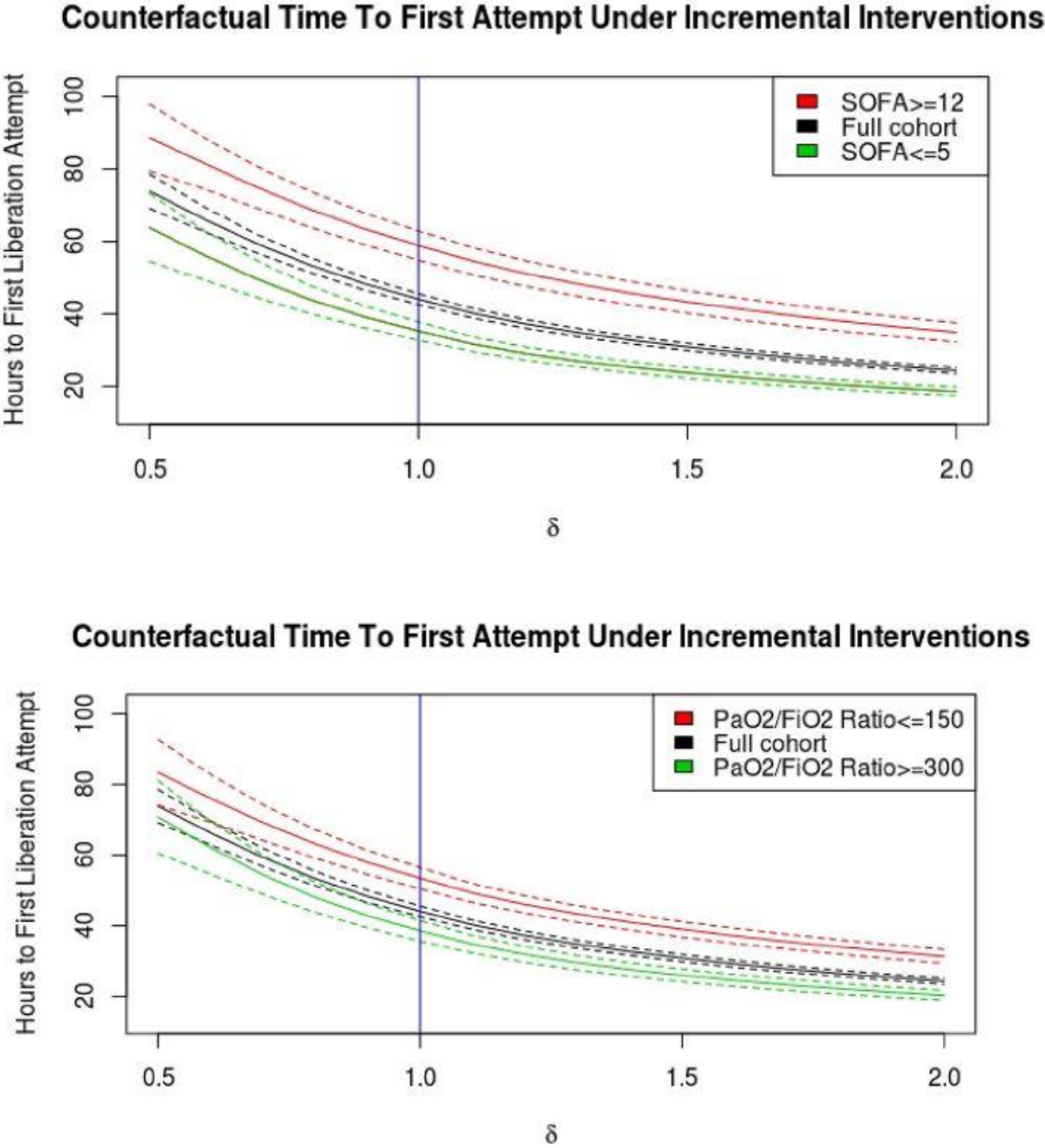


Fig. 4. Estimated average hours to first liberation attempt (and bootstrap confidence intervals) under a range of incremental interventions making liberation strategies more or less aggressive relative to usual care for the full cohort and subgroups defined in terms of baseline SOFA score and baseline PaO₂-FiO₂ ratio. The vertical lines at $\delta = 1$ indicate usual care. To the left of these lines are more conservative liberation strategies and to the right are more aggressive liberation strategies. The figure shows that incremental interventions do indeed have a large impact on the treatment of interest.

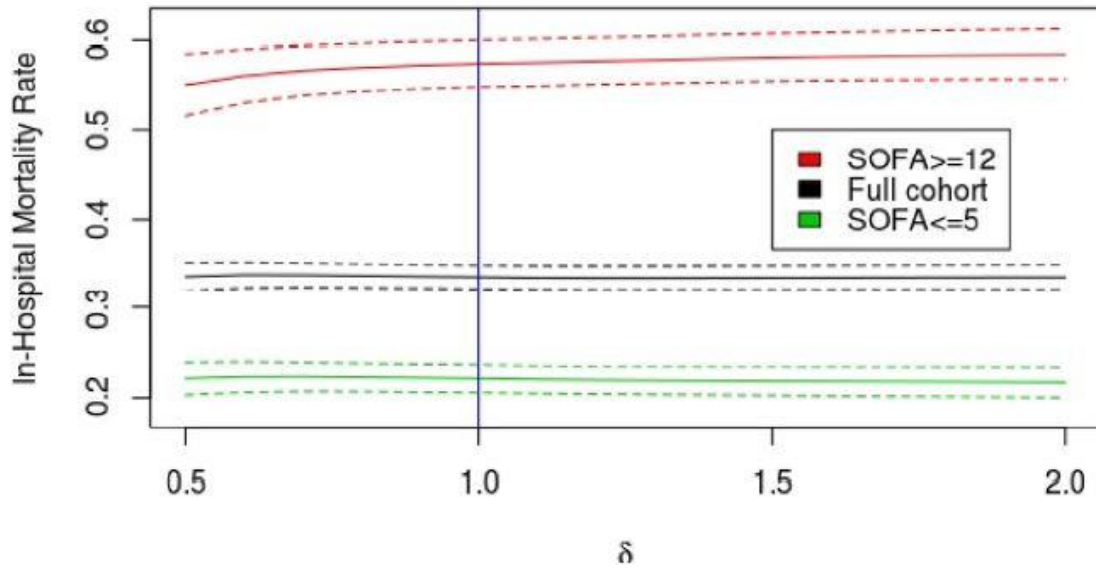
2.3. Effects of interest: incremental interventions

We estimated effects of incremental interventions adjusting for time-varying confounding via inverse probability weighting [24]. An incremental intervention multiplies the odds of liberation given patient history at a given time under usual care by a factor δ . Values of $\delta < 1$ correspond to conservative interventions that prolong the average time until the first liberation attempt, and values of $\delta > 1$ correspond to aggressive interventions that shorten the average time to first liberation attempt. For example, suppose that under usual care 1 out of every 10 patients who had a particular history of recorded covariates (vital signs, ventilator settings, etc.) would be liberated at a given hour under usual care. (So the odds of liberation for patients with this history at this hour under usual care are 1 to 9.) Under an aggressive incremental intervention ($\delta = 2$) doubling odds of liberation at each hour relative to usual care, the odds of liberation for patients with this history would become 2 to 9, meaning that 2 out of every 11 patients with this history would be liberated. Because incremental interventions are based on propensity to liberate under usual care, they do not call for unrealistic liberation attempts or delays that would never occur in practice. If a patient is very unlikely to be liberated at a given time under usual care, under the ‘aggressive’ intervention corresponding to $\delta = 2$ their odds of liberating at that time would be doubled, but they would still be unlikely to be liberated on an absolute scale. Thus, most of the impact of an incremental intervention is in patients in whom there would be variation in care under usual care, a desirable property. Figs. 2 and 3 illustrate the impact of incremental interventions on hourly propensity to liberate relative to usual care. Fig. 2 shows the impact of these interventions on the distribution of hourly propensity to liberate in the cohort, and Fig. 3 illustrates their impact using data from two specific patients.

To formalize, at a given time t , let ht denote a patient's covariate and treatment history through t . Let $\pi_t(ht)$ denote the probability under usual care of an initial liberation attempt at time t conditional on history ht and no previous liberation attempts prior to t . We estimated expected population outcomes under interventions that multiply the conditional odds

$\left(\frac{\pi_t(ht)}{1-\pi_t(ht)}\right)$ of an initial liberation attempt at each hour relative to usual care by a factor of δ , for δ in a range of values between 0.5 and 2.

Counterfactual Mortality Rates Under Incremental Interventions



Counterfactual Mortality Rates Under Incremental Interventions

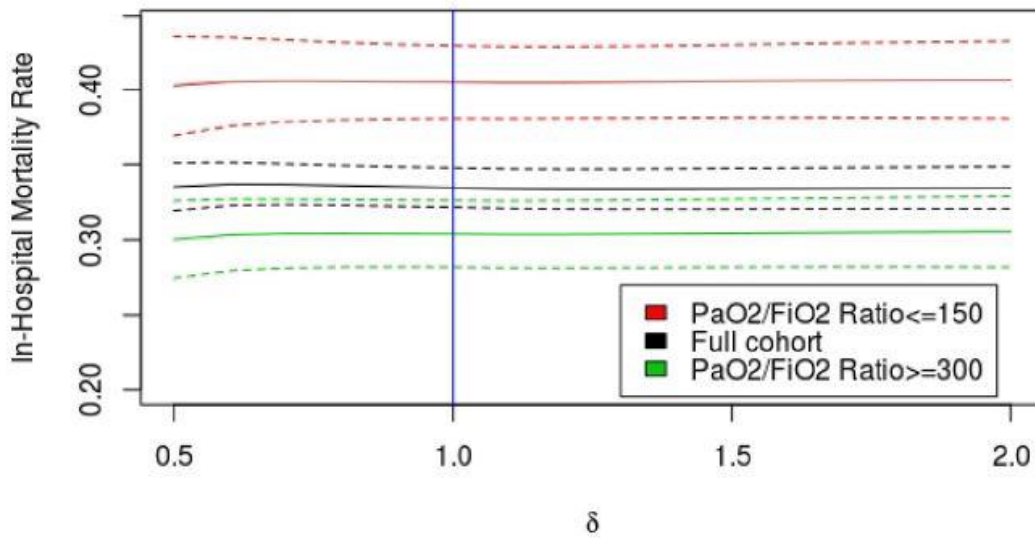


Fig. 5. Estimated in-hospital mortality rates (and bootstrap confidence intervals) under a range of incremental interventions making liberation strategies more or less aggressive relative to usual care for the full cohort and subgroups defined in terms of baseline SOFA score and PaO₂-FiO₂ ratio. The vertical lines at $\delta = 1$ indicate usual care. To the left of these lines are more conservative liberation strategies and to the right are more aggressive liberation strategies. Changing the aggressiveness of liberation strategies is estimated to have very little effect on mortality rate in the full cohort and PaO₂-FiO₂ ratio subgroups. More conservative strategies are estimated to lead to slightly lower mortality rates in the high SOFA subgroup.

2.4. Statistical analysis

For outcome Y , we estimate the expected value of Y under an intervention multiplying conditional liberation odds at each hour by δ (denoted $E[Y(\delta)]$ in counterfactual notation) adjusting for time-varying confounding via inverse probability weighting as

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

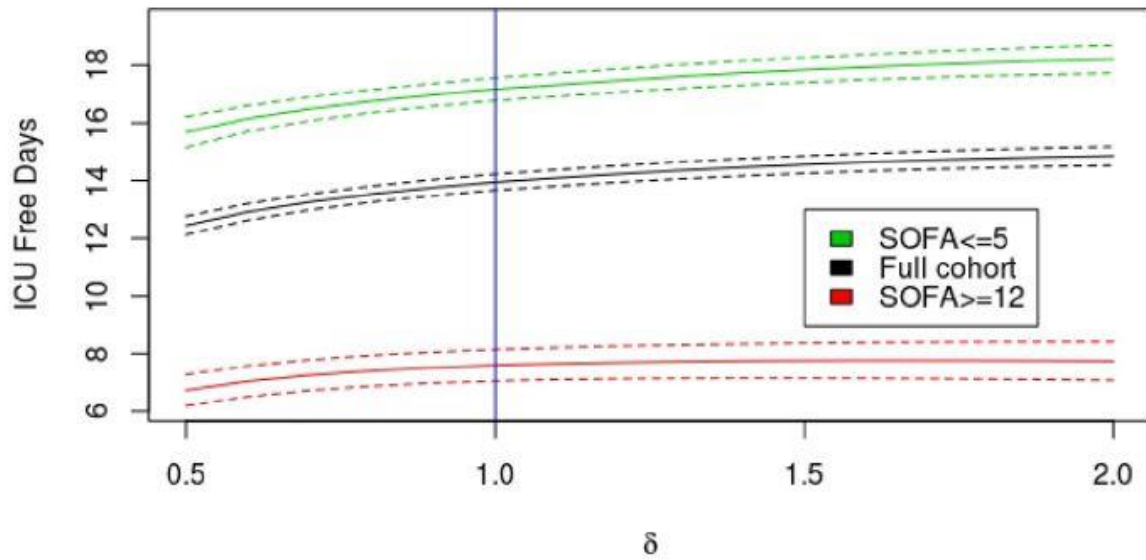
In the above formula, n is the sample size, patients are indexed by i and time (in hours) by t , and A_{it} indicates whether liberation occurred at hour t in patient i . $\widehat{\pi}(hit)$ is the estimated conditional probability of liberation in patient i at time t under usual care, which we obtain from a pooled logistic regression model using the most recent value of each covariate listed in the cohort construction section as predictors. We provide a summary of this probability of liberation model including all covariates in the supplementary materials. If our probability of liberation model is well specified and the covariates we included in that model contain the drivers of liberation decisions that are also associated with outcomes of interest (or appropriate rich proxies), then our estimates of incremental effects are approximately unbiased. We estimated confidence intervals via bootstrap. R code for the analysis is available at https://github.com/zshahn/when_to_liberate

2. Results

7433 patients met inclusion criteria and were included in the cohort for analysis. On average, patients in the cohort were liberated for the first time 43 h after baseline. The observed in-hospital mortality rate in the overall cohort was 34%. On average, patients had 14 ICU-free days and 17 ventilator free days out of the 30 days following baseline. Baseline characteristics of the cohort are described in detail in Table 1.

Incremental interventions multiplying the odds of a first liberation at each hour relative to usual care were estimated to have a large impact on the average time after baseline to first liberation attempt (Fig. 4). Under usual care (i.e. $\delta = 1$), the average time from baseline to first liberation attempt was about 43 h. Doubling the odds of liberation at each hour (i. e. $\delta = 2$), was estimated to decrease the average time to first liberation attempt to about 24 h (0.95 CI = [23,25]) after baseline. Halving the odds of liberation at each hour (i.e. $\delta = 0.5$), was estimated to increase the average time to first liberation attempt to about 74 h (0.95 CI = [69,78]).

Counterfactual ICU Free Days Under Incremental Interventions



Counterfactual ICU Free Days Under Incremental Interventions

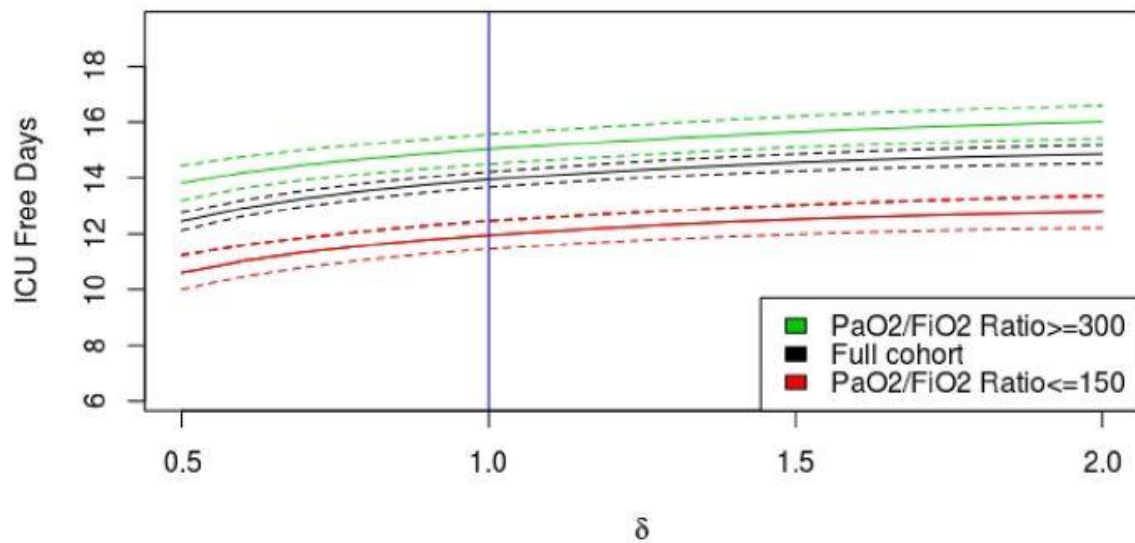


Fig. 6. Estimated average ICU free days (and bootstrap confidence intervals) under a range of incremental interventions making liberation strategies more or less aggressive relative to usual care for the full cohort and subgroups defined in terms of baseline SOFA score and baseline PaO₂-FiO₂ ratio. The vertical lines at $\delta = 1$ indicate usual care. To the left of the line are more conservative liberation strategies and to the right are more aggressive liberation strategies. More aggressive liberation strategies are estimated to increase ICU-free days in the general cohort. In the high SOFA subgroup, usual care is close to optimal in the class of strategies considered.

Despite their large impact on average time to liberation, incremental interventions making liberation more or less likely were estimated to have very little effect on the full cohort in-

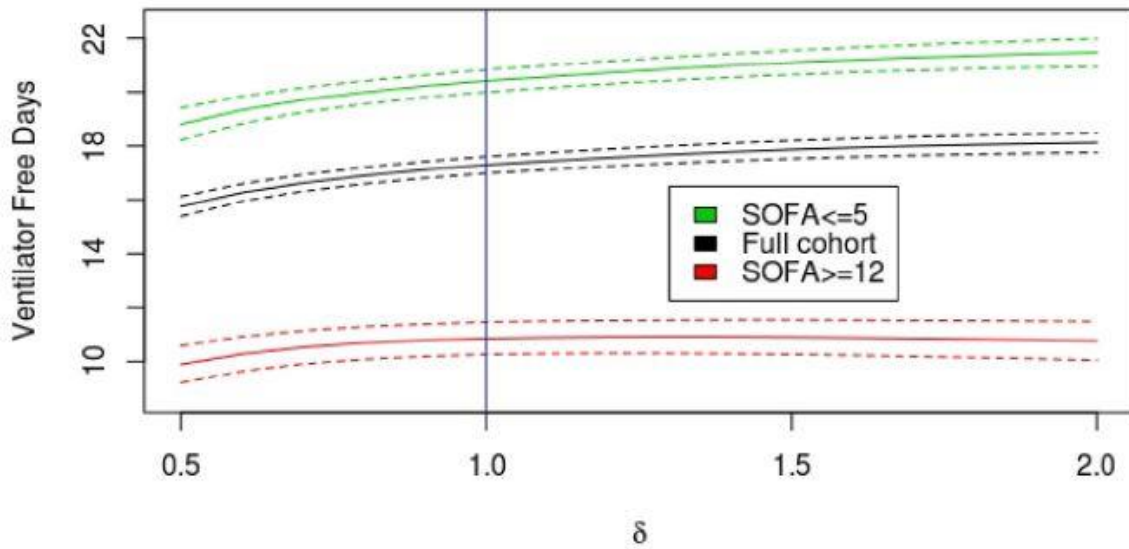
hospital mortality rate (Fig. 5). The difference between the minimum and maximum full cohort mortality rates under the range of interventions considered was 0.3% (0.95 CI = [0.2%,0.8%]). Similar results held in the low baseline PaO₂-FiO₂ ratio (≤ 150) subgroup ($n = 1837$), the high baseline PaO₂- FiO₂ ratio (≥ 150) subgroup ($n = 2024$), and the low SOFA (≤ 5) subgroup ($n = 2571$). However, incremental liberation interventions were estimated to have a moderate effect in the subgroup of patients with baseline SOFA ≥ 12 ($n = 1355$). The in-hospital mortality rate in this group was 57.4%. The estimated mortality rate under a strategy aggressive relative to usual care in the subgroup (i.e. $\delta = 2$) was 58.5% (0.95 CI = [55.7%,61.2%]). The estimated mortality rate under a strategy conservative relative to usual care in the subgroup (i.e. $\delta = 0.5$) was 55.1% (0.95 CI = [51.6%,58.6%]). While incremental interventions did not rise to the level of impacting mortality in the full cohort, they were estimated to affect ICU-free days (Fig. 6) and ventilator free days (Fig. 7). An aggressive liberation strategy (i.e. $\delta = 2$) was estimated to increase ICU-free days by 0.9 days (0.95 CI = [0.8,1.0]) and increase ventilator free days by 0.82 days (0.95 CI = [0.67,0.97]) relative to usual care in the full cohort. A conservative liberation strategy (i.e. $\delta = 0.5$) was estimated to decrease ICU-free days by 1.5 days (0.95 CI = [1.3,1.7]) and ventilator free days by 1.55 days (0.95 CI = [1.31,1.79]) relative to usual care in the full cohort. Similar results were obtained for the PaO₂-FiO₂ ratio subgroups and the low baseline SOFA subgroup. But incremental interventions were estimated to have much smaller effects on ICU and ventilator free days in the high baseline SOFA subgroup. In this subgroup, usual care was estimated to be very close to optimal (across the range of incremental interventions).

4. Discussion

4.1. Interpretation of results

There is a great deal of uncertainty surrounding liberation timing from control mode ventilation to spontaneous modes of ventilation in mechanically ventilated patients without data to guide decision making. With aggressive strategies, early liberation attempts could have the potential to lead to early weaning, which could have the beneficial effects of reducing the level of required sedation and the total duration of time ventilated, limiting the potential harm associated with these. Alternatively, liberating too early and allowing spontaneous breathing could lead to self-inflicted lung injury [19,25-27], which could theoretically prolong mechanical ventilation time and increase the burden of sedation leading to other adverse outcomes [11].

Counterfactual Ventilator Free Days Under Incremental Interventions



Counterfactual Ventilator Free Days Under Incremental Interventions

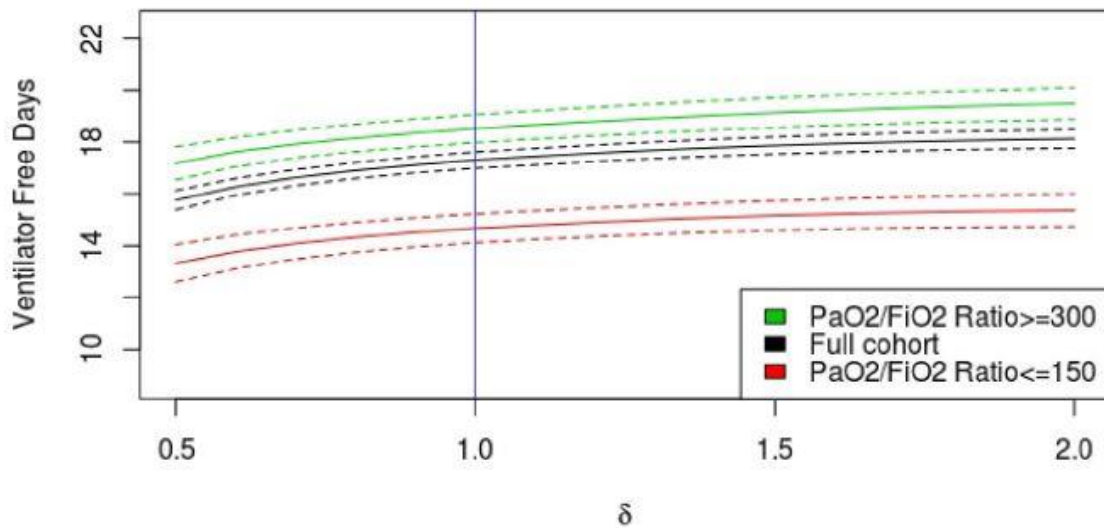


Fig. 7. Estimated average ventilator free days (and bootstrap confidence intervals) under a range of incremental interventions making liberation strategies more or less aggressive relative to usual care for the full cohort and subgroups defined in terms of baseline SOFA score and baseline PaO₂-FiO₂ ratio. The vertical lines at $\delta = 1$ indicate usual care. To the left of the lines are more conservative liberation strategies and to the right are more aggressive liberation strategies. More aggressive liberation strategies are estimated to increase ventilator free days in the general cohort. In the high SOFA subgroup, usual care is close to optimal in the class of strategies considered.

In this study, we estimated that on average interventions shifting liberation strategies to be more aggressive relative to usual care would increase ICU and ventilator free days to a

clinically meaningful and statistically significant degree while having very little impact on in-hospital mortality. (However, in the subgroup of patients with high baseline SOFA score (≥ 12), more conservative liberation strategies were estimated to moderately decrease mortality, while incremental interventions on liberation timing were estimated to have very little effect on ICU and ventilator free days.) The implication of our results for patient care (assuming the results are not due to confounding) is that on average physicians could look for earlier opportunities to liberate patients who do not have very high baseline SOFA scores or have other reasons to not pursue liberation due to their clinical state. More importantly, the results suggest a need for randomized trials testing actionable protocols for aggressive liberation strategies more conclusively, as they could have the potential to meaningfully impact clinical outcomes.

Although the precise reasons for the estimated beneficial effects of aggressive liberation strategies on ICU and ventilator free days need further exploration, it is plausible that harmful effects from prolonged sedation under more conservative strategies are on-average worse or more common than harm from lung injury or hemodynamic compromise resulting from spontaneous breathing. Trialing spontaneous breathing may have little negative impact in the majority of patients even if they are unable to continue weaning further, so long as they are not left on injurious settings for a prolonged duration. That beneficial effects of aggressive liberation strategies were observed to a much lesser extent in the high baseline SOFA subgroup might be explained by the fact that many of these patients have a fairly low ceiling on ICU and ventilator free days due to the severity of their condition.

4.2. Interpretation of incremental interventions

As we have previously stressed, incremental interventions are not directly actionable in that they do not specify exactly under which circumstances to attempt liberation. Rather, incremental interventions are stochastic and preserve the uncertainty that exists under usual care about who will be liberated when. Because incremental interventions are defined multiplicatively relative to usual care, they do not call for unrealistic interventions in situations where liberation is very unlikely under usual care for good reason. Of course, ideally we could identify optimal actionable treatment rules for liberation, or at least actionable treatment rules that improve on usual care. We only consider incremental interventions instead because they sidestep analytic challenges in estimating effects of complex treatment rules from observational data while remaining informative. Beneficial effects of incremental interventions that are aggressive relative to usual care do not inform clinicians which patients they might be waiting too long to liberate, but do suggest that clinicians look even harder for opportunities to liberate than they previously had been. Again, the most important interpretation of a beneficial effect of an aggressive incremental intervention is the need for randomized trials testing specific actionable aggressive liberation strategies.

4.3. Limitations

A limitation of our analysis is that the treatments we considered intervened only on the odds of liberation *conditional* on patient state, including sedation level. As such, our results do not

offer guidance on when to begin reducing sedation in preparation to liberate. Really, a joint sedation and liberation strategy is desired, and this analysis is just a step in that direction.

Another potential limitation of this analysis, as with any observational study attempting to estimate causal effects, is the potential presence of unobserved confounders. We believe that the set of baseline and time-varying confounders we adjusted for contained most relevant information about patient state that might influence liberation decisions and be associated with outcomes of interest. Further, we would expect similar unobserved confounders to bias estimates of effects on mortality and on ICU and ventilator free days, with healthier patients being liberated earlier and having better outcomes. It is therefore reassuring regarding the potential for unobserved confounding that we did not estimate any effect on mortality in the full cohort and a beneficial effect from *conservative* strategies in the high-risk subgroup. Still, we reiterate that we hope randomized trials might be conducted to more conclusively explore the effects of aggressive liberation strategies.

Authors contributions

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

Declaration of Competing Interest

This work was conducted by EBK with the support of a KL2 award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award KL2 TR002542). Funding was also provided by the MIT-IBM Watson AI Lab and NIH grant 5R01 EB017205. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health. EBK and DT having received lecturing fees for educational talks from Hamilton Medical Inc. ZS was primarily employed by IBM Research during much of the work.

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

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