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Estimating the Causal Effect of Lower Tidal Volume Ventilation on Survival in Patients with Acute Lung Injury †

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for for the NIH ARDS Network Investigators

Summary. Acute lung injury (ALI) is a condition characterized by acute onset of severe hypoxemia and bliateral pulmonary infiltrates. ALI patients typically require mechanical ventilation in an intensive care unit. Low tidal volume ventilation (LTVV), a time-varying dynamic treatment regime, has been recommended as an effective ventilation strategy. This recommendation was based on the results of the ARMA study, a randomized clinical trial designed to compare low vs. high tidal volume strategies (ARDSNetwork, 2000) . After publication of the trial, some critics focused on the high non-adherence rates in the LTVV arm suggesting that non-adherence occurred because treating physicians felt that deviating from the prescribed regime would improve patient outcomes. In this paper, we seek to address this controversy by estimating the survival distribution in the counterfactual setting where all patients assigned to LTVV followed the regime. Our estimation strategy is based on Robins's (1986) G-computation formula and fully Bayesian multiple imputation to handle intermittent missing data.

Keywords: Causal inference; Dynamic treatment regime; G-computation formula

1. Acute Lung Injury

Acute lung injury (ALI) is a condition characterized by acute onset of severe hypoxemia and bilateral pulmonary infiltrates. Acute Respiratory Distress Syndrome (ARDS) is a subset of ALI with more severe hypoxemia. The 1994 American-European consensus criteria for ALI are (1) acute onset, (2) bilateral infiltrates on chest radiography, (3) pulmonary-artery wedge pressure less than or equal to 18mm Hg when measured or the absence of clinical evidence of left atrial hypertension, and (4) ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) less than or equal to 300. A patient with ALI is considered to have ARDS if the $PaO_2 : FiO_2$ ratio is less than or equal to 200 (Bernard et al., 1994).

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ALI can be caused by direct injury to the lung as in pneumonia and aspiration of gastric contents, or indirect lung injury as in sepsis from a source other than the lung and pancreatitis. The majority of deaths among ALI patients are due to sepsis or multiorgan dysfunction rather than primary respiratory causes (Ware and Matthay, 2000). A recent large prospective study of the incidence and mortality of ALI in the United States (Rubenfeld et al., 2005) reported an incidence of 86 per 100,000 person-years with an in-hospital mortality rate of 38.5 percent.

1.1. Mechanical ventilation for ALI

ALI patients frequently require mechanical ventilation in an intensive care unit (ICU). There are many different ways to provide mechanical ventilation support for ALI patients. In this paper, we focus on the assist-control (volume-control) mode of ventilation used during the most acute phase of respiratory failure. This mode is often used immediately after initiation of mechanical ventilation. In this mode, the physician selects a minimum respiratory rate and tidal volume. If a patient's respiratory rate falls below the prescribed rate, the ventilator will "control" the breathing by raising pressure in the airway to deliver a breath at the prescribed tidal volume and at the prescribed minimum respiratory rate. If a patient's respiratory rate exceeds the prescribed minimum rate, the ventilator assists the patient's inspiratory efforts by raising pressure in the airway until the prescribed tidal volume is achieved. The best ventilation strategy for ALI patients has been controversial. The resting tidal volume of healthy people is about 6 to 7 ml per kilogram of predicted body weight (PBW) (Tobin et al., 1983). The predicted body weight is calculated from sex and height, which are good predictors of lung volume. Traditionally, a generous tidal volume of 10-15 ml/kg PBW was recommended for ALI patients to achieve normal arterial carbon dioxide levels at a relatively normal respiratory rate. However, in ALI patients, the volume of lung available for ventilation is substantially reduced due to the disease process. Consequently, generous tidal volumes may cause injury to the aerated lung from overdistention, causing further lung injury, known as barotrauma or volutrauma (Webb and Tierney, 1974; Dreyfuss and Saumon, 1998). This issue has led to several clinical trials of lung-protective methods of mechanical ventilation with lower tidal volumes for patients with ALI (Fan et al., 2005).

1.2. The ARMA Trial

The National Institutes of Health (NIH) ARDS Network conducted a randomized trial comparing mechanical ventilation using traditional tidal volumes versus lower tidal volume ventilation (LTVV). This study was dubbed the ARMA trial. A total of 429 and 432 patients were randomized to traditional and lower tidal volume ventilation, respectively. The assist-control ventilation mode was used until a patient was ready to be weaned from the ventilator. In the group treated with traditional tidal volumes, the initial tidal volume was set at 12 ml/kg PBW. This tidal volume was then adjusted downward if necessary to keep the airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) less than or equal to 50 cm H_2O. If the plateau pressure subsequently decreased below 45 cm H_2O, then tidal volumes were increased so that plateau pressure was greater than or equal to 45 cm H2O or tidal volume was 12 ml/kg PBW. In the group treated with low tidal volumes, the tidal volume was initially set to 6 ml/kg PBW and then decreased to a minimum of 4 ml/kg PBW if necessary to maintain the plateau pressure

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less than or equal to 30 cm H_2O. If the plateau pressure subsequently fell below 25 cm H_2O, then tidal volume was increased so that plateau pressure was greater than or equal to 25 cm H_2O or tidal volume was 6 ml/kg PBW. Tidal volumes greater than 6 ml/kg PBW were allowed if patients experienced severe dyspnea, provided the plateau pressure remained below 30 cm H_2O. In both arms, plateau pressures were allowed to go above the threshold levels (30 and 50 cm H_2O for the 6 ml/kg PBW and 12 ml/kg PBW arms, respectively) if the tidal volume was 4 ml/kg PBW or arterial pH was less than 7.15. In both study groups, most other aspects of the mechanical ventilation strategies, including positive end-expiratory pressure (PEEP), FiO_2, respiratory rate set on the ventilator, and inspiratory:expiratory ratio (I:E) were controlled according to explicit protocol rules.

The study demonstrated lower mortality, more ventilator-free days, and more organ failure-free days in ALI patients who received mechanical ventilation with the LTVV versus traditional strategy. The ARDS Network concluded that the LTVV strategy was better than the traditional strategy and recommended that the LTVV strategy be used for clinical management of ALI.

1.3. Controversy

The ARMA trial, its results, and the ARDS Network recommendation were considered controversial by some clinicians and researchers. Some argued that the recommendation of a tidal volume goal of 6 ml/kg PBW is not optimal because the traditional tidal volume strategy used in the trial did not accurately represent usual care approaches that clinicians were using when the trial was conducted (Eichacker et al., 2002; Tobin, 2000). In the trial, the most common tidal volumes prescribed by clinicians before their patients were enrolled were in the range of 9 - 11ml/kg PBW (Thompson et al., 2001). Another perspective that is consistent with this concern was expressed in the editorial that accompanied the ARMA trial publication (Tobin, 2000). The editorial argued that in 5 randomized trials of ALI mechanical ventilation strategies (including the ARMA trial), clinical outcomes were better in the study groups that received lower tidal volumes only when the mean plateau pressures in the traditional study groups exceeded 32 cm H_2O. This was interpreted by some to suggest that it was not necessary to reduce tidal volumes to 6 ml/kg PBW in patients whose plateau pressures were below 32 cm H_2O while they were receiving tidal volumes that exceeded 6 ml/kg (Tobin, 2004). In another review of these 5 clinical trials, the authors suggested that clinical outcomes would be optimized in most ALI patients with intermediate tidal volumes between 6 and 12 ml/kg PBW and plateau pressures of 28-32 cm H_2O (Eichacker et al., 2002).

In the ARMA trial, adherence to the LTVV protocol rules was not perfect. Specifications to determine adherence to LTVV used by the ARDS Network are listed in Table 1. Ventilation on a given day is considered adherent to LTVV if the settings are adherent to both the plateau presure specification and the tidal volume specification. Plateau presure adherence follows if lines 1 *or* 2 (Table 1) are satisfied; tidal volume adherence follows if *any* of lines 3-7 are satisfied. In the ARMA trial, clinicians sometimes deviated from these rules. Figure 1 (a) displays the observed plateau pressure/tidal volume combinations in the LTVV arm of the ARMA trial. Blue and red dots denote adherence and non-adherence with the LTVV protocol, respectively. Points falling inside the colored regions must satisfy the additional restrictions denoted in the legend. Overall, 28% of the observed ventilation days deviated from the LTVV protocol. It is important to note that the majority of the non-adherent points within the colored regions of Figure 1 were due to violations of the pH

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Table 1. Specifications to Determine Adherence to LTVV

	Plateau pressure specification	**Additional specification**
1	≤ 30	
2	> 30	tidal volume ≤ 4.5 or pH < 7.2
	Tidal volume specification	**Additional specification**
3	tidal volume ≥ 8.5	pH < 7.2 and set respiratory rate ≥ 35
4	$6.5 <$ tidal volume ≤ 8.5	(pH < 7.2 and set respiratory rate ≥ 35) or (plateau pressure ≤ 30 and severe dyspnea)
5	$5.5 \leq$ tidal volume ≤ 6.5	Plateau pressure≤ 30 or pH < 7.2
6	$4.5 <$ tidal volume < 5.5	$25 \leq$ Plateau pressure ≤ 30
7	$3.5 \leq$ tidal volume ≤ 4.5	Plateau pressure ≥ 25

restriction, potentially due to clinician concern regarding immediate adverse effect of low pH. According to the LTVV trial protocol, each non-adherent (red) point could have been adherent (blue) by adjustment of ventilator settings. Consider a non-adherent (red) point in the aqua region, which does not satisfy the LTVV regime because pH is greater than or equal to 7.2. By lowering tidal volume (with a consequential decrease in plateau pressure), pH will decrease, yielding adherence in the same region or movement to an alternative colored region (due to change in tidal volume and plateau pressure).

Some have argued that physicians deviated from the LTVV protocol when they thought specific aspects of the protocol were detrimental to their patients. For example, when patients appeared to be very dyspneic (short of breath) while receiving 6 ml/kg PBW, some physicians raised tidal volume above 6 ml/kg PBW in an attempt to alleviate the dyspnea. By making these deviations, clinical outcomes of some patients could have improved (Deans et al., 2006, 2005). Thus, there is continued controversy regarding the ARDS Network recommendation to use LTVV. To address this controversy, we seek to draw inference about the distribution of survival that would have resulted had all patients in the LTVV arm of the ARDSNet study strictly adhered to the LTVV protocol. We will compare this distribution to the observed LTVV survival curve that reflects imperfect adherence with the LTVV protocol. We will also evaluate the effect of a simpler regime, which is easier for clinicians to implement.

1.4. ALVEOLI Study

After the ARMA trial, the LTVV protocol was recommended by the ARDS Network and was used in subsequent trials conducted by ARDS Network. For example, ALVEOLI was a randomized trial designed to test the hypothesis that a higher positive end-expiratory pressure/lower FiO_2 ventilation strategy would reduce mortality in patients with ALI when compared to a lower positive end-expiratory pressure/higher FiO_2 ventilation strategy (The National Heart, Blood and Lung Institute ARDS Clinical Trials Network, 2004) . The ALVEOLI trial was stopped due to lack of efficacy after a total of 549 patients were enrolled. In this trial, the LTVV regime was used in both study arms and non-adherence was observed. Overall, 22% of the observed ventilation days were non-adherent with the LTVV protocol. As with the re-analysis of the ARMA trial, in this paper, we will estimate the distributions of survival under strict adherence to the complex LTVV protocol and under a simpler regime. We will then compare these results to the observed survival curve. Consistency of results

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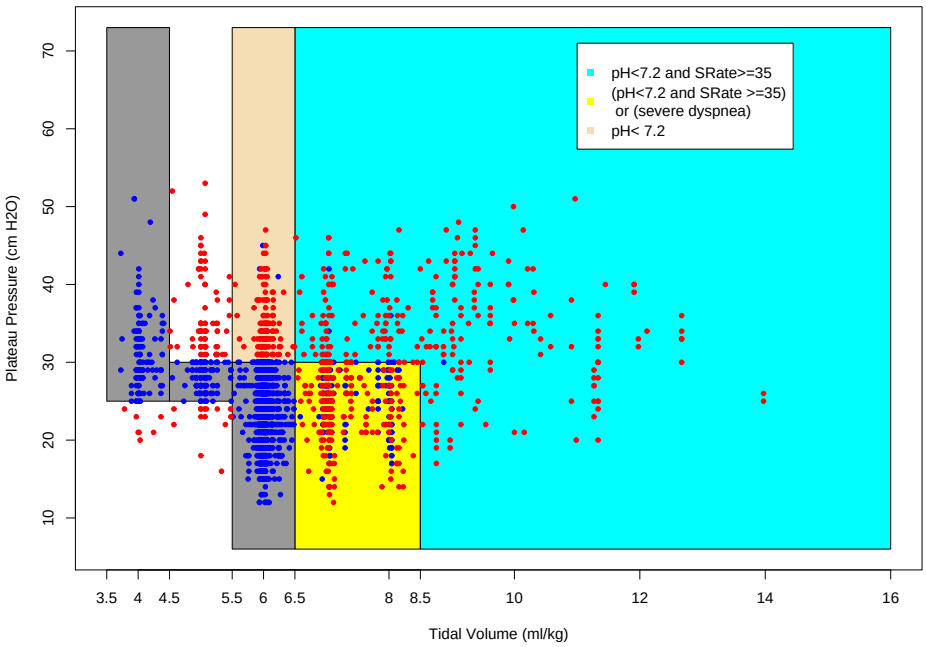
(a) ARMA



(b) ALVEOLI

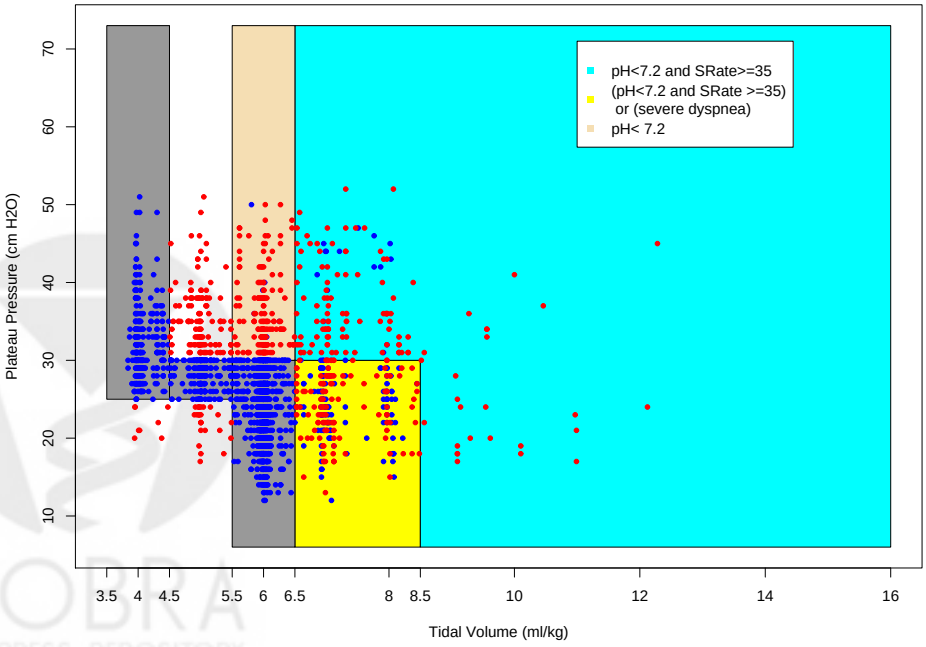


Fig. 1. Observed plateau pressures and tidal volumes. Blue and red dots indicate adherence and non-adherence with the LTVV algorithm.

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across the ARMA and ALEVOLI studies will provide greater support for our conclusions.

1.5. Statistical Challenges

There are four challenges in the statistical analysis. First, LTVV is a time-dependent dynamic treatment regime. Dynamic treatment regimes are individually tailored treatments (Murphy et al., 2001). In a dynamic treatment regime, the treatment is provided to patients only when it is needed and the level of treatment is adjusted based on time-dependent measurements of the patient's need for treatment. About 40% of ALI patients die in the ICU, generally while receiving mechanical ventilation. Recovering patients who remain on mechanical ventilation are evaluated daily by a weaning procedure to assess whether ventilation can be discontinued. According to her performance on the weaning procedure, the patient may begin unassisted breathing, change to other ventilation modes, or remain on assist-control mode. Only if the patient is alive and on assist-control mode, is she eligible or 'at risk' for LTVV. In contrast, in a non-dynamic (static) treatment regime the treatment level and type are specified before treatment is started. That is, the treatment regime is not changed with a patient's response, for example, administering a fixed drug dose for a fixed duration to a patient with a specific disease.

The second challenge arises from time-dependent confounding. In observational studies of time-dependent treatments, there often exist time-dependent covariates which are influenced by past treatments as well as predict future treatments and the outcome. Such covariates are called time-dependent confounders. For example, insufficient ventilation may result in severe hypercapnic acidosis, which may impair myocardial contractility and reduce responsiveness of adrenergic receptors or cause the autonomic nervous system to lose its ability to regulate blood flow to organs; too much ventilation may result in alkalosis, which can increase susceptibility to cardiac dysrhythmias. In addition, organ failure is believed to be both a risk factor for mortality and a predictor for future LTVV. In this situation, the challenge is to isolate the effect of LTVV from the confounding effect of organ failure and other time-dependent confounders. An analysis which estimates the survival curve among those who are observed to adhere to LTVV will likely over-estimate the counterfactual survival curve of interest. If LTVV is an effective regime, the counterfactual survival curve will likely be higher than the observed (i.e, unconditional) survival curve. We illustrate this phenomenom in

While there is a significant and growing body of literature focused on drawing inference about dynamic treatment regimes from observational data with time-varying confounders (Murphy et al., 2001; Lok et al., 2004), there have been very few applications of this technology to address important scientific problems. In this paper, we will utilize the G-computation algorithm, as developed by (Robins, 1986, 1987b,a, 1988b,a) and described nicely in (Lok et al., 2004), to estimate the counterfactual survival curve of interest.

1.6. Data

In the ARMA and ALVEOLI studies, reference measurements of ventilator parameters and other variables were taken on days 1,2,3,4,7,14,21,28. The ventilator parameters on the other days were not recorded. In addition to the reference measurements, the care providers recorded ventilator parameters, arterial pH and plateau pressure daily at randomly selected times to assess the accuracy of the ventilator settings relative to the protocol requirements. Because these random ventilator check data were scheduled to be collected daily during the

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Table 2. Missing values in the ARMA and ALVEOLI Studies

	ALI (n=2994)	ALVEOLI(n=2908)
Tidal Volume	2.8%	1.7%
Plateau Pressure	11.6%	13.2%
Set Rate	3.3%	1.4%
Arterial pH	28.7%	8.7%
Oxygen Saturation	16.7%	33.9%
PEEP	2.5%	1.4%

* n denotes the number at-risk person-days

entire study, we used them for our data analysis. However, missing data is a major problem for the random ventilator check data and for many observational studies (see Table 2). Handling this issue is our third challenge. We will address it by using fully Bayesian multiple imputation. This approach requires parametric specification of conditional distributions of the ventilation parameters and other factors. Figure 2 shows the distributions of the ventilation parameters on day 1. These distributions have biologically bounded support and thus, appropriate modeling of these distributions is required. This is our fourth challenge.

1.7. Outline

In Section 2, we introduce the data structure and notation including the definition of potential survival time under a dynamic treatment regime. In Section 3, we introduce assumptions necessary for identification of the distribution of the potential survival time. Section 4 introduces the G-Computation method for estimating the counterfactual survival curve of a dynamic treatment regime and the bootstrap method for estimating standard errors. In Section 5, we describe multiple imputation for handling missing data. In Section 6, we apply the methods in the previous sections to our data. Section 7 is devoted to a discussion.

2. Data structure and notation

The notation used in this article is listed in Table 3. With this notation, the scheduled observed data on day t ($t = 1, \ldots, 28$) for a living patient ($T > t$; $S_t = 1$) are denoted by

$$\begin{aligned} L_t \quad = \quad & (HSP_t, (ICU_t, OF_t) : HSP_t = 1, VNT_t : HSP_t = ICU_t = 1, \\ & (PE_t, PH_t, PP_t, SO_t, SR_t, VT_t, LC_t) : R_t = 1). \end{aligned}$$

Notice that our definition respects the fact that ventilator parameters, arterial pH and SpO_2 were only available if a patient was ventilated on assist-control mode. In our study $L_0 = AP$. Let $\bar{L}_t = (L_0, ..., L_t)$. In general, we use a bar over a variable to denote that variable and all the past values of that variable. Let H_t be the severity measurements on day t, which is a subset of L_t. Together with an indicator of surviving day t (S_t), LTVV adherence history ($\bar{A}_{t-1}$) and severity history ($\bar{H}_{t-1}$), H_t is used to determine the treatment on day t. In discussion with physicians, we defined $H_t = (HSP_t, ICU_t : HSP_t = 1, VNT_t : HSP_t = ICU_t = 1, OF_{t-1} : HSP_{t-1} = 1, (LC_t, PE_t, PH_t) : R_t = 1)$ and $H_0 = AP$. Let K be the maximum length of treatment ($K = 28$ days in our study).

A dynamic treatment regime $\bar{g}_K$ is a vector of functions:

$$\bar{g}_K = (g_1(S_1, \bar{H}_1), g_2(S_2, \bar{H}_2), ..., g_K(S_K, \bar{H}_K),$$

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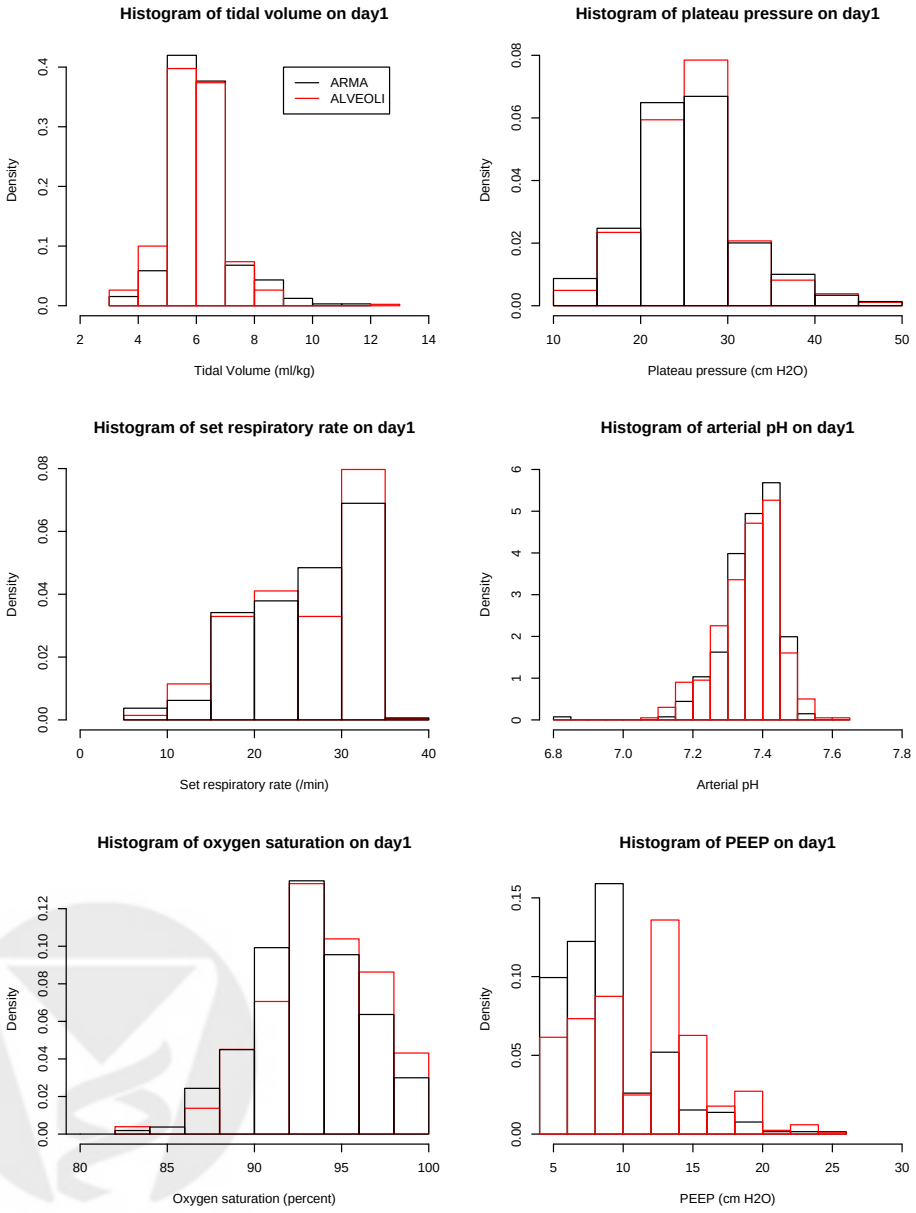

Fig. 2. Histograms of the random ventilation check data

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Table 3. Notation

Symbol	Meaning
$T_{\bar{g}_K}$	Minimum of time-to-death under treatment regime $\bar{g}_K$ and 29 days
T	Observed minimum of time-to-death and 29 days
S_t	Indicator of surviving day t
HSP_t	Indicator of being treated in hospital on day t
ICU_t	Indicator of being treated in intensive care unit on day t
VNT_t	Indicator of ventilation on volume-assist-control mode on day t
R_t	$I(HSP_t = 1, ICU_t = 1, VNT_t = 1)$ (at risk status)
A_t	Indicator of adherence with LTVV
OF_t	Indicator of severe or extreme organ failure on day t
PE_t	Positive end-expiratory pressure on day t
PH_t	Arterial pH on day t
PP_t	Plateau pressure on day t
SO_t	Oxygen saturation (SpO2) on day t in percentage
SR_t	Respiratory rate (/min) on day t
VT_t	Tidal volume per predicted body weight (ml/kg PBW) on day t
LC_t	Lung compliance on day t, which is equal to the total tidal volume (ml) divided by the difference in plateau pressure and positive end-expiratory pressure
AP	Baseline APACHE III score
L_t	$(HSP_t, (ICU_t, OF_t) : HSP_t = 1, VNT_t : HSP_t = ICU_t = 1, (PE_t, PH_t, PP_t, SO_t, SR_t, VT_t, LC_t) : R_t = 1)$
n	Total number of patients

where $g_t(S_t, \bar{H}_t)$ is a mapping from $(S_t, \bar{H}_t)$ to treatment on day t, i.e., A_t. We define the LTVV dynamic regime $\bar{g}_K^1 = (g_1^1, ..., g_K^1)$ as:

$$g_t^1(s_t, \bar{h}_t) = \begin{cases} \text{undefined} & s_t = 0 \\ \text{no volume-assist-control ventilation,} & s_t = 1 \text{ and } r_t = 0 \\ \text{LTVV} & s_t = 1 \text{ and } r_t = 1 \end{cases} \quad (1)$$

We also define the simple LTVV dynamic regime, where an individual is considered adherent if tidal volume is less than or equal to 6.5 ml/kg PBW *and* their plateau pressure is less than or equal to 30. We will refer to this regime as $\bar{g}_K^2$.

The potential time-to-death under a treatment regime $\bar{g}_K$, denoted by $T_{\bar{g}_K}$, is the time-to-death a patient would have had if he or she had followed the regime $\bar{g}_K$. Under certain assumptions, we can estimate the population distribution of $T_{\bar{g}_K}$. That is, the distribution of survival if everyone in the population had followed regime $\overline{g}_k$.

3. Assumptions

Not all treatment regimes' counterfactual survival distributions can be estimated from the data. A treatment regime $\bar{g}_K$ is evaluable if whenever the regime was followed until some time t by some positive fraction of the population, then it is also followed in the interval $(t, t+1]$ (Lok et al., 2004). That is, if a group of patients have been treated with the regime until day t, at least some of them will continue to be treated with the regime on day $t+1$.

ASSUMPTION 1 (Evaluable treatment regimes) *With a slight abuse of probabilistic nota-*

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tion, a treatment regime $\bar{g}_K$ is called evaluable if, for each t and each possible value $\bar{h}_t$,

$$\begin{aligned} & P(\bar{H}_t = \bar{h}_t, \bar{A}_{t-1} = \bar{g}_{t-1}(1, \bar{h}_{t-1}), T > t) > 0 \\ \Rightarrow \quad & P(\bar{H}_t = \bar{h}_t, \bar{A}_t = \bar{g}_t(1, \bar{h}_t), T > t) > 0. \end{aligned}$$

We also assume consistency, i.e., the potential outcome $T_{\bar{g}_K}$ is equal to the observed outcome T if the patient has followed $\bar{g}_K$. This will be true if treatment of one patient does not influence the survival of any other patient.

ASSUMPTION 2 (Consistency) *For any treatment regime $\bar{g}_K$, each t and each possible value $\bar{h}_t$,*

$$\begin{aligned} & \{T_{\bar{g}_K} > t+1, \bar{H}_t = \bar{h}_t, \bar{A}_t = \bar{g}_t(1, \bar{h}_t), T > t\} \\ = \quad & \{T > t+1, \bar{H}_t = \bar{h}_t, \bar{A}_t = \bar{g}_t(1, \bar{h}_t,), T > t\} \end{aligned}$$

In addition to consistency, we assume that there is no unmeasured confounding.

ASSUMPTION 3 (No unmeasured confounding) *For any treatment regime $\bar{g}_K$,*

$$A_t \perp T_{\bar{g}_K} | \bar{H}_t, \bar{A}_{t-1}, T > t.$$

This assumption will hold if $\bar{H}_t$ includes all the risk factors, other than the treatment history $\bar{A}_{t-1}$, that are used by the physician to determine the patient's treatment on day t. In our study, we assume that given a patient's baseline APACHE III score, his most recent 'at-risk' status (on volume-assist-control mode or not), organ failure, lung compliance, arterial pH, PEEP and most recent LTVV adherence status, the decision of using LTVV or not is like a flip of a coin, whose probability depends upon the treatment and covariate history up to that day.

Before introducing the estimator of the counterfactual survival distributions in our study, we want to point out a difference in the causal inferences that we seek relative to other evaluations. The LTVV treatment regime as defined in Equation (1) is a complex regime. There are many different ways of being adherent with the regime. For example, one physician can set the tidal volume to 6 ml/kg PBW and the other may decide to use 5.5 ml/kg PBW. A patient's survival time may not be the same under these two different settings even though both are adherent with LTVV. The counterfactual survival distribution of the LTVV regime should be understood as a weighted average over all the possible ways of being adherent with the regime, with weights proportional to the observed distribution of adherent ventilation parameters.

4. G-Computation

Under assumptions 1-3, the counterfactual survivor function at day m ($m \leq K$) is identified via the following G-computation formula:

$$\begin{aligned} & P(T_{\bar{g}_K} > m) \\ & = \int_{h_1} \cdots \int_{h_{m-1}} \Big[P(T > m | \bar{H}_{m-1} = \bar{h}_{m-1}, \bar{A}_{m-1} = \bar{g}_{m-1}(1, \bar{h}_{m-1}), T > m-1) \\ & \qquad \times \prod_{t=1}^{m-1} \big\{ P(T > t | \bar{H}_{t-1} = \bar{h}_{t-1}, \bar{A}_{t-1} = \bar{g}_{t-1}(1, \bar{h}_{t-1}), T > t-1) \\ & \qquad\qquad \times dF(h_t | \bar{H}_{t-1} = \bar{h}_{t-1}, \bar{A}_{t-1} = \bar{g}_{t-1}(1, \bar{h}_{t-1}), T > t) \big\} \Big] \end{aligned} \quad (2)$$

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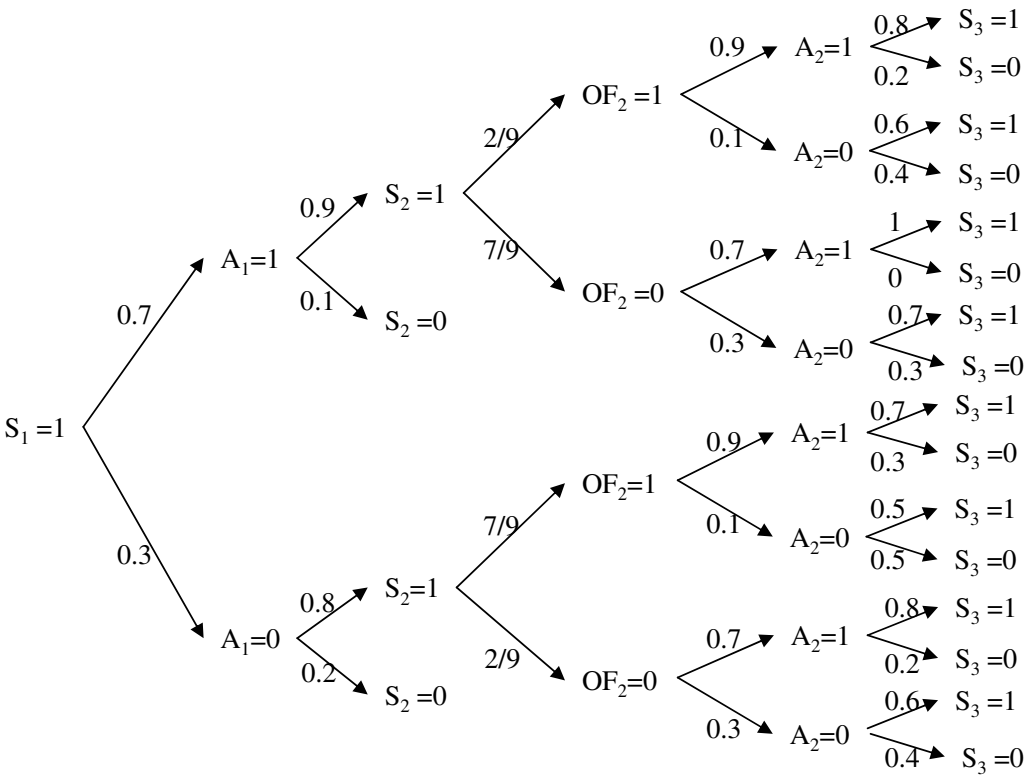

Fig. 3. Hypothetical example of G-Computation

To illustrate how the formula works, consider the following simple example.

4.1. Simple Example

Consider the treatment of patients with ALI on the first two days. Suppose that (1) all patients are on volume-assist-control or 'at-risk' on day one, (2) half the patients on day 1 are treated with LTVV ($A_1 = 1$) and the other half with conventional ventilation ($A_1 = 0$), (3) the assignment of treatment on day one is completely random, (4) on day two, all living patients ($S_2 = 1$) are assessed for organ failure ($H_2 = OF_2$), are assumed to still be in the ICU and on mechanical ventilation ($S_2 = 1$ if and only if $R_2 = 1$), and the ventilation strategy (A_2) used depends on organ failure, and (5) on day 3, survival (S_3) is recorded. The distribution of the observed data is represented by the decision tree in Figure 3.

We are interested in comparing the probability of surviving past day 3 under the LTVV dynamic regimes ($\bar{g}_2^1$) to (a) the overall probability of surviving past day 3 and (b) the probability of surviving past day 3 among patients who are observed to adhere to the LTVV regime. Using the G-computation formula and noting that there is no H_1 in the

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example, we obtain

$$
\begin{aligned}
&P(T_{\bar{g}_2^1} > 3) \\
&\quad = \sum_{h_2=0}^{1} P(T>3|H_2=h_2, \bar{A}_2 = \bar{g}_2^1(1,\bar{h}_2), T>2) P(T>2|A_1 = g_1^1(1,\emptyset), T>1) \\
&\qquad\qquad \times P(H_2 = h_2|A_1 = g_1^1(1,\emptyset), T>2) P(T>1) \\
&\quad = P(S_3=1|OF_2=0, \bar{A}_2=(1,1), S_2=1) P(S_2=1|A_1=1, S_1=1) \\
&\qquad\qquad \times P(OF_2=0|A_1=1, S_2=1) P(S_1=1) + \\
&\qquad P(S_3=1|OF_2=1, \bar{A}_2=(1,1), S_2=1) P(S_2=1|A_1=1, S_1=1) \\
&\qquad\qquad \times P(OF_2=1|A_1=1, S_2=1) P(S_1=1) \\
&\quad = 1 \times 0.9 \times 0.5 \times 1 + 0.6 \times 0.9 \times 0.5 \times 1 = 0.72
\end{aligned}
$$

In contrast, the three-day survival probability for those who adhere to the LTVV regime is 0.76. The overall three-day survival probability is 0.59. In this example, organ failure serves as a time-varying confounder. That is, organ failure on day 2 is affected by treatment on day 1 and predicts subsequent treatment. Organ failure at day 2 is also negatively related to survival on day 3. The three-day survival probability for those who adhere to the LTVV regime is higher than the counterfactual survival probability because those who adhere to therapy tend to have less organ failure than those who do not. The overall three-day survival probability is even lower because non-adherence to therapy is associated with greater organ failure and worse survival, regardless of organ failure status.

4.2. Estimation

In the above hypothetical example, we used the true probability distributions in the G-computation formula and the integral reduced to a summation because the time-varying covariate was discrete. In the ARMA and ALVEOLI studies the time-varying covariates are high-dimensional (i.e., multiple discrete and continuous factors) and the distributions need to be estimated from the data. Because of the curse of dimensionality, we use parametric models to estimate these distributions. We also impose Markovian assumptions of the following form:

$$
\begin{aligned}
& P(T>t|\bar{H}_{t-1} = \bar{h}_{t-1}, \bar{A}_{t-1} = \bar{g}_{t-1}(1,\bar{h}_{t-1}), T>t-1) \\
= \;& P(T>t|(H_{t-1}, H_0) = (h_{t-1}, h_0), A_{t-1} = g_{t-1}(1,\bar{h}_{t-1}), T>t-1)
\end{aligned}
$$

and

$$
\begin{aligned}
& P(H_t = h_t|\bar{H}_{t-1} = \bar{h}_{t-1}, \bar{A}_{t-1} = \bar{g}_{t-1}(1,\bar{h}_{t-1}), T>t) \\
= \;& P(H_t = h_t|(H_{t-1}, H_0) = (h_{t-1}, h_0), A_{t-1} = g_{t-1}(1,\bar{h}_{t-1}), T>t).
\end{aligned}
$$

As a result, we need to specify parametric models for:

a. distribution of baseline (i.e. day 1) APACHE III score
b. probability of being alive
   b.1 on day 1 given baseline APACHE III score,
   b.2 on day t ($t>1$), given alive and on ventilator on day $t-1$, lung compliance, PEEP, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

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b.3 on day t ($t > 1$) given alive, in ICU and not on ventilator on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

b.4 on day t ($t > 1$) given alive, in hospital and not in ICU on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

c. probability of being in hospital

c.1 on day t ($t > 1$) given alive on day t, in hospital and not in ICU on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

c.2 on day t ($t > 1$) given alive on day t, in hospital, in ICU, and not on ventilator on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score.

d. probability of being in ICU

d.1 on day t ($t > 1$) given alive and in hospital on day t, in ICU and not on ventilator on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

d.2 on day t ($t > 1$) given alive and in hospital on day t, in ICU and on ventilator on day $t-1$, lung compliance, PEEP, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

e. probability of ventilation

e.1 on day 1 given alive and in ICU and baseline APACHE III score,

e.2 on day t ($t > 1$), given alive and on ventilator on day $t-1$, lung compliance, PEEP, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

e.3 on day t ($t > 1$) given alive, in ICU and not on ventilator on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

f. Lung compliance

f.1 on day 1, given on ventilator on day 1, APACHE III score

f.2 on day t ($t > 1$), given alive and on ventilator on day $t-1$, lung compliance, PEEP, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

f.3 on day t ($t > 1$) given alive, in ICU and not on ventilator on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score,

g. PEEP

g.1 on day 1, given on ventilator on day 1, lung compliance on day 1 and baseline APACHE III score

g.2 on day t ($t > 1$), given alive and on ventilator on day $t-1$, lung compliance on day t, PEEP, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

g.3 on day t ($t > 1$) given alive, in ICU and not on ventilator on day $t-1$, lung compliance on day t, organ failure on day $t-1$ and baseline APACHE III score,

h. pH

h.1 on day 1, given on ventilator on day 1, lung compliance and PEEP on day 1 and baseline APACHE III score

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h.2 on day t ($t > 1$), given alive and on ventilator on day $t-1$, lung compliance and PEEP on day t, pH, organ failure, and adherence on day $t-1$ and baseline APACHE III score,

h.3 on day t ($t > 1$) given alive, in ICU and not on ventilator on day $t-1$, lung compliance and PEEP on day t, organ failure on day $t-1$ and baseline APACHE III score,

i. probability of organ failure

i.1 on day 1 given alive and in ICU, ventilation status on day 1, and baseline APACHE III score,

i.2 on day t ($t > 1$), given alive, in hospital on day t and not in ICU on day $t-1$, organ failure on day $t-1$ and baseline APACHE III score

i.3 on day t ($t > 1$), given alive, on ventilator on day t, lung compliance, PEEP, pH and adherence on day t, organ failure on day $t-1$ and baseline APACHE III score

i.4 on day t ($t > 1$), given alive, in ICU, not on ventilator on day t, on ventialtor on day $t-1$, lung compliance, PEEP, pH, adherence and organ failure on day $t-1$ and baseline APACHE III score.

i.5 on day t ($t > 1$), given alive, in ICU, not on ventilator on day t and $t-1$, organ failure on day $t-1$ and baseline APACHE III score.

The exact form of these models used in our data analysis are discussed in Section 6. The parameters of these models are estimated from the observed data using maximum likelihood.

In addition to specification of these models, the integral in the G-computation formula, cannot be evaluated directly; therefore we use Monte Carlo integration (Robins, 1986, 1987b,a, 1988b,a). The Monte Carlo algorithm proceeds by simulating a very large cohort of patients, say 10,000, and predicting their survival if everyone in the cohort had complied completely with the dynamic treatment regime. For each simulated patient, simulate baseline APACHE III score from the estimated distribution in a. above. Then, sequentially in time ($t = 1, \ldots, 28$): on day t, using the estimated probabilities from models b-f, simulate whether a patient is alive, whether in hospital if alive, organ failure and whether in ICU if in-hospital, whether on assist-control model if in ICU, with all adherence indicators for the LTVV protocol set equal to 1; for those who are in the ICU, simulate lung compliance, arterial pH and PEEP using the estimated distribution in g. with adherence indicators for the LTVV protocol set equal to 1. Then, estimate the survival probability at a given day as the proportion of simulated patients who survive past that day. Variability of the estimator can then be assessed using bootstrap methods, by re-sampling with replacement patients from the original dataset and re-estimating the statistic of interest on the bootstrapped samples. We use the same technique for the simple LTVV regime, $\bar{g}_K^2$

5. Multiple Imputation for Missing Data

As we have mentioned in Section 1.6, the dataset contains missing data on key time-varying factors. In the ARMA study, only 139 out of the 467 patients had complete data. Since the data are unlikely to be missing completely at random, an analysis based on complete cases will likely be biased. Multiple imputation (Rubin, 1987) is one method for handling missing

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data. It replaces each missing value by $m > 1$ simulated versions. The m imputed complete datasets are then analyzed using the G-computation methods discussed in the previous section. The m results are then combined to obtain an overall estimate and standard error. The overall standard error is a function of estimates of the within-imputation and between-imputation variances. Typically, m is chosen to be between 3 and 10. In our analysis, we set $m = 5$.

5.1. Imputation Model

To perform the imputation, we impose a probability model for the data scheduled to be collected $(T, \bar{L}_{T-1})$. For $t < T$, let $\bar{L}_t = (\bar{L}_t^{obs}, \bar{L}_t^{mis})$, where $\bar{L}_t^{obs}$ and $\bar{L}_t^{mis}$ are the observed and missing components of $\bar{L}_t$, respectively. The m simulated versions of a missing values are drawn from the predictive distribution of $\bar{L}_{T-1}^{mis}$ given $\bar{L}_{T-1}^{obs}$ and T.

In the ARMA and ALVEOLI studies, the likelihood function for a patient's scheduled observed data can be written as

$$Lik = f(L_0) \prod_{t=1}^{K} f(L_t|\bar{L}_{t-1}, S_t = 1)^{S_t} f(S_t|S_{t-1} = 1, \bar{L}_{t-1})^{S_{t-1}}.$$

In our models, we assume that a patient's status on day t only depends on his most recent history and the baseline APACHE III score (L_0), that is,

$$Lik = f(L_0) \prod_{t=1}^{K} f(L_t|L_{t-1}, L_0, S_t = 1)^{S_t} f(S_t|S_{t-1} = 1, L_{t-1}, L_0)^{S_{t-1}}.$$

In these studies, whenever a patient is on ventilator on day $t-1$, she either dies or remains in the hospital and in the ICU at time t. Furthermore, once a patient leaves the hospital (ICU), she does not return the hospital (ICU). In consultation with physicians, we decided

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to sequentially factorize the likelihood function as follows:

$$Lik = f(L_0)\prod_{t=1}^{K}\Big\{f(S_t|S_{t-1}=1,R_{t-1}=1,L_{t-1},L_0)^{S_{t-1}R_{t-1}} \tag{3}$$
$$\times f(S_t|S_{t-1}=1,R_{t-1}=0,HSP_{t-1},\{(ICU_{t-1},OF_{t-1}):HSP_t=1\},L_0)^{S_{t-1}(1-R_{t-1})}$$
$$\times f(HSP_t|S_t=1,HSP_{t-1}=1,R_{t-1}=0,OF_{t-1},ICU_{t-1},L_0)^{S_tHSP_{t-1}(1-R_{t-1})}$$
$$\times f(ICU_t|S_t=1,HSP_t=1,ICU_{t-1}=1,R_{t-1}=0,OF_{t-1},L_0)^{S_tHSP_tICU_{t-1}(1-R_{t-1})}$$
$$\times f(VNT_t|S_t=1,HSP_t=1,ICU_t=1,R_{t-1}=1,L_{t-1},L_0)^{S_tHSP_tICU_tR_{t-1}} \tag{4}$$
$$\times f(VNT_t|S_t=1,HSP_t=1,ICU_t=1,R_{t-1}=0,OF_{t-1},L_0)^{S_tHSP_tICU_t(1-R_{t-1})}$$
$$\times f(SO_t|S_t=1,R_t=1,L_{t-1},L_0)^{S_tR_t} \tag{5}$$
$$\times f(VT_t|S_t=1,R_t=1,SO_t,L_{t-1},L_0)^{S_tR_t} \tag{6}$$
$$\times f(SR_t|S_t=1,R_t=1,VT_t,SO_t,L_{t-1},L_0)^{S_tR_t} \tag{7}$$
$$\times f(PH_t|S_t=1,R_t=1,SR_t,VT_t,SO_t,L_{t-1},L_0)^{S_tR_t} \tag{8}$$
$$\times f(PE_t|S_t=1,R_t=1,PH_t,SR_t,VT_t,SO_t,L_{t-1},L_0)^{S_tR_t} \tag{9}$$
$$\times f(PP_t|S_t=1,R_t=1,PE_t,PH_t,SR_t,VT_t,SO_t,L_{t-1},L_0)^{S_tR_t} \tag{10}$$
$$\times f(OF_t|S_t=1,R_t=1,L_t,OF_{t-1},L_0)^{S_tR_t} \tag{11}$$
$$\times\ f(OF_t|S_t=1,HSP_t=1,ICU_t,R_t=0,OF_{t-1},L_0)^{S_tHSP_t(1-R_t)}\Big\}$$

Notice that the indicator of adherence with LTVV (A_t) and lung compliance (LC_t) do not appear in the likelihood because they are functions of measurements which are already included in the likelihood. The overall likelihood is a product of the likelihood for all patients.

The conditional distributions that are not numbered in the above display do not require modeling in the imputation process. This follows since the conditional distributions do not depend on any missing variables (see Table 2). The conditional distributions that are numbered require modeling. For the binary factors S_t, VNT_t and OF_t, we used logistic regression models. As shown in Section 1.6, the continuous variables are bounded. For each of these variables, we modeled the conditional distribution using a truncated normal distribution. The boundary for each variable was chosen in consultation with physicians as well as careful review of the data. For tidal volume, the boundary is [3, 14 ml/kg PBW], oxygen saturation rate [45, 100%], set respiratory rate [6,40/minute], pH [6.6, 7.6], PEEP [0,28 cm H_2O]. Since plateau pressure should always be higher than PEEP and the difference is believed to fall in the range of [7, 35 cm H_2O], we transformed plateau pressure to the difference between plateau pressure and PEEP and used the transformed variable throughout the imputation. We model the mean of the normal distribution before truncation to be a linear function of covariates and the variance to be homoskedastic.

5.2. Bayesian Imputation

Suppose the collection of all the parameters in the above models are denoted by θ. If θ were known, we could draw the missing values from the distribution of $\bar{L}_{T-1}^{mis}$ given $\bar{L}_{T-1}^{obs}$ and T. Data augmentation with Gibbs sampling (Tanner and Wong, 1987) is an iterative method

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for simulating the distributions of the missing values as well as the unknown parameters θ. It starts with an initial value of θ, $\theta^{(0)}$. Given a value $\theta^{(t)}$ of θ on iteration t:

Imputation Step: For each individual i, draw $\bar{L}_{T-1,i}^{mis,(t+1)}$ from $f(\bar{L}_{T-1}^{mis}|\bar{L}_{T-1,i}^{obs}, T_i; \theta^{(t)})$

Posterior Step: Draw $\theta^{(t+1)}$ from density $f(\theta|\{\bar{L}_{T-1,i}^{obs}, \bar{L}_{T-1,i}^{mis,(t+1)} : i = 1, \ldots, n\})$

The conditional distribution in each step, were sequentially factorized into a sequence of univariate conditional distributions. The components of the vectors to be simulated, were then simulated sequentially according to the order of the sequential factorization. We sampled the parameters of both the logistic regression models and the truncated normal models using the Metropolis-Hastings algorithm (Metropolis et al., 1953; Hastings, 1970). For both logistic and truncated normal regression models, the priors on the regression parameters were assumed to be $N(0, 100)$. The priors on the variances of the truncated normal models were assumed to be Inverse-Gamma$(10^{-6}, 10^{-6})$, independent of the priors on the regression parameters. After a burn-in period of 10,000 iterations, we took five samples 200 iterations apart, yielding 5 complete datasets for each study. The G-computation analysis was then performed on each dataset and the results combined using Rubin's combining rules (Rubin, 1987).

Tables 4, 5, and 6 display the posterior means and 95% credible intervals for the regression parameters from the 11 models. The results for the time-specific intercepts are not displayed. The form of the models were based on clinical judgement and no model selection procedures were used. To highlight associations, we have placed the posterior means, whose 95% credible intervals do not contain zero, in bold font. There are some notable differences in associations between the ARMA and ALVEOLI studies. In model (7), organ failure has a stronger association with set rate in the ARMA than the ALVEOLI study. In model (9), organ failure at day $t-1$ has a stronger association with PEEP on day t among those not on the ventilator on day $t-1$ in the ARMA than the ALVEOLI study. In model (10), baseline APACHE score has a stronger association with plateau pressure on day t among those not ventilator on day $t-1$ in the ARMA than the ALVEOLI study. In model (11), arterial pH has a stronger association with organ failure in the ALVEOLI than the ARMA study.

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Table 4. ARMA: Bayesian Imputation models: posterior mean and 95% credible intervals for model parameters

	S_t (3)	VNT_t (4)	SO_t (5)	VT_t (6)	SR_t (7)	PH_t (8)	PE_t (9)	PP_t (10)
VNT_{t-1}				**-3.94**	-5.40	**-4.41**	**-62.04**	-6.87
				(-8.43, -0.33)	(-37.46, 26.69)	**(-4.91, -4.05)**	**(-85.74, -39.44)**	(-60.97, 52.34)
$AP \cdot R_{t-1}/100$	**-1.23**	**0.39**	0.42	-0.03	0.04	-0.01	-0.08	-0.06
	(-2.22, -0.39)	**(0.03, 0.81)**	(-0.15, 1.05)	(-0.17, 0.09)	(-0.62, 0.83)	(-0.02, 0.01)	(-0.30, 0.18)	(-0.78, 0.66)
$OF_{t-1}R_{t-1}$	0.04	0.12	**-1.54**	-0.01	**0.80**	-0.00	-0.10	0.32
	(-1.42, 0.85)	(-0.13, 0.36)	**(-2.02, -0.98)**	(-0.09, 0.11)	**(0.21, 1.41)**	(-0.01, 0.01)	(-0.31, 0.08)	(-0.25, 0.79)
$SO_{t-1}R_{t-1}$	**0.11**	**-0.06**	**0.40**					
	(0.06, 0.17)	**(-0.10, -0.02)**	**(0.34, 0.46)**					
$VT_{t-1}R_{t-1}$	-0.13	0.02	0.00	**0.93**				
	(-0.28, 0.03)	(-0.07, 0.11)	(-0.11, 0.14)	**(0.90, 0.95)**				
$SR_{t-1}R_{t-1}$	-0.03	0.01	**-0.03**	0.00	**0.92**			
	(-0.07, 0.02)	(-0.00, 0.03)	**(-0.06, -0.01)**	(-0.00, 0.01)	**(0.88, 0.95)**			
$PH_{t-1}R_{t-1}$	**5.69**	**-4.10**	0.73	-0.18	**-8.18**	**0.63**		
	(2.24, 9.12)	**(-6.46, -1.95)**	(-1.92, 3.69)	(-0.68, 0.28)	**(-11.27, -3.70)**	**(0.58, 0.67)**		
$PE_{t-1}R_{t-1}$	**-0.09**	**0.29**	**-0.16**	0.00	**0.12**	-0.00	**0.83**	
	(-0.15, -0.02)	**(0.25, 0.34)**	**(-0.22, -0.11)**	(-0.01, 0.01)	**(0.06, 0.18)**	(-0.00, -0.00)	**(0.81, 0.86)**	
$PP_{t-1}R_{t-1}$	-0.01	**0.06**	-0.01	**-0.01**	**0.05**	-0.00	-0.00	**0.71**
	(-0.06, 0.04)	**(0.04, 0.08)**	(-0.04, 0.03)	**(-0.01, -0.00)**	**(0.02, 0.09)**	(-0.00, -0.00)	(-0.02, 0.01)	**(0.67, 0.75)**
$AP(1 - R_{t-1})/100$			-1.12	**0.23**	**2.56**	**-0.03**	**0.58**	**-2.39**
			(-2.19, 0.48)	**(0.04, 0.43)**	**(0.83, 4.32)**	**(-0.05, -0.02)**	**(0.06, 1.15)**	**(-3.93, -0.91)**
$OF_{t-1}(1 - R_{t-1})$			**-1.37**	**-0.29**	**2.79**	0.01	**1.19**	0.78
			(-2.38, -0.51)	**(-0.49, -0.12)**	**(1.85, 3.80)**	(-0.00, 0.02)	**(0.75, 1.63)**	(-0.43, 1.98)
SO_tR_{t-1}				0.01	-0.04	0.00	**-0.06**	-0.03
				(-0.01, 0.02)	(-0.10, 0.02)	(0.00, 0. 00)	**(-0.08, -0.03)**	(-0.09, 0.03)
$SO_t(1 - R_{t-1})$				0.01	**-0.44**	0.00	**-0.36**	0.16
				(-0.01, 0.03)	**(-0.58, -0.26)**	(0.00, 0.01)	**(-0.44, -0.31)**	(-0.00, 0.29)
VT_tR_{t-1}					**-0.44**	0.00	**0.05**	**0.50**
					(-0.55, -0.27)	(0.00, 0.00)	**(0.01, 0.10)**	**(0.37, 0.63)**
$VT_t(1 - R_{t-1})$					**-1.44**	0.00	0.06	**1.07**
					(-1.77, -1.10)	(-0.00, 0.01)	(-0.08, 0.21)	**(0.60, 1.45)**
SR_tR_{t-1}						-0.00	0.01	**0.04**
						(-0.00, -0.00)	(-0.00, 0.03)	**(0.01, 0.07)**
$SR_t(1 - R_{t-1})$						-0.00	**0.05**	**0.23**
						(-0.00, -0.00)	**(0.03, 0.08)**	**(0.16, 0.30)**
PH_tR_{t-1}							**-3.66**	**-9.24**
							(-4.86, -2.56)	**(-11.93, -6.77)**
$PH_t(1 - R_{t-1})$							**-7.44**	**-11.92**
							(-10.18, -4.93)	**(-17.78, -5.47)**
PE_tR_{t-1}								-0.07
								(-0.12, 0.01)
$PE_t(1 - R_{t-1})$								**-0.20**
								(-0.34, -0.00)

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Table 5. ALVEOLI: Bayesian Imputation models: posterior mean and 95% credible intervals for model parameters

	S_t (3)	VNT_t (4)	SO_t (5)	VT_t (6)	SR_t (7)	PH_t (8)	PE_t (9)	PP_t (10)
VNT_{t-1}				**-5.58**	3.33	**-4.62**	**-77.71**	**-78.86**
				(-8.52, -2.34)	(-25.47, 31.94)	**(-4.95, -4.32)**	**(-102.83, -47.78)**	**(-147.54, -20.75)**
$AP \cdot R_{t-1}/100$	**- 2.36**	0.16	**-0.69**	-0.10	0.42	-0.01	0.07	0.33
	(-3.42, -1.36)	(-0.19, 0.57)	**(-1.48, -0.03)**	(-0.20, 0.04)	(-0.35, 1.07)	(-0.02, 0.00)	(-0.30, 0.47)	(-0.34, 0.95)
$OF_{t-1}R_{t-1}$	-0.21	**0.72**	-0.57	-0.02	-0.05	-0.00	-0.09	0.15
	(-1.08, 0.59)	**(0.45, 1.00)**	(-1.13, 0.07)	(-0.10, 0.05)	(-0.58, 0.53)	(-0.01, 0.01)	(-0.39, 0.28)	(-0.34, 0.69)
$SO_{t-1}R_{t-1}$	**0.10**	**-0.06**	**0.45**					
	(0.02, 0.17)	**(-0.10, -0.03)**	**(0.38, 0.54)**					
$VT_{t-1}R_{t-1}$	-0.09	-0.03	-0.03	**0.80**				
	(-0.32, 0.17)	(-0.15, 0.10)	(-0.19, 0.15)	**(0.76, 0.83)**				
$SR_{t-1}R_{t-1}$	0.00	0.02	**-0.03**	0.00	**0.92**			
	(-0.05, 0.06)	(0.00, 0.04)	**(-0.06, -0.01)**	(-0.00, 0.01)	**(0.89, 0.95)**			
$PH_{t-1}R_{t-1}$	**12.03**	**-5.04**	**2.81**	-0.04	**-10.93**	**0.63**		
	(8.96, 15.07)	**(-6.79, -3.22)**	**(0.39, 5.62)**	(-0.48, 0.31)	**(-14.00, -7.99)**	**(0.60, 0.67)**		
$PE_{t-1}R_{t-1}$	0.07	**0.17**	**-0.07**	**-0.01**	0.03	-0.00	**0.87**	
	(-0.00, 0.12)	**(0.14, 0.19)**	**(-0.11, -0.02)**	**(-0.02, -0.01)**	(-0.03, 0.08)	(-0.00, 0.00)	**(0.84, 0.90)**	
$PP_{t-1}R_{t-1}$	0.01	**0.07**	0.01	**-0.02**	**0.05**	-0.00	-0.01	**0.74**
	(-0.06, 0.07)	**(0.04, 0.09)**	(-0.03, 0.06)	**(-0.02, -0.01)**	**(0.01, 0.08)**	(-0.00, -0.00)	(-0.04, 0.02)	**(0.69, 0.78)**
$AP(1-R_{t-1})/100$			-0.36	-0.15	**4.99**	**-0.07**	0.33	-0.60
			(-1.59, 0.79)	(-0.35, 0.02)	**(3.76, 6.11)**	**(-0.08, -0.05)**	(-0.43, 1.07)	(-2.41, 1.41)
$OF_{t-1}(1-R_{t-1})$			**-1.42**	-0.08	-0.30	-0.00	0.54	-0.63
			(-2.42, -0.61)	(-0.20, 0.01)	(-1.11, 0.70)	(-0.01, 0.01)	(-0.12, 1.05)	(-1.48, 0.22)
SO_tR_{t-1}				-0.00	**-0.07**	0.00	**-0.06**	-0.03
				(-0.01, 0.01)	**(-0.15, -0.01)**	(-0.00, 0.00)	**(-0.10, -0.02)**	(-0.11, 0.04)
$SO_t(1-R_{t-1})$				-0.02	**-0.54**	0.00	**-0.22**	-0.14
				(-0.04, 0.00)	**(-0.68, -0.42)**	(0.00, 0.00)	**(-0.32, -0.11)**	(-0.42, 0.06)
VT_tR_{t-1}					**-0.53**	0.00	**-0.13**	**0.33**
					(-0.71, -0.29)	(-0.00, 0.00)	**(-0.26, -0.01)**	**(0.02, 0.64)**
$VT_t(1-R_{t-1})$					**-2.27**	0.00	**-0.78**	-0.20
					(-2.60, -2.00)	(0.00, 0.01)	**(-1.12, -0.49)**	(-0.65, 0.24)
SR_tR_{t-1}						-0.00	**0.03**	**0.12**
						(-0.00, -0.00)	**(0.01, 0.05)**	**(0.08, 0.15)**
$SR_t(1-R_{t-1})$						-0.00	**0.06**	**0.17**
						(-0.00, -0.00)	**(0.02, 0.09)**	**(0.11, 0.23)**
PH_tR_{t-1}							**-2.55**	**-7.76**
							(-3.98, -1.14)	**(-10.06, -4.64)**
$PH_t(1-R_{t-1})$							**-9.25**	**-14.74**
							(-12.10, -6.13)	**(-19.61, -8.94)**
PE_tR_{t-1}								**-0.23**
								(-0.27, -0.18)
$PE_t(1-R_{t-1})$								**-0.56**
								(-0.73, -0.46)

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Table 6. Bayesian Imputation models for organ failure (11): posterior mean and 95% credible intervals for model parameters

	ALI study	ALVEOLI study
AP	0.00	-0.00
	(-0.00, 0.01)	(-0.01, 0.00)
OF_{t-1}	**2.97**	**2.41**
	(2.69, 3.28)	**(2.18, 2.65)**
SO_t	**-0.13**	**-0.11**
	(-0.17, -0.08)	**(-0.15, -0.07)**
VT_t	0.09	0.06
	(-0.00, 0.18)	(-0.04, 0.22)
SR_t	**0.04**	**0.02**
	(0.02, 0.06)	**(0.01, 0.04)**
PH_t	-0.62	**-3.72**
	(-3.56, 2.38)	**(-5.2, -1.72)**
PP_t	0.01	0.02
	(-0.02, 0.03)	(0.00, 0.05)
PE_t	**0.16**	**0.05**
	(0.12, 0.20)	**(0.02, 0.08)**

6. Analysis of ARMA and ALVEOLI Studies

In this section, we apply the G-computation algorithm to the ARMA and ALVEOLI trials.

We used logistic models for the hazard of survival (models b.1-b.4) and the binary factors HSP_t (model c.1-c.2), ICU_t(model d.1-d.2) , VNT_t (model e.1-e.3) and OF_t (model i.1-i.5) . The "gam" package from library "mgcv"in R was used to include smooth functions of continuous covariates. We used a truncated normal model for the baseline APACHE III score (bounded between 0 and 299; model a.), PH_t (model h.1-h.3), PE_t (model g.1-g.3) and lung compliance(model f.1-f.3, LC_t, bounded between 12 and 80). The "optim" function in R was used to directly obtain the MLE for the model parameters and we used parametric natural splines with 3 degrees of freedom for continuous covariates.

In Figures 4 and 5, we display some of the results of these model fits for the first imputed dataset, for the ARMA and ALVELOLI studies. For each study, the results were similar for the other four imputed datasets.

In the day 1 models, the results show that patients with higher baseline APACHE scores (i.e., higher severity of illness) have a higher risk of dying on day 1, and among those who survive day 1, have a higher risk of being on a ventilator and experiencing organ failure . Among those on a ventilator on day 1, those with higher PEEP tend to have lower pH.

For patients who are in the hospital on day t, but not in the ICU on day $t-1$, higher levels of APACHE tend to increase the risk of dying and organ failure. In these models, organ failure on day $t-1$ is associated with 0.1-fold (95% CI: 0-0.5) increase in the odds of surviving on day t and with 45.6-fold (95% CI: 30.9-67.3) increase in the odds of organ failure on day t in the ARMA study. In the ALVEOLI study, organ failure on day $t-1$ was not significantly associated with survival on day t, but was associated with a 54.6-fold(95% CI: 38.9-77.8) increase in the odds of organ failure on day t. Among patients who survive day t but are not in the ICU on day $t-1$ (model c.1), organ failure on day $t-1$ is associated with an increase in the odds of hospitalization on day t of 3.7 (95% CI: 1.7-8.1) and 1.6 (95% CI: 1.1-2.5) in the ARMA and ALVEOLI studies, respectively.

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Figure 4 shows the effects of baseline APACHE in four models: (1) model c.2 (first row) - hospitalization on day t among those alive on day t and in the ICU but not on ventilation on day $t-1$; (2) model d.1 (second row): - ICU at day t among those in hospital on day t and in ICU but not on ventilator on day $t-1$; (3) model e.3 (third row) - ventilation on day t among those in the ICU on days t and $t-1$, but not on ventilation on day $t-1$; and (4) model i.5 (fourth row) - organ failure on day t (fourth row, model i.5) among those in ICU on days t and $t-1$ but not on ventilator on those days. In the ARMA study, there is a statistically significant positive association between risk of being in the ICU and APACHE score (row 2, first graph). In the ALVEOLI study, higher baseline APACHE score is significantly associated with hospitalization, ventilation, and organ failure, but not the need for intensive care. Among the respective cohorts of patients, organ failure on day $t-1$ was associated with a 7.9 (95% CI: 2.8-22.7) and a 3.8 (95% CI: 1.3-11.4) increase in the odds of hospitalization, a 2.1 (95% CI: 1.6-2.8) and a 1.9 (95% CI: 1.5-2.4) increase odds of being in intensive care, a 2.7 (95% CI: 2-3.7) and a 1.4 (95% CI: 1.1-1.9) increase odds of being ventilated, and a 14.1 (95% CI: 11.3-17.6) and a 14.4 (95% CI: 11.8-17.7) increase odds of organ failure on day t for the ARMA and ALVEOLI studies, respectively. Among patients in the ICU but not on ventilation on day $t-1$, organ failure on day $t-1$ was also associated with an increase of 5 (95% CI: 2.0-16.7) and 3.3 (95% CI: 1.3-6.7) in the odds of dying on day t (model b.3). Organ failure on day $t-1$ was also associated with higher levels of PEEP on day t (model g.3) in the ARMA study.

For those alive and on ventilation on day $t-1$, Figure 5 displays the association of lung compliance, PEEP, and pH at day $t-1$, and baseline APACHE III on the probability of surviving day t (model b.2). The graphs indicate that, while there is no effect of lung compliance on survival in both studies, there is a non-linear, negative effect of PEEP in the ARMA study and a slightly positive, linear effect of PEEP in the ALVEOLI study. This finding may be because the ALVEOLI study was a randomized trial comparing higher PEEP versus lower PEEP. The results for pH and APACHE III are clinically sensible, with positive effects of higher pH and negative effects of APACHE III on survival in both studies. There are no significant effects of organ failure or adherence with the LTVV regime on day $t-1$ on surviving day t.

For those alive on day t and on ventilator on day $t-1$, the results show that patients with lower lung compliance, higher PEEP, and lower pH on day $t-1$ have a higher risk of being of being on a ventilator on day t. These results are consistent across both studies. Baseline APACHE III score was not significantly associated with ventilation in the ARMA study, but non-linearly related to the risk of ventilation in the ALVEOLI study. Organ failure on day $t-1$ increased the odds of ventilation by a factor of 2.0 (95% CI: 1.6-2.5) in the ALVEOLI study. There are no significant effects of adherence with LTVV on day $t-1$ on the risk of ventilation on day t.

There is a positive association of prior day lung compliance, PEEP, and pH with the following day's values of these factors (models f.2, g.2, h.2, respectively), among patients who are on ventilator on days t and $t-1$. Organ failure on day $t-1$ was associated with higher PEEP values on day t and adherence to LTVV was associated with slightly higher pH values on day t in the ARMA study. In the ALVEOLI study, adherence to LTVV on day $t-1$ was associated with lower PEEP values on day t and slightly higher pH values on day t.

In the model of organ failure on day t, among those alive, in ICU, not on ventilator on day t but on ventilator on day $t-1$ (model i.4), higher PEEP on day $t-1$ and higher baseline APACHE III are significantly associated with organ failure on day t in the ARMA

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and ALVEOLI studies, respectively. For these types of patients, organ failure on day $t-1$ increases the odds of organ failure on day t by 12.8 (95% CI: 7.7-21.5) in the ARMA study and by 11.2 (95% CI: 7.3-17.2) in the ALVEOLI study.

Among those alive, in ICU, and on ventilator on day t, higher PEEP and lower pH on day t are significantly associated with the risk of organ failure on day t in both studies (model i.3). For these patients, organ failure on day $t-1$ increases the odds of organ failure on day t by 20 (95% CI: 14.7-27.3) in the ARMA study and by 10.7 (95% CI: 8.3-13.7) in the ALVEOLI study.

Finally, Figure 6 displays the counterfactual survival curves for the LTVV and simpler regimes for the ARMA and ALVELOLI studies. The figure also displays the observed survival curves for the two studies. In both studies, we did not find statistically significant differences between the potential 28-day survival rate assuming strict adherence to the LTVV protocol and the observed 28-day survival (ARMA: 74.38 percent versus 74.52 percent, P=0.97; ALVEOLI: 78.72 versus 77.30, P=0.65). Furthermore, we did not find statistically significant differences between the potential 28-day survival rate under the simple regime and strict adherence to the LTVV protocol (ARMA: 74.35 percent versus 74.38 percent, P=0.99; ALVEOLI: 79.03 versus 77.30, P=0.89). For purpose of comparison, the 28 day survival probability for those who were observed to adhere to therapy at all timepoints (approximately 51 percent in ARMA, 64 percent in ALVEOLI) was 82.0% (95% CI: 76.3%-86.6%) and 79.9% (95% CI: 75.2% - 83.8%) in the ARMA and ALVEOLI studies, respectively. Together, these results show that there is a great deal of selection bias with regards to who adheres to therapy and that deviation from the LTVV protocol does not improve survival.

7. Discussion

In this paper, we used multiple imputation and the G-computation formula to estimate the counterfactual survival distribution under the dynamic LTVV treatment regime for patients with acute lung injury. Our results demonstrate that deviations from the LTVV algorithm did not lead to decreased mortality, as has been suggested in the clinical literature. We also showed that specification of a simpler regime based on just tidal volume and plateau pressure yields comparable results to the more complex LTVV regime. The analysis should add further evidence to the critical care literature that LTVV is an effective regime for the treatment of patients with acute lung injury. Further, simplification of the LTVV regime, to facilitate easier implementation, may not change the mortality benefit of LTVV.

Our methodology relies on the untestable assumption of no unmeasured confounding. That is, we have assumed that we have measured all the time-dependent confounders that, when conditioned upon, make compliance with LTVV on a given day, a random process, akin to flipping a possibly biased coin (Assumption 3.3). This assumption cannot be empirically validated from the observed data. Thus, future work should focus on exploring the sensitivity of our conclusions to deviations from this assumption.

In our imputation, we modeled the basic variables scheduled to be measured at the patient level. These variables serve as the building blocks to define important derived variables such as adherence to LTVV and lung compliance, which were used in our analysis. Since, we specified models separately for the imputation and G-computation analysis, we face the issue of model incompatibility. While this problem is widespread in statistical applications, we see it as a potential source of bias of our approach. Many of the distributions needed for

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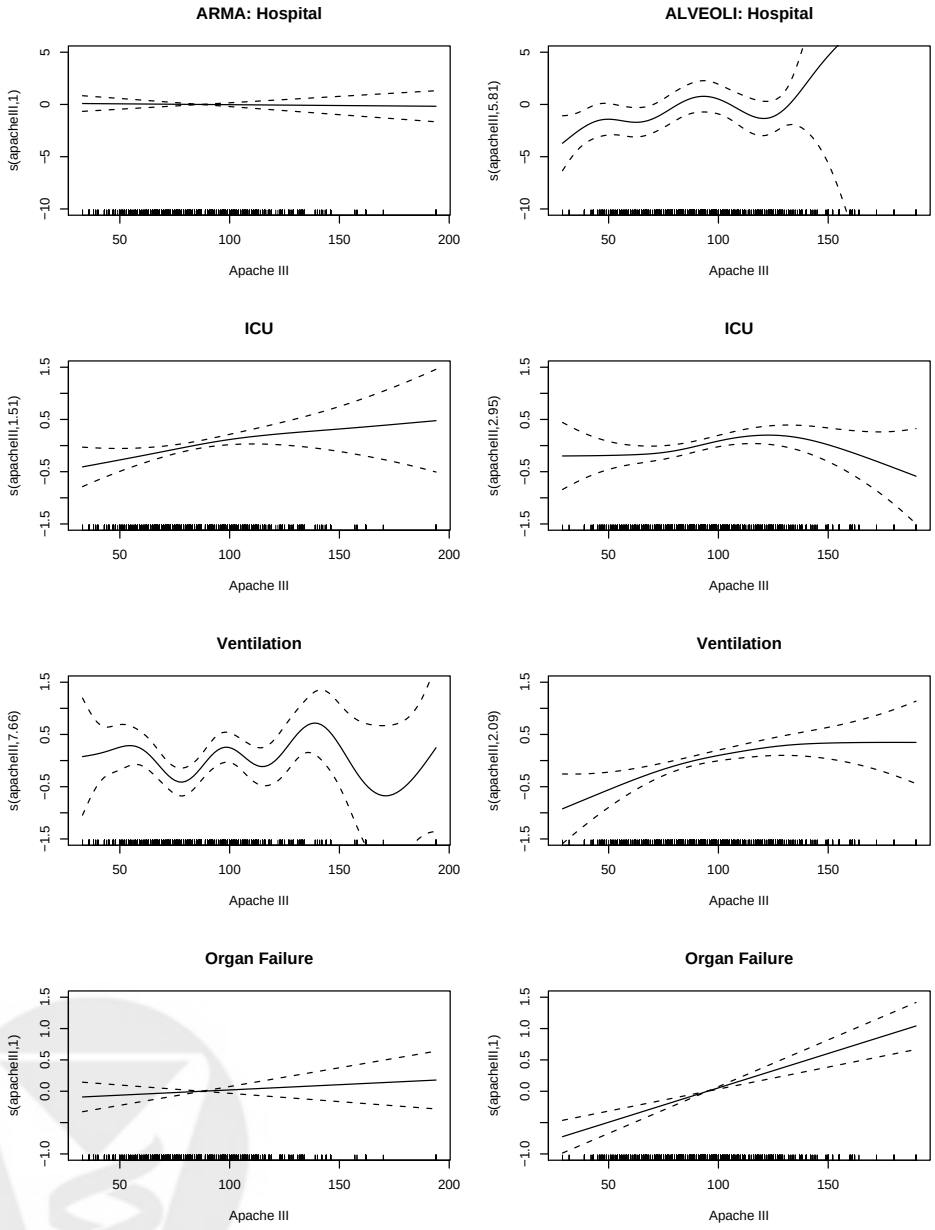

Fig. 4. Estimates of the effects of baseline APACHE on survival at day t (first row, model b.3) among those in the ICU but not on ventilator on day $t-1$, on hospitalization on day t (second row, model c.2) among those alive on day t and in the ICU but not on ventilation on day $t-1$, on being in ICU at day t (third row, model d.1) among those in hospital on day t and in ICU but not on ventilator on day $t-1$, on ventilation on day t (fourth row, model e.3) among those in the ICU on days t and $t-1$, but not on ventilation on day $t-1$, and organ failure on day t (fifth row, model i.5) among those in ICU on days t and $t-1$ but not on ventilator on those days.

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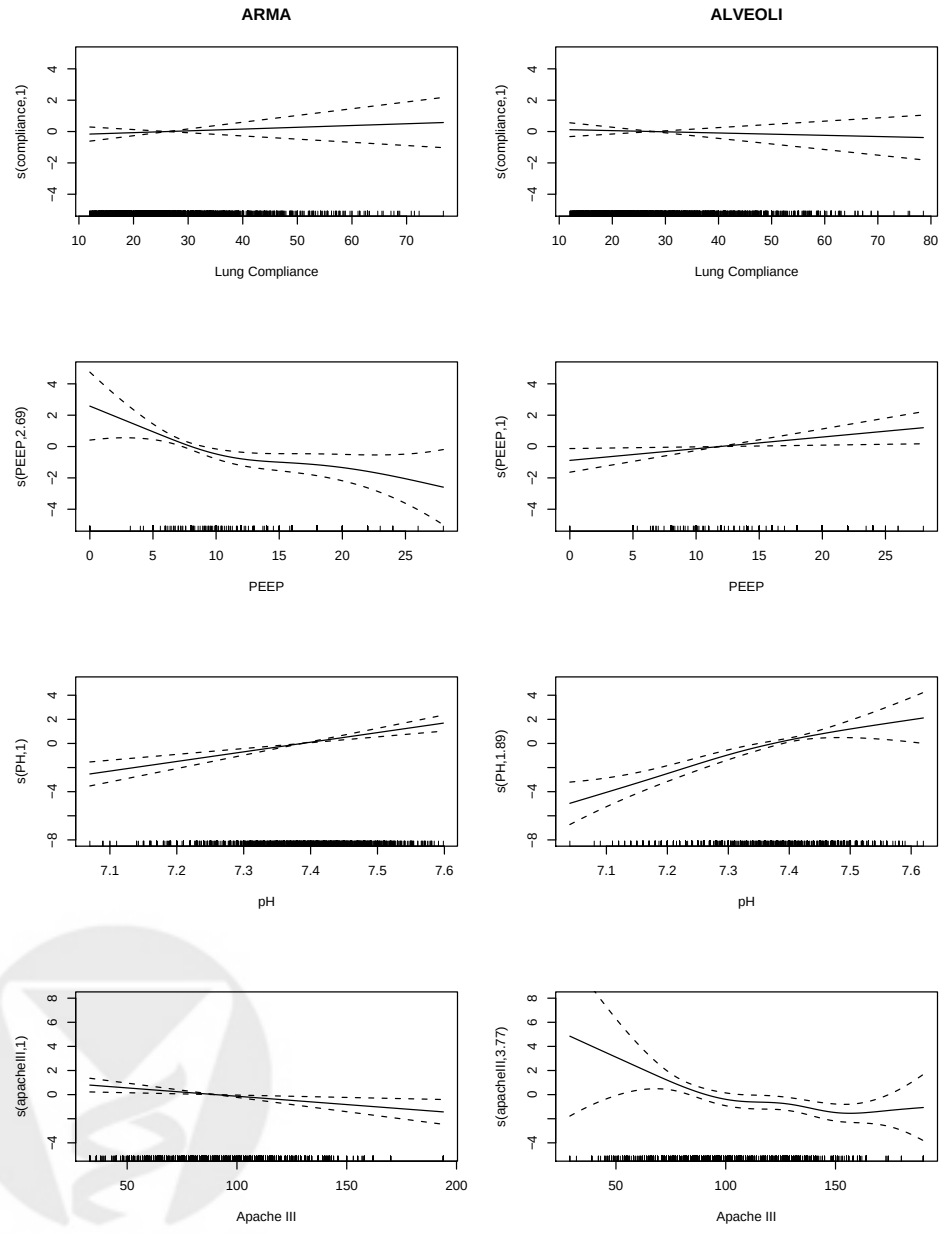

Fig. 5. Estimates of the effect of lung compliance, PEEP, and pH on day $t-1$, and baseline APACHE III on probability of surviving day t, among those on a ventilator on day $t-1$ (model b.2).

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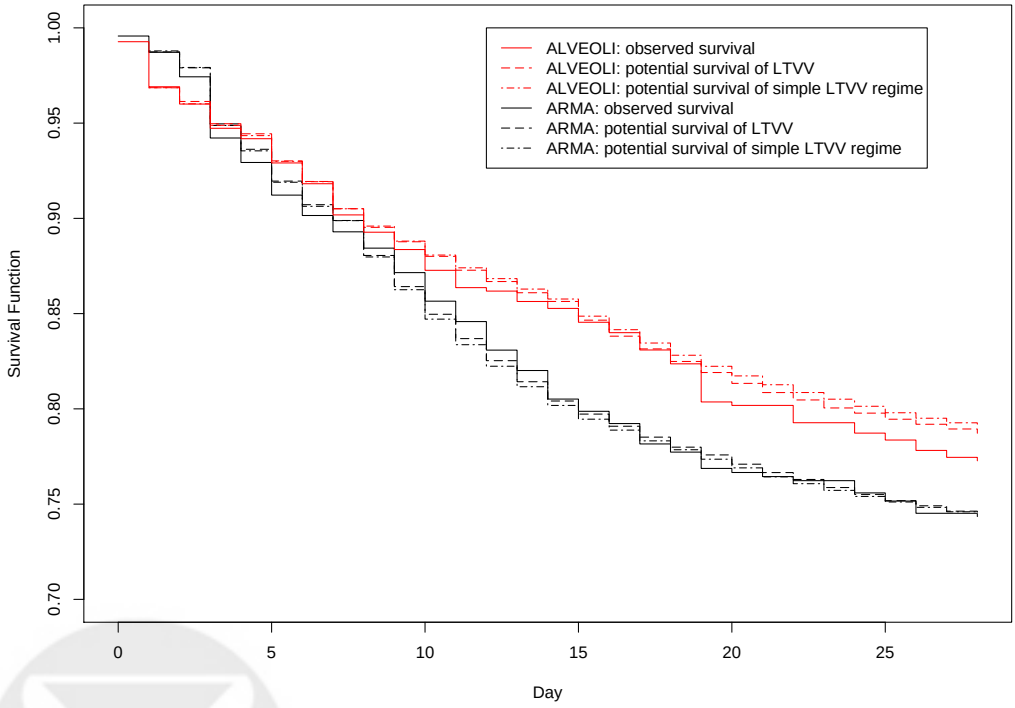

Fig. 6. Observed survival rate and potential survival rates of LTVV and the simpler regimes

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the G-computation analysis can be theoretically derived from the imputation distributions; however, they involve integrations over multiple continuous variables that do not have a closed form. We could use Monte-Carlo integration to estimate each conditional distribution, but such integration would have to be performed for each level of the conditioning arguments. As a result, there would be an orders of magnitude increase in the computational burden, which is already high. Such burden could be reduced if, in our imputation models, we were to work directly with only the basic and derived variables used in the analysis phase. By doing so, however, we would be discarding valuable information on basic variables (e.g., oxygenation saturation and set rate) that have established relationships with the variables (e.g., organ failure, PEEP and pH) used in our analysis.

In our analysis, the imputation and estimation was performed separately. It is possible to combine these procedures. In the posterior step of the data augmentation, in addtion to updating the parameters in imputation models, we could also update the parameters in the conditional distributions of the G-computation formula and estimate the survival function using the G-computation integral. This fully Bayesian approach does not require the idea of multiple imputation. The posterior distribution of the counterfactual survival distribution, however, could be different than the true posterior distribution (had the induced conditional distributions been used in the G-computation formula). We judged the computational burden to be too intense. In addition, using the multiple imputation approach afforded us the oppotunity to refine our discussions about the analysis long after the imputation was complete.

The G-computation has been criticized becuase it can suffer from the "null paradox." When one uses the G-computation formula to estimate the means of a collection of counterfactural outcomes indexed by level of treatment, the paradox states that one can falsely reject the null hypothesis of no variation in means across levels of treatment because of the need (due to the curse of dimensionality) to parametrically specify the component distributions in the G-computation integral. Our analysis which compares the LTVV regime or its simpler version to the non-parametric observed survival curve does not suffer from this particular problem because we are not comparing G-computation estimates to each other. When we compare the LTVV regime to its simpler version, the null paradox is a potential concern, but since we do not reject the null hypothesis of no regime effect, this concern is mitigated.

There are alternatives to our G-computation analysis. Murphy *et al.* (2001) proposed an inverse-weighting procedure in which individuals who adhere to the dynamic treatment regime are inverse-weighted by their probability of being adherent through their course of follow-up. These weights are the inverse of the product of as many as 28 conditional probabilities. In implementing this procedure, we found that some of the weights became prohibitly large and the variances of the resulting estimates were too large to be of practical use. Truncation of weights was considered as a method of trading off bias with variance, but the results were highly sensitive to the choice of the truncation threshold. Another approach that has been advocated is structual nested failure time models (Lok et al., 2004). In these models, one specifies, for each day t, the conditional (on time-varying factors up to day t) quantile-quantile mapping between the distribution of the counterfactual survival time had patients followed the dynamic regime through day t and not followed the regime after day t and the distribution of the counterfactual survival time had patients followed the regime through day $t-1$ and not followed the regime after day t. This is an interesting avenue to explore, which ultimately involves less overall modeling than the G-computation algorithm and does not suffer from the "null paradox". However, given the difficulty expert

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physicians had with regards to the modeling assumptions in this paper, we think this latter approach wouldl be even more difficult to apply.

In conclusion, we have demonstrated statistical methods for addressing the complexities of evaluating the effectiveness of dynamic treatment regimes. We believe that our detailed model-based analysis of observational data will add important information to the clinical literature regarding the treatment of acute lung injury.

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