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Data-Driven Methods for the Characterization of the Implementation of Evidence-Based Medical Practices

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ABSTRACT

The goal of the work reported here was to answer two important questions with regards to LTVV use for patients with ARDS: 1) How do we measure adoption? and 2) What are the drivers of provider adoption? To this end, I have demonstrated the influence of patient height, hypoxemia severity, and ARDS documentation on tidal volume selection for ARDS patients. I have shown evidence that the association of patient height with standardized tidal volume is not an ARDS-specific phenomenon, but instead is an effect of mechanical ventilation for hypoxemia. This finding suggests the clinician use of a simple height-based heuristic for tidal volume selection. Further, I have validated these associations in an international cohort, implying that my results are generalizable to the patient population worldwide. Then, I provide methods to measure ARDS recognition at both the population and individual clinician level that account for these effectors. Using this metric, I show that local team-based culture is a stronger driver of ARDS recognition than specific position within an interaction network, which raises questions about the previously utilized opinion leader targeting approach for adoption interventions. Finally, I demonstrate that different local cultures report different barriers to implementation and that engagement with the studied innovation should be considered when evaluating the importance of specific reported barriers. In summary, this work provides methods for the characterization of the adoption process as well as specific insights for the design of future implementation interventions.

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CHAPTER 1: Introduction

The overall goal of evidence-based medicine is to provide the best possible patient care by integrating the results of medical research into everyday medical practice. Unfortunately, the adoption of evidence-based practices (EBPs) by healthcare teams is frequently not spontaneous and may require significant focused effort. The integration of anything new into a workflow becomes increasingly difficult when the stakes are high, the information sources are diverse, and the innovation is technologically complex (1). Medicine is a good example of a field that faces all three of these challenges and has struggled to rapidly and effectively implement advances. Of all the EBPs developed in medicine, only half are thought to have made it to widespread use, and even then, the transition took an average of 17 years (2). To help address this delay, this work focuses on developing analytical methods at the intersection of the fields of implementation science, clinical medicine, and data science. Due to the multidisciplinary nature of this work, reviews of implementation science and the studied pathology/treatment pair will be provided in this section and more specific summaries of the current literature will be detailed at the beginning of each relevant chapter.

1.1 Implementation Science

The field of implementation science aims to address the gap in high quality healthcare delivery and promote the adoption of evidence-based practices (3). Implementation science is a new field, developing over the last 10-15 years, as the areas of healthcare quality and patient safety have gained traction on the local and national levels (3). So far, the focus within the field has been on qualitative methods when assessing barriers to adoption and designing implementation interventions. These methods include semi-structured interviews, focus groups,

theoretical frameworks, and surveys (3). However, these approaches can introduce biases and can lack both scalability and external validity.

With the integration of the electronic health record into many healthcare practices, data on care delivery processes are readily available and growing every day, holding promise for quantitative analysis. However, data-driven methods for analyzing these data have largely focused on making patient care decisions - such as using the synthesis of population data to assess an individual patient's risk for a procedure or medication (4,5). Very few studies have attempted to use these data to address issues of implementation and adoption. This work aims to help fill this gap and develop quantitative methods for measuring the implementation process and factors that may affect it. I employ computational methods that can be automated and integrated into the electronic health record in order to tackle issues of scalability. For a specific underutilized evidence-based practice, I focus on the use of low tidal volume ventilation in patients with acute respiratory distress syndrome.

1.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a condition found in critically-ill patients, where the oxygen-gas exchange capabilities of the lung are dangerously compromised. Originally observed in injured soldiers during the Vietnam War, ARDS presents with the pattern of a patient who responds to initial resuscitation, only to succumb to respiratory failure much later (days to over a week) (6). Clinically, ARDS can look very similar to pulmonary edema from heart failure, but there is no evidence that heart failure is the source. ARDS is believed to be the result of immunologic damage to the pulmonary capillary endothelium (6). As the exact

mechanism of injury for ARDS is not yet known (6), ARDS is defined as a clinical syndrome and is diagnosed using the Berlin Definition (7):

1. Hypoxemia: P_aO_2/F_IO_2* ≤ 300 mm Hg
    a. *Mild*: 200 < P_aO_2/F_IO_2 ≤ 300
    b. *Moderate*: 100 < P_aO_2/F_IO_2 ≤ 200
    c. *Severe*: P_aO_2/F_IO_2 ≤ 100
2. Bilateral Infiltrates: involvement of both lungs on chest imaging (x-ray or computed tomography)
3. Presence of at least one known risk factor from a predefined list:
    a. *Direct lung injury*: Pneumonia, aspiration of gastric contents, inhalational injury, pulmonary contusion, pulmonary vasculitis, drowning
    b. *Indirect lung injury*: Non-pulmonary sepsis, major trauma, pancreatitis, severe burns, non-cardiogenic shock, drug overdose, multiple transfusions/transfusion-associated lung injury
4. Rule out of cardiac origin of respiratory distress

* P_aO_2: arterial partial pressure of O_2, F_IO_2: fraction of inspired O_2. P_aO_2/F_IO_2 is a measurement of the efficiency of oxygen transfer by the lungs into circulation.

Introduced in 2012, the Berlin Definition of ARDS is the most recent effort to develop diagnostic criteria that are minimally invasive, clinically useful, and accurate to the underlying pathophysiology in a heterogeneous patient population. Classically, ARDS is associated with pulmonary histological changes – diffuse alveolar damage, hyaline membrane formation, and cell necrosis and/or fibrosis (6). Definitive methods for detecting these changes would include an

autopsy or a lung biopsy, both of which are invasive and only one of which is clinically useful. Recent definitions have moved away from invasive procedures to clinical criteria in order to allow for easier and faster diagnosis. The Berlin Definition was an extension of its 1994 predecessor (the American-European Consensus Conference definition) by incorporating patient data as well as expert opinion. Under the Berlin Definition, the stages of hypoxemia correlate to mortality and duration of ventilation, with more severe hypoxemia bearing a higher risk of mortality and longer ventilation (7). Furthermore, the Berlin Definition is thought to be easier to implement, requiring only one lab value (to assess hypoxemia), imaging (lungs and heart), and chart review – data that are readily obtainable in the routine care of a critically-ill patient.

ARDS imposes a high burden on multiple levels of patient care. First, for the individual patient, ARDS carries a mortality rate of 27-45% depending on the severity of hypoxemia (6). Furthermore, ARDS is not often an isolated entity; any one of the predefined risk factors on its own is serious enough to require a long hospital stay. The longer the hospital stay, the higher chance of a patient developing additional complications, such as nosocomial infections and pressure ulcers (8). These complications will require additional outpatient follow-up and care at the very least. Second, for the healthcare delivery system, ARDS is relatively common and costly. ARDS has an estimated incidence of 10.4% of intensive care unit (ICU) admissions (9), contributing about 3.6 million associated hospital days annually (10). Third, the treatment of ARDS – including invasive mechanical ventilation, prone positioning, and extracorporeal membrane oxygenation – is not simple. The interventions require large and experienced patient care teams and a significant face-to-face care time investment. Additionally, they have considerable effects on patient quality of life. ARDS represents an important public health

problem and any improvement in ARDS care would have a sizeable impact on patient outcomes and system burdens.

1.3 Low Tidal Volume Ventilation (LTVV)

One of the mainstays of ARDS treatment is low tidal volume ventilation (LTVV). Patients with ARDS often require invasive mechanical ventilation. In contrast to the natural breathing mechanism which uses negative pressures, mechanical ventilation uses positive pressures (11). As a result, the use of mechanical ventilation comes with a risk of pulmonary barotrauma – damage to the lung tissue as a result of the pressure differences in an enclosed body cavity (11). While the mechanisms of ventilator-associated barotrauma are not fully known, there is evidence to support overdistension of alveoli can lead to inflammatory changes and/or possible alveolar rupture. ARDS is a syndrome of compromised alveolar function thought to arise from inflammatory damage to the lungs; therefore, the goal of low tidal volume ventilation is to minimize additional ventilator-associated barotrauma and possible perpetuation of ARDS (12). This is accomplished by lowering the tidal volume – volume of a single breath – to avoid alveolar overdistension.

Between 1998 and 2006, there have been nine major randomized controlled trials evaluating low tidal volume ventilation vs traditional tidal volume ventilation, seven of which were published by 2000 (13). The largest study was the ARMA study, which included 861 patients from 10 different hospitals and was stopped prematurely due to the strength of the evidence for mortality reduction in patients receiving LTVV as opposed to traditional volumes (22% relative reduction) (12). In the ARMA study, low tidal volume ventilation was defined as

6.5 mL/kg predicted body weight (PBW) and traditional volumes were defined as 12.0 mL/kg PBW. Subsequent evaluation of the evidence of the nine trials has led to the incorporation of LTVV for ARDS into clinical guidelines (13). While the American Thoracic Society guideline defines LTVV as 4-8 mL/kg PBW, this work will define LTVV as 6.5 mL/kg PBW as that was the threshold used in the ARMA trial and our data comes from before the guideline publication. Despite the strength of the evidence for the benefits of LTVV for ARDS patients, the utilization of LTVV has remained as low as 19% of eligible patients (9,14–21), suggesting the need for further study into the barriers preventing LTVV use.

1.4 Thesis Organization

The primary motivation of my thesis work is to develop our scientific understanding of how to design interventions that promote the adoption of evidence-based treatments. My guiding assumption is that interventions that leverage and integrate with the natural flow of information within the healthcare delivery system will have a better chance of success. In order to accomplish my goal, I addressed two critical questions:

1. How do we measure adoption?
2. What are the drivers of provider adoption?

My thesis work focuses on answering these questions in the test case of LTVV use for patients with ARDS. Because the two questions are inextricably linked, addressing them requires iteration between the two.

First, I explore the factors affecting LTVV use for ARDS patients using two different datasets: 700 patients from four Chicagoland hospitals (Chapter 2) and 3777 patients from the international LUNG SAFE dataset from 50 countries (Chapter 3). I introduce a novel hypoxemic

"control" cohort as a means of evaluating which factors affecting LTVV use are associated with ARDS in particular and which factors are a result of mechanical ventilation for hypoxemia. For ARDS patients, I show that both ARDS documentation in the patient's chart and hypoxemia severity are associated with lower tidal volumes. Furthermore, I demonstrate in both cohorts that patient height has an association with tidal volumes and that taller patients have a better chance of receiving LTVV, regardless of whether they have ARDS or not. Surprisingly, in the ARDS cohort, patient height has a stronger association than hypoxemia severity or ARDS documentation. Finally, I show that these associations (patient height, hypoxemia severity, ARDS documentation) hold true for both datasets. These results suggest that a portion of LTVV is unintentional and a result of the effects of patient height. Thus, measuring LTVV utilization is not trivial.

For this reason, in Chapter 4, I develop two models of clinician recognition of ARDS that estimate overall recognition rates while accounting for the effects of the previously mentioned factors. I focused on ARDS recognition because it is the prerequisite for LTVV use and prior studies suggest that belief in LTVV is very high. These models produce recognition rates that increase with hypoxemia severity, which is consistent with prior literature, what one would expect. In all three hypoxemia categories, the LUNG SAFE dataset had higher ARDS recognition rates as compared to the Chicago dataset. The two datasets had the closest recognition rates in the severe hypoxemia category, despite having different documentation rates. This discrepancy is potentially due to the fact that LUNG SAFE offered its site investigators additional training regarding ARDS diagnosis prior to the beginning of the study and the

Chicago sites did not. Given the higher difficulty of recognition, the biggest differences would be expected in the less severe categories, which I observe.

In Chapter 5, I build on these recognition models and design a metric that tailors ARDS recognition rates for individual clinicians. The characteristics of the cared-for patient population can vary significantly between individual clinicians or even for the same clinician over time. To address this issue, I designed a metric that accounts for the diversity of each clinician's cared for patient population, comparing expected recognition rates to observed recognition rates. I show that our metric is robust to several patient characteristics, such as height and hypoxemia severity.

Having developed a more accurate metric of ARDS recognition, I evaluate in Chapter 6 the association between ARDS recognition and a clinician's position within interaction networks. Previous studies have identified socially popular individuals as opinion leaders within the social network and targeted them for adoption interventions. However, these interventions have had only moderate success. After accounting for clinician demographics, such as care-team membership or number of intensive care units worked in, I find no association between our ARDS recognition metric and several network position measures. Instead, the clinician demographics were stronger predictors of ARDS recognition. This finding suggests the effects of a local culture outweigh the idiosyncratic characteristics of the individual, raising questions about the opinion leader targeting approach for adoption interventions.

In Chapter 7, I quantify the effects of local culture with a secondary analysis of previously published survey data. Prior surveys have been used to identify barriers to LTVV use by evaluating which barriers are named most often in specific questions or free text. When I split clinicians by the driving demographic characteristics (care-team, number of units worked in), I

find that those belonging to subgroups with higher recognition rates more often report difficulties with ARDS recognition or LTVV implementation than those belonging to subgroups with lower recognition rates. This finding suggests that providers that make a specific diagnosis or implement a specific treatment are more familiar with the difficulties of the process. Even if a minority of providers name something as a barrier, the barrier could still be significant as the few providers reporting it may be the ones engaging with the process more intentionally.

CHAPTER 2: Effectors of Tidal Volume Selection for ARDS Patients

The work in this chapter was published in the following paper: Bechel MA, Pah AR, Shi H, Mehrotra S, Persell SD, Weiner S, et al. (2019) A quantitative approach for the analysis of clinician recognition of acute respiratory distress syndrome using electronic health record data. PLoS ONE 14(9): e0222826. https://doi.org/10.1371/journal.pone.0222826

2.1 Introduction

The common goal of many implementation science studies is to identify barriers to and facilitators of adoption and subsequent design of interventions promoting implementation. The primary methodologies in these studies have been largely qualitative methods - semi-structured interviews, focus groups, theoretical frameworks, and surveys (3). In spite of their strengths and the advances they have enabled, these methods can introduce significant biases such as the subjective reporting, the observer effect, and priming (Table 1). These biases can in some cases limit the generalizability of the results gleaned from these methods. Moreover, due to the high resource and time requirements of qualitative methodologies, adopting these methods at larger or lower-resource settings is often not an option. Clearly there is a need for quantitative and scalable methods.

Table 1: Bias definitions and examples

Bias	Definition	Examples
Subjective reporting	Also called 'recall bias', it is the concept that humans are not perfect historians. A person may be more or less likely to report an exposure/experience given their own specific circumstances and experiences.	- Individuals often report themselves as better at specific tasks than they objectively are. - An individual is more likely to report that delays in lab tests are a big problem if they do not like the lab staff for unrelated reasons.
Observer effect	Also called the 'Hawthorne effect', it is the tendency of people to change their behavior when they are the target of special interest and attention, regardless of the specific nature of the intervention they might be receiving.	- Patients participating in clinical trials will do better than patients who receive the same treatment not in a trial setting. - The rate of surgical site infections decreases when the number is being recorded by the department and increases after the recording period ends.
Priming	A psychological process in which exposure to a stimulus activates a concept in memory that is then given increased weight in subsequent judgment tasks.	- An individual over-reports the incidence of a disease after receiving training on how to identify that disease. - An individual answers 'Strongly Agree' on a survey question about systems barriers when they would not have mentioned systems barriers in an interview.

While surveys have been used to study the delay of LTVV use uptake (Ch 7), there has been progress towards the integration of quantitative methods through the use of the cohort comparison study. Specifically, these studies compare the characteristics of patients with ARDS who received LTVV and those that did not receive LTVV and attempt to identify effectors of ventilator management decisions (16,18,20–28). The commonly identified categories of potential effectors include: overall disease severity (16,18–20,23,24,26,27), severity of pulmonary illness

(16,18–21,24,26–28), gender/height (16,18,19,21,23,24,26–28), clinician recognition of ARDS (19,24,26,27), ICU team training/organization (16,18,21,22,24,26,27), and ARDS risk factors (16,18,21,22,24,26,27) (Table 2). However, the evidence is not clear because the studies have reported conflicting results (Figure 1).

Table 2: Overall and pulmonary disease burden measurements

Category	Factor	Description
Overall disease burden	Acute Physiology and Chronic Health Evaluation (APACHE)	Clinical scoring system to predict risk of patient mortality based on physiological measures on day of admission to the ICU
	Sequential Organ Failure Assessment (SOFA)	Clinical scoring system to predict risk of patient mortality based on physiological measures from six major organ systems within the same 24h period. Used to track a patient's progress during an ICU stay.
	Charlson Comorbidity	Clinical scoring system to predict 10-year survival in patients based on age and specific coexisting conditions such as AIDS, dementia, diabetes, etc.
	Mortality Probability Model	Clinical scoring system to predict hospital mortality for ICU patients based on physiological measurements, diagnoses, and requirement of ventilation.
Pulmonary disease burden	P_aO_2/F_IO_2	Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. Measurement of the efficiency of oxygen transfer across the pulmonary endothelium.
	Static compliance	Measurement of lung tissue elasticity: the change in volume for any given applied pressure.
	Plateau Pressure	A proxy for lung tissue elasticity: the pressure applied to the small airways and alveoli. Measured as the pressure during an inspiratory hold.
	Lung Injury Score	Clinical scoring system to stratify severity of ARDS based on chest x-ray findings, PaO2/FiO2, and static compliance.

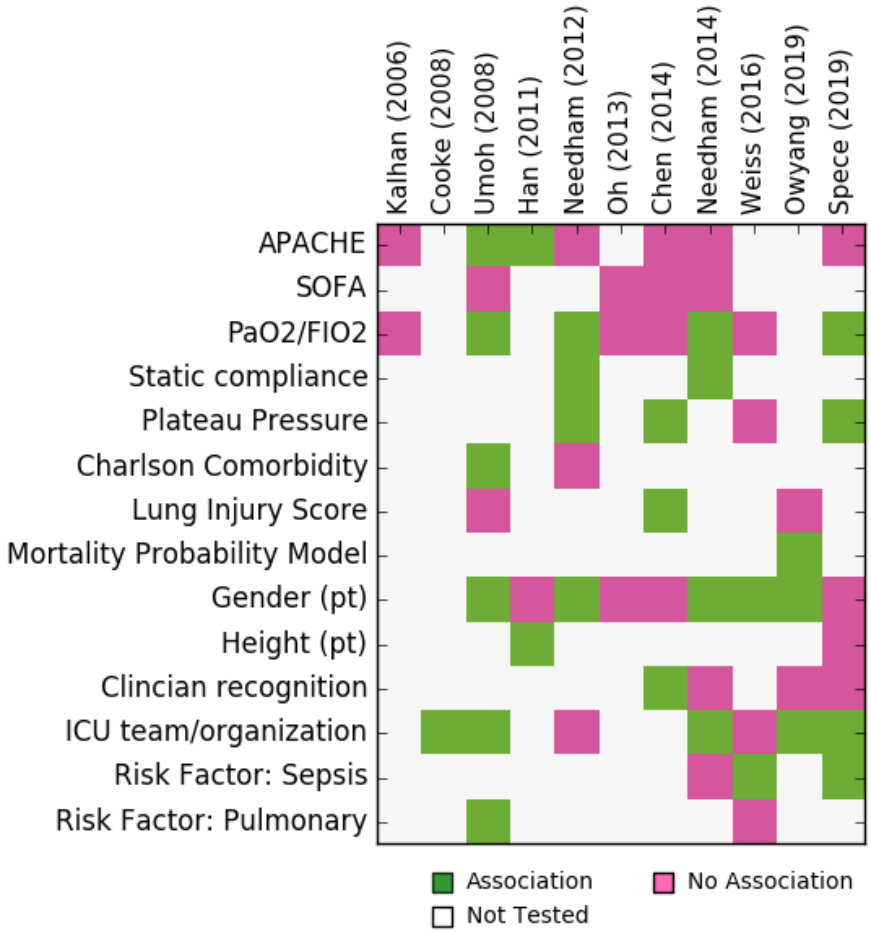


Figure 1: Cohort comparison studies for LTVV use for ARDS.
Eleven studies (x-axis) have compared ARDS patients that receive LTVV versus those that do not. Different studies have reported associations (green) or lack of associations (pink) between LTVV use and several commonly evaluated effectors (y-axis).

For a few cases, there is consensus. For example, all studies that examine the role of SOFA (Sequential Organ Failure Assessment score) agree that while it has been shown to predict overall mortality in ICU patients (29), it is not a helpful predictor for LTVV use (18,19,24,28). In contrast, static compliance (measure of lung tissue elasticity) is reported as a good predictor of LTVV use in the minority of studies that examine it (16,24). The situation is less clear for most of the other effectors studied, with some factors being heavily studied and almost evenly divided

in conclusion, such as P_aO_2/F_IO_2 (part of the Berlin Criteria) and patient gender. The question then becomes which studies to consider when trying to generalize the findings and to do this, one usually considers the conditions under which the study took place.

Table 3: ARDS cohort comparison study parameters

Study	Patients Enrolled (n)	Study Sites (n)	Academic (%)	Risk Factor Limits?	LTVV bins (mL/kg PBW)	Significance Threshold
Kalhan	88	1	100	No	$\hat{V}_T \leq 7.5$ $7.5 < \hat{V}_T$	0.05
Cooke	759	23	60	No	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T < 8.0$ $\hat{V}_T \geq 12.0$	0.05
Umoh	250	3	100	No	$\hat{V}_T \leq 6.5$ $\hat{V}_T \leq 8.5$	0.05
Han	421	7	100	Yes – sepsis only	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T \leq 8.0$ $8.0 < \hat{V}_T$	0.05
Needham (2012)	485	4	100	No	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T$	0.05
Oh	104	28	NR	Yes – influenza only	$\hat{V}_T \leq 7.0$ $7.0 < \hat{V}_T \leq 9.0$ $9.0 < \hat{V}_T$	0.10
Chen	111	1	NR	No	$\hat{V}_T \leq 7.5$ $7.5 < \hat{V}_T$	0.05
Needham (2014)	482	4	100	No	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T$	0.05
Weiss	362	4	100	No	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T$	0.05
Owyang	446	1	100	No	$\hat{V}_T \leq 8.0$ $8.0 < \hat{V}_T$	0.01
Spece	214	1	100	No	$\hat{V}_T \leq 6.5$ $6.5 < \hat{V}_T$	0.05

NR: Not reported
$\hat{V}_T$: standardized tidal volume (mL/kg predicted body weight).

Looking over Table 3, there are a few important differences between the studies. First, we must consider how the primary outcome (standardized tidal volume, $\hat{V}_T$) is defined. Some

studies opt for the ARMA cut off of 6.5 mL/kg PBW (16,18,21–24,27) while others choose 7.0 or 7.5 (19,20,28) or even split patients into three categories instead of two (22,23,28). Second, the selection of patient cohorts have considerable variation as well. Some studies include all patients that meet the definition of ARDS (16,18,20–22,24–27), but others restrict to just those with a specific risk factor (23,28). Third, while most studies use a significance threshold of 0.05, there are two studies that deviate from this, one using the more relaxed 0.10 (28) and the other using the stricter 0.01 (26). Finally, the trends that each study is capturing may vary, given the diversity of study sites used. Studies that pull data from a single site may be focusing in on local cultural barriers, whereas other studies – such as Oh, which uses all 28 national hospitals in Korea – may only capture overriding trends given that variation between sites may balance out some effectors as non-significant.

All of this speaks to the diversity of institutional environments in which these studies are being conducted, which can have a considerable influence on the implementation of a new medical practice. If we consider the case of a more traditional study where the goal is to evaluate the success of a treatment against a disease process, the environment in which the treatment is given is controlled via patient selection and standardized protocols. In this case, the primary outcome is instead the success of a clinician vs the conditions they're in (patient population, institutional organization, available resources, etc). Thus, it could be possible that some studies report certain factors as important while others do not. They may not be conflicting, but instead both true, for their circumstances. While it is possible that some studies are simply underpowered, with all of these sources of heterogeneity, the results of the cohort comparison

study can still be difficult to generalize. To build on their advancements and address this issue, we propose the inclusion of a novel control cohort to the methodology.

2.2 Data Used in These Analyses

2.2.1 Cohort development

The development of the ARDS cohort used in this study has been previously described (21). It includes 362 patients who met the Berlin Definition of ARDS (7) via independent clinician review and were admitted to an ICU at one academic and three community hospitals in the Chicago region between June 24, 2013 and December 31, 2013.

For this study, we developed an additional cohort from the same time period and initial screening population at two of the same hospitals (one academic, one community): 388 patients with acute hypoxemic respiratory failure requiring mechanical ventilation with at least one instance of $P_aO_2/F_IO_2 \leq 300$ but not with ARDS according to the above Berlin Definition ("control cohort"). The majority of patients (n=215 (55.4%)) did not have bilateral pulmonary involvement. We excluded patients with missing key information (predicted body weight [PBW], gender, tidal volumes), intubation duration less than 5.67 hours (the shortest duration of intubation in the ARDS cohort), and PBW less than 25 kg (Figure 2). This control cohort represents patients that would require mechanical ventilation, but in which LTVV would be not be indicated. At the time of data collection, LTVV was only studied and indicated as a ventilatory management strategy in patients with ARDS and it has since been shown that it is not an effective strategy for patients without ARDS (30).

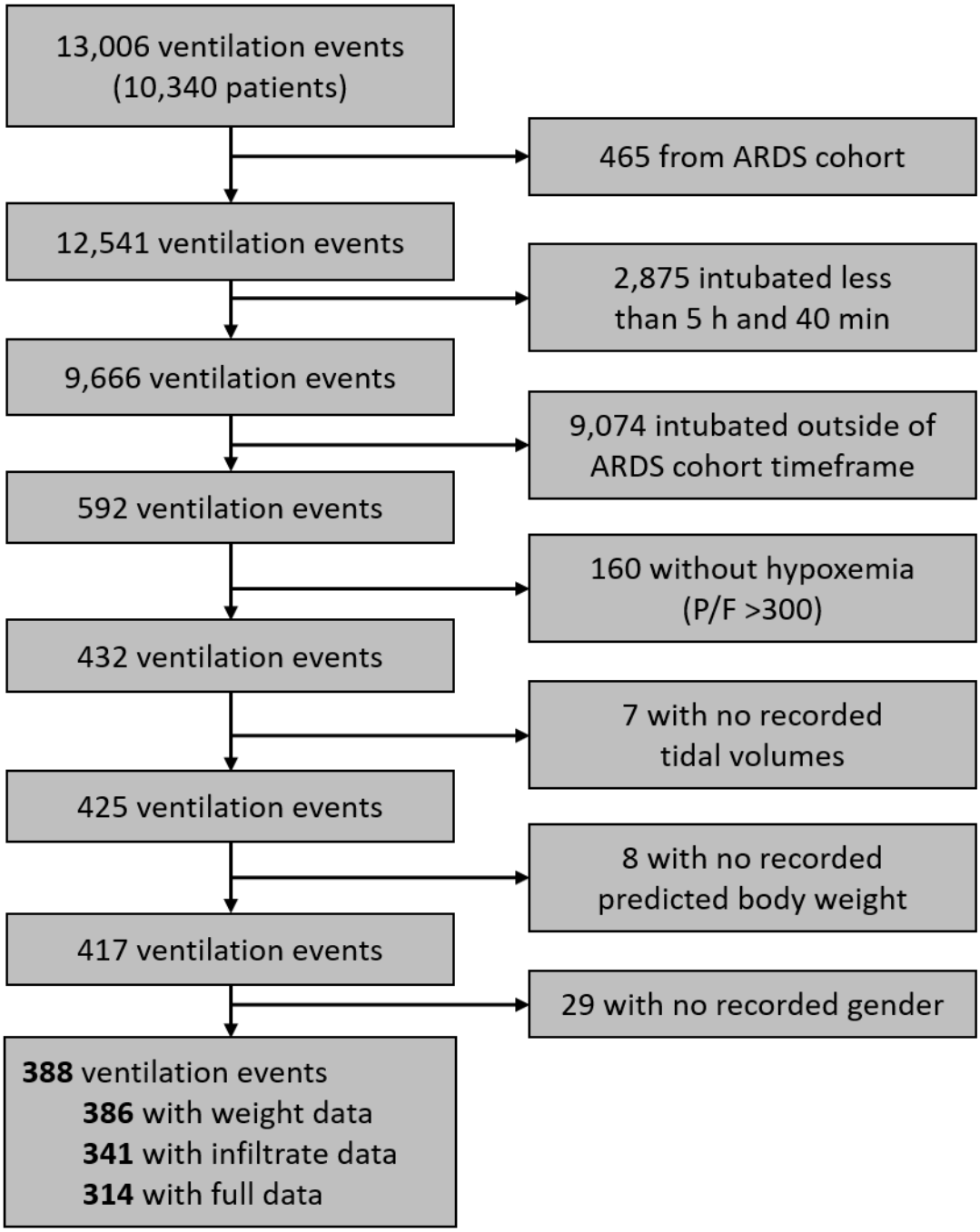


Figure 2:Flow of patient screening and enrollment for control cohort

Patients were not actively recruited for either cohort, but instead all data was mined from the electronic health record. The ARDS and control cohorts were similar across several clinical and demographic measures (Supp Table 1). These cohorts are representative of the larger population of patients with ARDS and non-ARDS acute hypoxemic respiratory failure due to our broad inclusion criteria, and their similarity to larger cohorts (e.g., LUNG SAFE (9)) with respect to height, weight, and hypoxemia severity. This study was approved by the Northwestern University Institutional Review Board (STU00208049) with a waiver of consent on October 30, 2018.

2.2.2 Data Acquisition

All patient data were obtained from the electronic health records serving the participating hospitals. We defined study entry as the start of ARDS for the ARDS cohort and the first instance of $P_aO_2/F_IO_2 \leq 300$ in the control cohort. Study end was defined as the earlier of extubation, death, or ICU discharge. We recorded gender, height, and all PaO2/FIO2 and weights between ICU admission and study end. We recorded all tidal volumes (V_T) and plateau pressures (P_{plat}) between intubation and study end where available (P_{plat} was not recorded at two hospitals). Note that 22% of the ARDS cohort and 44% of the control cohort only had one unique tidal volume over their study duration. We recorded which ICU the patient was treated in and whether an ARDS diagnosis was documented in the critical care physician's notes. For the control cohort, we recorded whether or not bilateral infiltrates were present for all chest radiographs or computed tomography scans between intubation and study end. For data availability for both cohorts and all subgroups, see Supp Table 2. Patients who met cohort inclusion criteria but were

missing other data points were only excluded from analyses that required those missing data points.

In this study, we used PBW as a gender-adjusted and gender-neutral measurement of height because LTVV thresholds are defined using PBW. Any references to patient height refer to PBW (kg) and any references to patient weight refer to a patient's weight measured at ICU admission (kg). We calculated PBW according to the ARDS Network definition (see below) and defined LTVV as a standardized tidal volume ($\hat{V}_T$) $\leq$ 6.5 mL/kg PBW.

Predicted Body Weight Equations [7]:

Male: PBW (kg) = 50 + 2.3*(height (in) – 60)

Female: PBW (kg) = 45.5 + 2.3*(height (in) – 60)

PBW is used when calculating LTVV thresholds because lung volume scales with patient height, not body mass. The nomenclature is unfortunate and potentially misleading, which led us to include it as a potential barrier to LTVV use (see 2.3.1).

2.2.3 Significance Testing

We used $\alpha = 0.01$ instead of 0.05 to ensure the statistical strength of our findings (31) and applied the Bonferroni correction for multiple hypotheses. In the regression analyses (see Section 2.3), there were 33 comparisons where $\hat{V}_T$ was the dependent variable, thus we set $p < 0.0003$ (0.01/33) as the threshold for statistical significance for these analyses. For the covariate analyses, the threshold was $p < 0.005$ (0.01/2). For the Kolmogorov–Smirnov tests in Model Approach #2, the threshold was $p < 0.003$ (0.01/3).

2.3 Potential Factors in Tidal Volume Selection

2.3.1 Factors assessed

We used the lowest standardized tidal volume ($\hat{V}_T$) (mL/kg PBW) for each patient as the dependent variable in both univariable and multivariable ordinary least squares (OLS) regressions. $\hat{V}_T$ was used as a continuous variable. OLS regressions were implemented using the statsmodels (version 0.6.1) Python package. In the ARMA trial, LTVV was defined as $\hat{V}_T \leq 6.5$ mL/kg PBW, but is defined as a range of 4.0-8.0 mL/kg PBW in the current guidelines (published after data collection) (13). In the ARMA trial, "traditional" tidal volumes were defined as 12 mL/kg PBW.

We determined the relationship between several factors and $\hat{V}_T$, choosing variables that have been identified previously in the literature as potential barriers or facilitators of LTVV use (15,23,32–35): first $P_aO_2/F_IO_2 \leq 300$, lowest P_aO_2/F_IO_2, highest P_{plat}, patient weight at ICU admission, ARDS documentation in the patient chart, presence of bilateral infiltrates on chest imaging(control only), admitting ICU (ARDS only), and patient height (we used the gender neutral PBW). These factors comprise measures of illness severity (P_aO_2/F_IO_2, P_{plat}, radiographic findings), patient characteristics (height, weight), and physician behaviors (ARDS documentation, patient weight). While patient gender has been included in past studies (Figure 1), we did not include it as a factor due to its covariance with height (23). ARDS documentation was defined as an attending physician writing 'ARDS', 'acute respiratory distress syndrome', 'ALI', or 'acute lung injury' in the patient's chart, because ARDS did not have a billing code at the time of data collection. Plateau pressure was included due to the previously reported practice of physicians not lowering tidal volumes in ARDS patients when $P_{plat} \leq 30$ cm H_2O (26,33). Patient weight was included due to the previously reported barrier of physicians using actual body weight instead of predicted body weight in the LTVV threshold calculation (26,32,33).

Note that we use a standardized tidal volume ($\hat{V}_T$) as opposed to the recorded tidal volume (V_T) and PBW is included as a control variable. Since $\hat{V}_T$ is already normalized for PBW, we expected no additional remaining relationship between PBW and $\hat{V}_T$. Input variables were rescaled between 0 and 1 to allow for comparison of regression coefficients.

2.3.2 Univariable analysis

The relationship between each factor and $\hat{V}_T$ was investigated through univariable OLS regressions for the ARDS and control cohorts (Table 4). Standardized tidal volume ($\hat{V}_T$) decreased toward the LTVV threshold with worsening hypoxemia (lower P_aO_2/F_IO_2) and the presence of ARDS documentation in the ARDS cohort ($p < 0.0003$), but not in the control cohort (Figure 3, Table 4). In both cohorts, $\hat{V}_T$ decreased with increasing PBW (gender neutral height, $p < 0.0003$, Figure 4 and Table 4) – a surprising result since $\hat{V}_T$ already takes PBW into consideration. Plateau pressure, weight at ICU admission, P_aO_2/F_IO_2 at study start, admitting ICU (ARDS cohort only), and the presence of bilateral infiltrates (control cohort only) were not associated with significant changes in standardized tidal volume in any cohort or subgroup (Table 4, Figure 5).

Table 4: Predictors of lowest $\hat{V}_T$ (mL/kg PBW) (β-coefficient [99% CI])

Factor	ARDS		Control	Pooled Documented
	univariable	multivariable	univariable	univariable
Predicted body weight	**-3.8*** **[-4.7, -2.8]**	**-3.7*** **[-4.8, -2.7]**	**-5.1*** **[-6.0, -4.1]**	**-3.2*** **[-5.2, -1.2]**
P_aO_2/F_IO_2 ratio (lowest)	**1.3*** **[0.4, 2.4]**	1.1 [0.3, 1.9]	0.8 [-0.1, 1.6]	2.3 [-0.3, 4.9]
Documentation	**-1.3*** **[-1.9, -0.6]**	**-1.2*** **[-1.9, -0.6]**	-1.2 [-2.3, -0.2]	
P_aO_2/F_IO_2 ratio (first)	0.7 [-0.19, 1.5]		0.3 [-0.6, 1.1]	1.2 [-0.9, 3.2]
P_{plat} (highest)	-2.2 [-4.1, -0.3]		-1.5 [-3.2, 0.1]	-3.5 [-6.0, -1.0]

ICU admission weight	0.12 [-1.8, 2.0]	-0.4 [-1.7, 0.9]	-0.6 [-3.3, 2.2]
Bilateral infiltrates**		-0.5 [-0.9, 0.0]	
Admitting ICU	-0.9 [-1.9, 0.1]		

* ***p* < 0.0003**
** At least once after hypoxemia onset.
Empty cells indicate category was not used due to data being unavailable or not relevant.

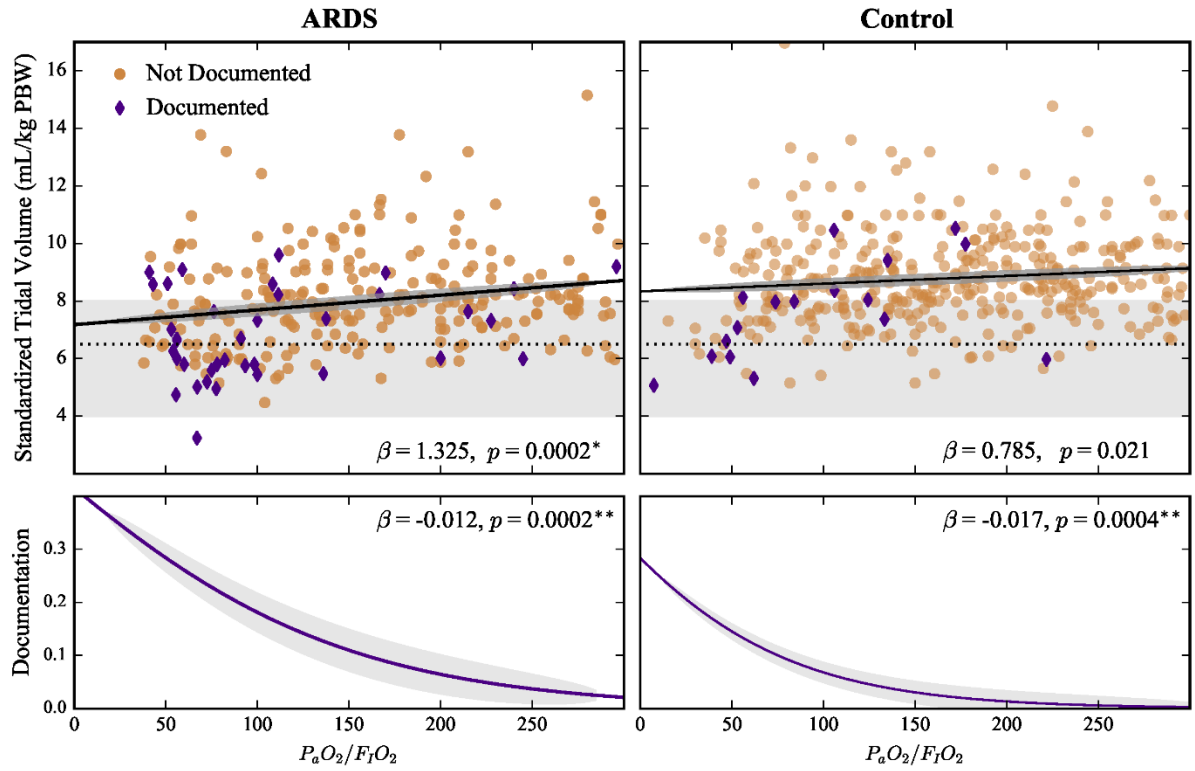


Figure 3:Effects of lowest PaO2/FIO2 ratio on standardized tidal volume ($\hat{V}_T$) and ARDS documentation in ARDS and control cohorts.
Top panels show patients with ARDS documented in their chart (purple diamonds) and non-documented patients (tan circles). Gray areas indicate LTVV range from current guidelines (13), with dashed line at 6.5 mL/kg PBW from currently recommended threshold. Solid lines show linear ($\hat{V}_T$) fits for scatter plot data (shaded regions, 95% confidence bands). Bottom panels show probability of documentation as calculated from logistic regression (solid line with shaded regions, 95% confidence bands). Reported beta coefficients are for standardized inputs. * $p <$ 0.0003, ** $p < 0.0005$.

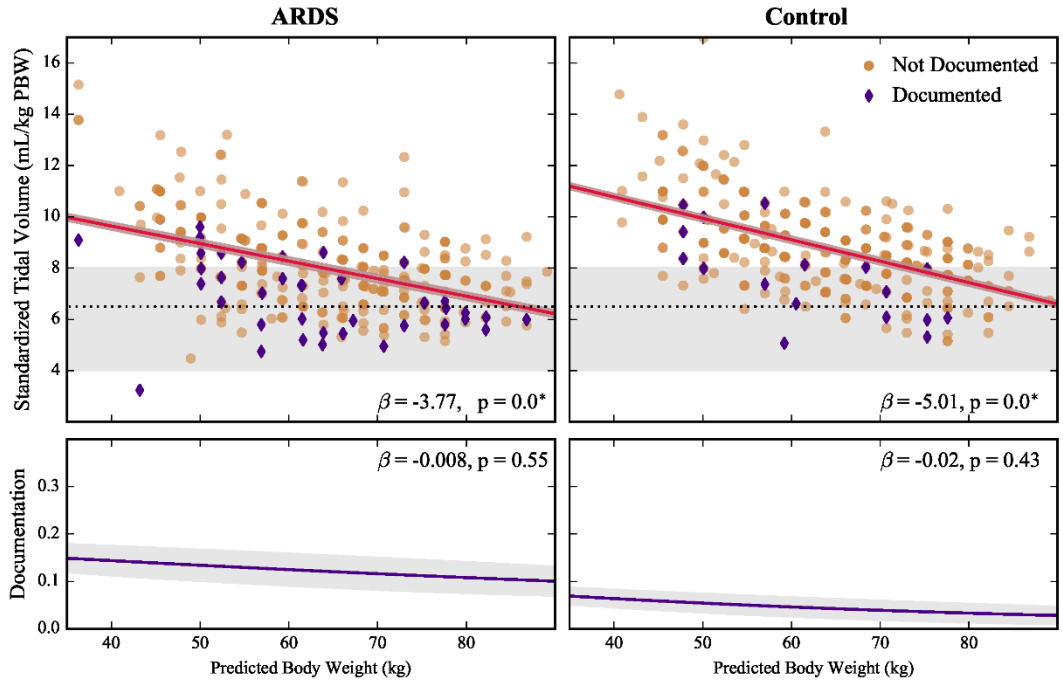


Figure 4: Effects of predicted body weight (gender neutral height) on standardized tidal volume ($\hat{V}_T$) and ARDS documentation in ARDS and control cohorts.
Top panels show patients with ARDS documented in their chart (purple diamonds) and non-documented patients (tan circles). Gray areas represent LTVV range from current guidelines (13), with dashed line at 6.5 mL/kg PBW at current recommended threshold. Solid lines show linear ($\hat{V}_T$) fit for scatter plot data (shaded regions, 95% confidence bands). Bottom panels show probability of documentation as calculated from logistic regression (solid line with shaded regions, 95% confidence bands). Reported beta coefficients are for standardized inputs. * $p <$ 0.0003.

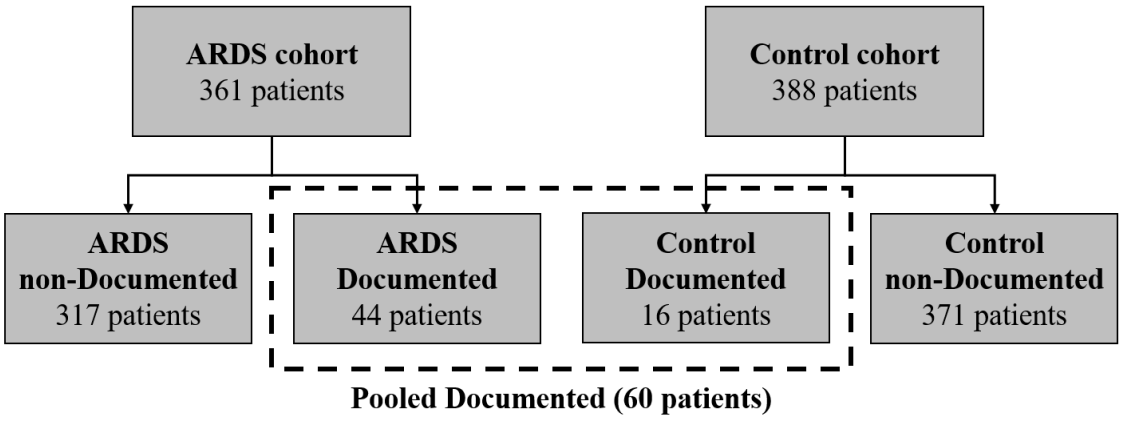


Figure 5: Cohort and subgroup definitions

2.3.3 Covariate Analysis

The factors demonstrating a significant association with $\hat{V}_T$ in the univariable analyses were evaluated for covariance with each other using OLS regression. Three factors were evaluated for covariance: PBW, lowest P_aO_2/F_IO_2, and documentation of ARDS. PBW was not associated with increasing documentation probability (Figure 4) in both cohorts, which was anticipated. Documentation and lowest P_aO_2/F_IO_2 were significantly correlated ($p < 0.005$) in both cohorts (Figure 3). This association was also anticipated as sicker patients are easier to recognize. To test the strength of the documentation and lowest P_aO_2/F_IO_2 association, we repeated the univariable analysis on the three major subgroups (ARDS non-documented, control non-documented, and pooled documented) (Figure 5). Only PBW was associated with lower $\hat{V}_T$ in all three subgroups (Table 4, Table 5). There was no association between PBW and lowest P_aO_2/F_IO_2 in both cohorts.

Table 5:Predictors of lowest $\hat{V}_T$(mL/kg PBW) in non-documented subgroups (β-coefficient [99% CI])

Factor	ARDS non-documented univariable	Control non-documented univariable
Predicted body weight	**-4.0*** **[-4.9, -3.0]**	**-5.0*** **[-6.0, -4.1]**
P_aO_2/F_IO_2 ratio (lowest)	0.9 [-0.1, 1.9]	0.5 [-0.4, 1.3]
P_aO_2/F_IO_2 ratio (first)	0.3 [-0.6, 1.2]	-0.05 [-1.0, 0.9]
P_{plat} (highest)	-1.0 [-3.1, 1.1]	-0.4 [-2.0, 1.2]
ICU admission weight	0.1 [-1.8, 2.1]	-0.4 [-1.7, 0.9]

* $p < 0.0003$

2.3.4 Multivariable analysis

Significant factors from the univariable analyses were included in multivariable regressions comprised of all possible linear combinations of the factors and appropriate interaction terms. Seven models were constructed using all combinations of PBW, Documentation, and lowest P/F ratio as independent variables and a P/F ratio Documentation interaction term (Table 6). In each model, the continuous variables were scaled between 0 and 1. AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) were calculated for each model to select the "best" model. AIC and BIC were calculated using the python package statsmodels (version 0.6.1).

Table 6: Multivariable models of lowest standardized tidal volume (mL/kg PBW) in ARDS cohort

Model	AIC	BIC
$\hat{V}_T$ ~ PBW	1043.818	1051.095
$\hat{V}_T$ ~ lowest_PF	1090.127	1097.404
$\hat{V}_T$ ~ Documentation	1085.523	1092.799
$\hat{V}_T$ ~ PBW + lowest_PF	1026.321	1037.236
$\hat{V}_T$ ~ PBW + Documentation	1015.874	1026.789
$\hat{V}_T$ ~ PBW+ lowest_PF +Documentation	**1006.425**	**1020.979**
$\hat{V}_T$ ~ PBW + lowest_PF + Documentation + Documentation:lowest_PF	1008.166	1026.358

AIC: Akaike Information Criterion for goodness of fit
BIC: Bayesian Information Criterion for goodness of fit

In the ARDS cohort, the multivariable regression model that included PBW, lowest P_aO_2/F_IO_2, and documentation as independent variables with no interaction terms resulted in the

lowest AIC and BIC (Table 6). In this model, PBW and documentation were significantly correlated with $\hat{V}_T$ ($p < 0.0003$), while lowest P_aO_2/F_IO_2 was not. Of these variables, PBW had the greatest effect on $\hat{V}_T$ (β -3.7, 99% CI -4.8 – -2.7). For the control cohort, only PBW was associated with $\hat{V}_T$, and therefore no multivariable analysis was performed.

2.3.5 Sensitivity Analyses

To test the robustness of our cohort definitions, we conducted two sensitivity analyses: 1) patients with a study duration longer than 12 hours, and 2) patients within the 2.5-97.5 percentiles of PBW. The first sensitivity cohort is intended to capture clinician behavior, which may require longer time scales, such as a shift change and/or patient rounds. The second sensitivity cohort aimed to evaluate a potential disproportionate effect of PBW outliers on linear trends. Neither sensitivity analyses yielded any difference in the regression results.

2.4 Discussion

We quantified the potential impact of patient characteristics and physician behaviors on the decision-making behavior for tidal volume selection by physicians for patients with ARDS and a novel control cohort. These analyses have allowed us to establish several important findings.

First, we corroborated prior studies' findings that height, hypoxemia severity, and ARDS documentation are associated with the use of lower tidal volumes in ARDS patients (9,23,27,33–35). We found no evidence for an association between other clinical factors - such as plateau pressure or patient weight - and lower tidal volume use, which have been identified as potential barriers to LTVV use in prior studies (15,23,27,33). These barriers may still have an impact at

the level of the individual physician, but the lack of generalizability to the entire physician population makes them suboptimal for future intervention targets at this site.

Second, our analyses provide additional insight into the previously established relationships between patient height and LTVV use (23,35). The most common lowest V_T reported in the ARDS and control cohorts were identical (450, 500, and 600 mL), and constitute 51% and 63% of the tidal volumes for the ARDS and control cohorts, respectively. This prevalence of a small number of lowest V_T suggests that clinicians are not following the canonical relationship between height and lung size originally established in animal studies (36), but instead use a simpler heuristic based on where the patient falls on the height spectrum of their particular gender. This theory is supported by the idea that humans select fast and frugal heuristics under time and knowledge limitations (37), which would both be present in clinical medicine and heightened in critical care. The utilization of this heuristic would translate to a general use of a lower standardized tidal volume ($\hat{V}_T$) for taller patients that is closer to or, in some cases, below the LTVV threshold; which would lead to our observation of the strong relationship between PBW and $\hat{V}_T$, despite that $\hat{V}_T$ already includes PBW in its calculation. Our findings are strong evidence that at least some delivery of LTVV may be unintentional - i.e., solely of a default V_T (450, 500, or 600 mL) - and not based on ARDS recognition or other clinical decision-making factors. While evidence for this physician behavior phenomenon has been previously reported in ARDS patient cohorts (27,35), our findings observe this behavior in a diverse control cohort, implying that the simpler tidal volume selection heuristic use is not restricted to ARDS patients alone.

Alternative explanations for the association between height and LTVV use in both cohorts include some physicians believing in LTVV for patients in the control cohort or some of those patients being classified by physicians as having ARDS. Supporting the latter possibility, 4.2% of control cohort patients had a physician-documented diagnosis of ARDS. Nonetheless, these alternative explanations are less likely because of the low ARDS documentation rate, low use of LTVV in both cohorts, and the strong correlation between PBW (gender neutral height) and $\hat{V}_T$ in both cohorts. Another alternative explanation is physicians using a non-linear relationship between tidal volume and PBW, but this is less likely given the low variability in chosen tidal volumes in both cohorts. Our results suggest that the relationship between PBW (gender neutral height) and $\hat{V}_T$ should be accounted for when measuring LTVV use and when designing implementation strategies to improve LTVV use.

This analysis has several limitations. First, it was conducted in a single metropolitan area, so we were unable to address regional or national differences. Second, we were limited to the patient data recorded in the EHR, which may be overlooked by physicians in lieu of other information, such as a visual estimation of height (38). Third, we did not evaluate physician knowledge of ARDS or LTVV, specifically the Berlin criteria and what standardized tidal volume threshold they believe qualifies as LTVV. Alternative LTVV thresholds may be justified by the layout of the ARDS Network tidal volume table, which appears to suggest that tidal volumes ranging from 4 to 8 mL/kg PBW qualify as LTVV (7). Finally, we acknowledge that it is possible that our application of the Berlin definition may have been biased, leading to misclassification of ARDS or control status—this could also explain why some patients classified as control were documented by their physicians as having ARDS.

CHAPTER 3:

Effectors of Tidal Volume Selection for ARDS Patients - LUNG SAFE

The work in this chapter is being prepared for publication with contributions from Luís A. Nunes Amaral, Curtis H. Weiss, and the LUNG SAFE consortium.

3.1 Introduction

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) dataset is one of the largest datasets on hypoxemic and ARDS patients. It includes data from 459 ICUs in 50 countries, collected over the course of four weeks in the winter of 2014. The primary goal of the analysis was to evaluate worldwide epidemiological trends in ARDS incidence, outcomes, and treatment. To accomplish this goal, each study site screened all ICU patients for acute hypoxemic respiratory failure, defined as all of the following: 1) $P_aO_2/F_IO_2 \leq 300$, 2) new pulmonary abnormalities on chest imaging, and 3) ventilatory support. If patients met the inclusion criteria, they were entered into the study and data were recorded on days 1, 2, 3, 5, 7, 10, 14, 21, and 28 with a standardized case report form (Appendix B) that collected chemistries, imaging, ventilator settings, ARDS adjunct therapies, and SOFA score. The presence of ARDS was determined post-data collection via computer algorithmic application of the Berlin Definition (9).

The initial analysis focused solely on patients that had developed ARDS on study day 1 or 2. It reported the prevalence of ARDS in the ICU population as 10.4% of ICU admissions and 23.4% of mechanically-ventilated patients. Additionally, the study reported on factors associated with lower standardized tidal volumes. Rather than a traditional cohort comparison study, which compares those that received LTVV and those that did not, the LUNG SAFE study evaluated

differences in tidal volume between different groups of patients split on disease severity, ventilator modes, and demographics. They report significant differences in standardized tidal volumes between: a) mild and severe hypoxemia and b) spontaneous and non-spontaneous ventilator modes. They also report a non-significant difference in standardized tidal volumes between those patients with and without a plateau pressure ≥ 30 cm H_20. Furthermore, they report no effect of clinician recognition on selected tidal volumes, which was assessed at study entry and end (Ch 4).

We sought to expand on this analysis and explore the external validity of our results from Chapter 2. We repeat our methods in this chapter on the LUNG SAFE dataset, developing a novel control cohort from the same screened population as the ARDS cohort in order to evaluate the effectors of tidal volume selection. Specifically, we seek to assess if the previously demonstrated relationships between standardized tidal volume and patient height, ARDS documentation, and hypoxemia hold at the international level or if these are specific to the Chicago hospitals.

3.2 Data Used in These Analysis

3.2.1 Cohort Development

The ARDS cohort used in this chapter includes all patients in the LUNG SAFE dataset designated as having ARDS (n=2707). The algorithm used in the LUNG SAFE study to define ARDS is as follows:

1. Presence of acute hypoxemic respiratory failure:
    a. $P_aO_2/F_IO_2 \leq 300$ mm Hg **AND**
    b. New pulmonary abnormalities on chest imaging **AND**

   c. Ventilatory support including continuous positive airway pressure (CPAP), expiratory positive pressure (EPAP), or positive end-expiratory pressure (PEEP) of 5 cm H_20 or more.

2. Acute time course:
   a. Onset of #1 within 1 week of initial insult **OR**
   b. Worsening respiratory symptoms within 1 week
3. Bilateral infiltrates: involvement of both lungs on chest imaging (x-ray or computed tomography)
4. Rule out of cardiac origin of respiratory distress

For the control cohort, we included all patients that met the requirements for acute hypoxemic respiratory failure (#1 in the above algorithm) and therefore study entry, but did not meet the additional criteria (#2-4) for ARDS (n=1261). The control cohort represents a group of patients for which LTVV was not indicated. This study was designated by the Northwestern University Institutional Review Board as exempt on July 14, 2017 (STU 00205441).

3.2.2 Data Acquisition

Data were collected on days 1, 2, 3, 5, 7, 10, 14, 21, and 28 with a standardized case report form (Appendix B) as close to 10 am local time as possible (9). Site investigators were responsible for the integrity of the data, which underwent quality control screening to evaluate for outliers and errors (9). Data availability for each variable is available in Supp Tables 3 and 4. All data used in my thesis work were managed and maintained by the LUNG SAFE consortium.

Per the secondary analysis agreement, no data were released to me and all analysis scripts were sent to and implemented by a consortium-appointed data steward.

3.2.3 Significance Testing

As in Chapter 2, we used $\alpha = 0.01$ and applied the Bonferroni correction for multiple hypotheses. In the regression analyses (see Section 3.3), there were 111 comparisons where $\hat{V}_T$ was the dependent variable, thus we set $p < 0.00009$ (0.01/111) as the threshold for statistical significance for these analyses. For the covariate analyses, the threshold was $p < 0.001$ (0.01/10).

3.3 Potential Factors in Tidal Volume Selection

3.3.1 Factors assessed

We included all factors from the previous analysis (Ch 2) as independent variables in OLS regressions, except for admitting ICU and bilateral infiltrates (first $P_aO_2/F_IO_2 \leq 300$, lowest P_aO_2/F_IO_2, highest P_{plat}, patient weight at ICU admission, ARDS documentation in the patient chart, and patient height [PBW]). Admitting ICU was not an available data point. The bilateral infiltrates variable was instead replaced with involved chest x-ray quadrants (ranged 0 to 4). Additionally, ARDS documentation was handled differently. During data collection, site investigators were asked about the possible presence of ARDS in patients at two time points: study entry and study end. At study entry, site investigators were asked to select all potential sources of the patient's hypoxemia from a list that included ARDS. At study end, site investigators were asked if the patient ever had ARDS during their hospital course. Thus, we

used three documentation variables: documentation beginning (study entry), documentation end (study end), and documentation both (ARDS indicated at both entry and end).

We included four additional variables that were available in the LUNG SAFE dataset: Sequential Organ Failure Assessment (SOFA) score, region, ventilator modality, and study age. Region refers to the geographical region the patients were located in (Africa, Asia, Europe, North America, Oceania, or South America). Ventilator modality refers to the ventilator modality that the patient was documented as being on most often via the daily collection sheet. Study age measures at what point during the study a patient was enrolled and is calculated as the number of days that have passed between the start of data collection at a particular site and the enrollment of a specific patient. Finally, due to the entry and end assessment of ARDS documentation, several variables were assessed in the format of: study entry, study end, most severe measurement during study. These include: P_aO_2/F_IO_2, chest x-ray quadrants, plateau pressure, and SOFA.

3.3.2 Univariable analysis

The relationship between each factor and $\hat{V}_T$ was investigated through univariable OLS regressions for the ARDS and control cohorts (Table 7). Standardized tidal volume ($\hat{V}_T$) decreased toward the LTVV threshold with worsening hypoxemia (lowest P_aO_2/F_IO_2) in the ARDS cohort, but not in the control (Figure 6, Table 7). Standardized tidal volumes decreased with increasing height (PBW) in both cohorts ($p<0.00009$, Figure 7, Table 7). Additionally, in the ARDS cohort, standardized tidal volumes decreased with increasing quadrants on chest x-ray

(entry, end, highest), ARDS documentation (beginning, end, both), and higher plateau pressure (highest) ($p<0.00009$, Table 7).

Table 7: Predictors of lowest $\hat{V}_T$ (mL/kg PBW) (β-coefficient [95% CI])

Factor	ARDS univariable	ARDS multivariable	Control univariable	Documented** univariable
Predicted body weight	**-4.2*** **[-4.7,-3.8]**	**-4.1*** **[-4.5, -3.6]**	**-7.6*** **[-8.5, -6.7]**	**-4.2*** **[-4.9, -3.4]**
P_aO_2/F_IO_2 ratio				
Entry	**0.64*** **[0.35, 0.93]**		0.26 [-0.23, 0.75]	0.72 [0.18, 1.3]
End	0.10 [-0.38, 0.58]		-0.58 [-1.5, 0.31]	-0.40 [-1.2, 0.37]
Lowest	**1.3*** **[0.94, 1.6]**	**1.2*** **[0.90, 1.53]**	0.54 [0.02, 1.1]	**1.4*** **[0.81, 2.0]**
Documentation				
Entry	**-0.39*** **[-0.54, -0.24]**		-0.12 [-0.57, 0.33]	
End	**-0.41*** **[-0.56, -0.26]**		-0.43 [-0.72, -0.14]	
Both	**-0.39*** **[-0.55, -0.23]**	**-0.33*** **[-0.48, -0.18]**	-0.59 [-1.1, -0.1]	
P_{plat}				
Entry	-1.0 [-1.7, -0.34]		-0.28 [-1.1, 0.58]	-0.54 [-1.5, 0.40]
End	-1.2 [-1.9, -0.47]		-0.57 [-1.5, 0.39]	-0.8 [-1.6, 0.084]
Highest	**-1.5*** **[-2.3, -0.87]**		-1.1 [-2.1, -0.19]	-1.2 [-2.1, -0.25]
Chest imaging quadrants				
Entry	**-0.49*** **[-0.65, -0.33]**		-0.42 [-0.79, -0.05]	-0.79 [-1.2, -0.36]
End	**-0.69*** **[-1.0, -0.39]**		-0.56 [-1.2, 0.05]	-0.43 [-0.96, 0.11]
Highest	**-1.4*** **[-1.7, -1.1]**		-0.77 [-1.2, -0.36]	**-1.5*** **[-2.1,-0.86]**
SOFA				
Entry	0.1		0.21	0.57

	[-0.44, 0.64]	[-0.53, 0.96]	[-0.31, 1.5]
End	0.0 [-0.53, 0.58]	0.95 [0.04, 1.9]	0.52 [-0.43, 1.5]
Highest	-0.39 [-0.88, 0.09]	0.25 [-0.52, 1.0]	0.23 [-0.6, 1.1]
ICU admission weight	-1.2 [-2.0, -0.51]	-0.52 [-1.8, 0.78]	-2.7 [-4.1, -1.3]
Study Age	-0.38 [-1.3, 0.56]		0.29 [-0.89, 1.5]
Region	-0.8 [-1.1, -0.52]	1.7 [0.86, 2.5]	
Modality	0.18 [-0.15, 0.50]	0.02 [-0.53, 0.56]	-0.51 [-1.1, 0.13]

* ***p* < 0.00009** ** Documentation both
Empty cells indicate category was not used due to data being unavailable or not relevant.

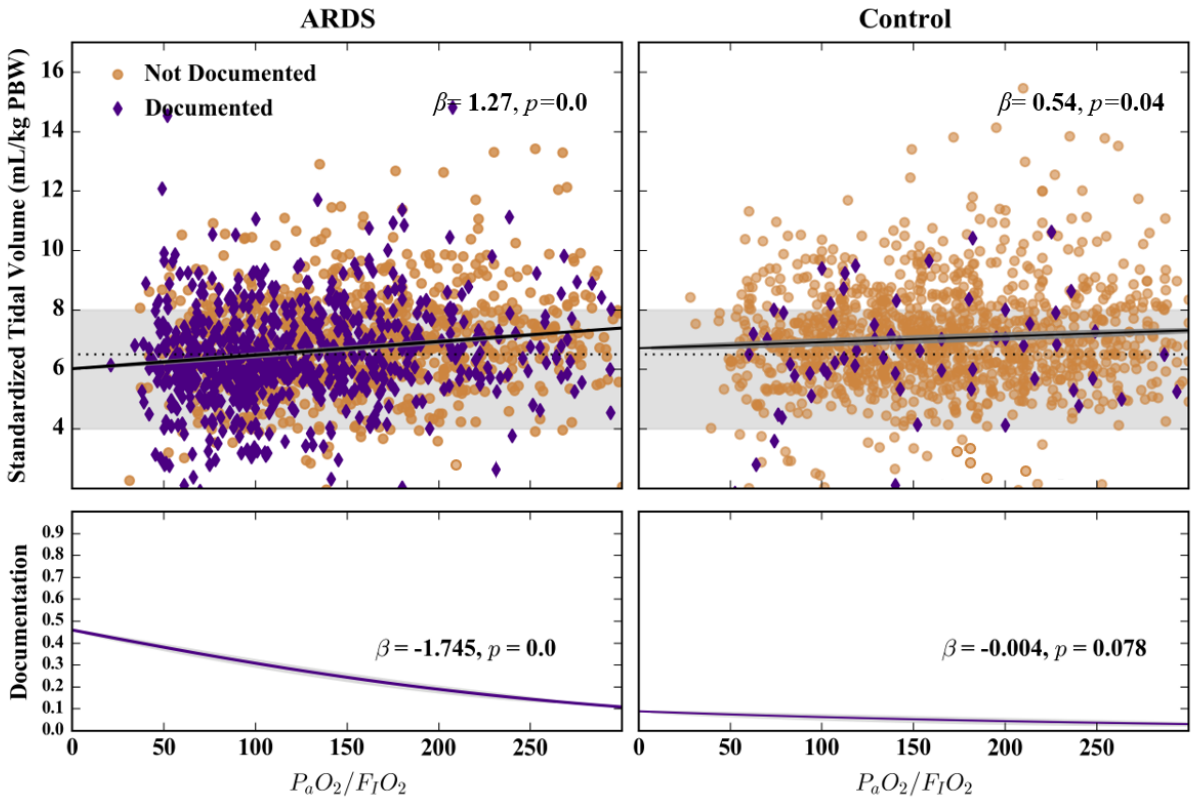


Figure 6: Effects of lowest P_aO_2/F_IO_2 ratio on standardized tidal volume ($\hat{V}_T$) and ARDS documentation in ARDS and control cohorts.
Top panels show patients with ARDS documented in their chart (purple diamonds) and non-documented patients (tan circles). Gray areas indicate LTVV range from current guidelines(13),

with dashed line at 6.5 mL/kg PBW from currently recommended threshold. Solid lines show linear ($\hat{V}_T$) and logistic (documentation) fits for scatter plot data (shaded regions, 95% confidence bands). Reported beta coefficients are for standardized inputs.

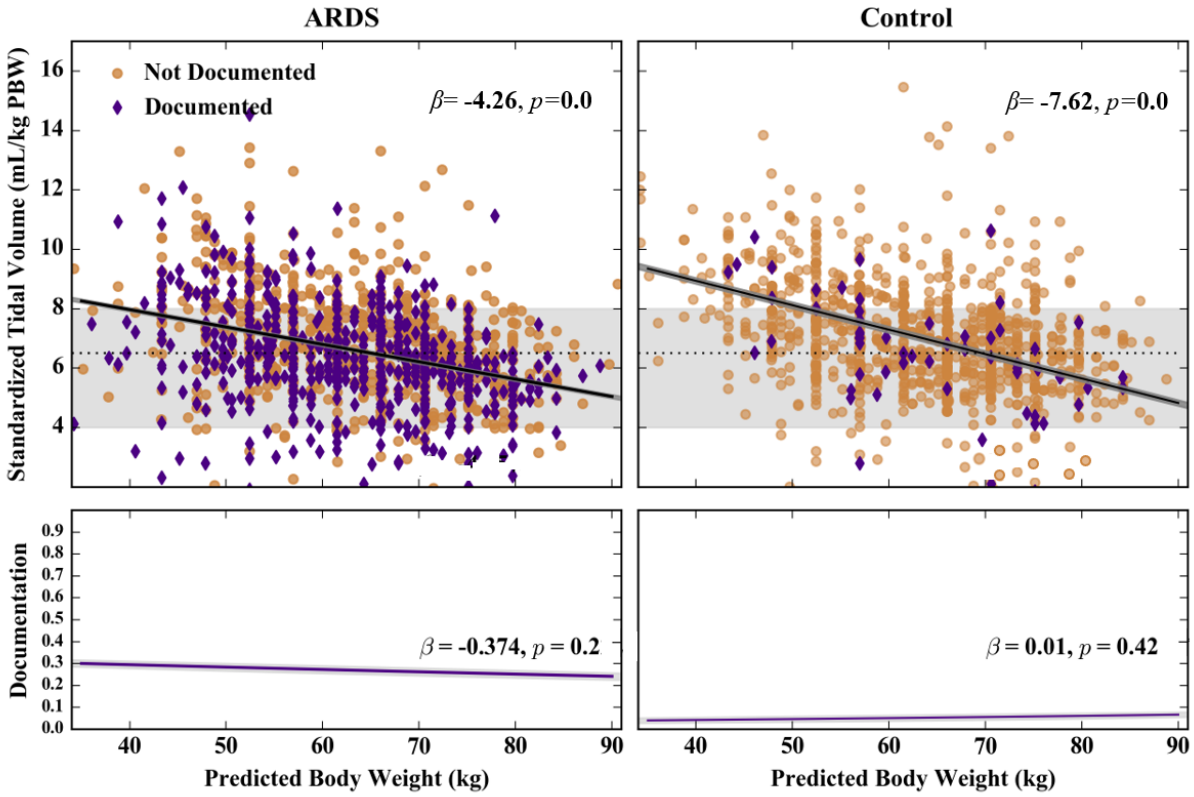


Figure 7: Effects of predicted body weight (gender neutral height) on standardized tidal volume ($\hat{V}_T$) and ARDS documentation in ARDS and control cohorts.
Top panels show patients with ARDS documented in their chart (purple diamonds) and non-documented patients (tan circles). Gray areas represent LTVV range from current guidelines(13), with dashed line at 6.5 mL/kg PBW at current recommended threshold. Solid lines show linear ($\hat{V}_T$) and logistic (documentation) fits for scatter plot data (shaded regions, 95% confidence bands). Reported beta coefficients are for standardized inputs.

3.3.4 Covariate Analysis

The factors demonstrating a significant association with $\hat{V}_T$ in the univariable analyses were evaluated for covariance with each other using OLS regression. Eight factors were evaluated for covariance: lowest P_aO_2/F_IO_2, PBW, chest x-ray quadrants (entry, end, highest),

ARDS documentation (entry, end), and P_{plat} (highest). Lowest P_aO_2/F_IO_2, highest chest x-ray quadrants, chest x-ray quadrants at study end, highest P_{plat}, and ARDS documentation at study end were all covariate with each other ($p<0.00009$). ARDS documentation at study entry was correlated with chest x-ray quadrants at study entry. PBW was not associated with any severity markers or documentation (Figure 7), which was anticipated.

To test the strength of the documentation covariant associations, we split the ARDS and control cohorts into three major subgroups (ARDS non-documented, control non-documented, and pooled documented) and then repeated the univariable analysis (Figure 8, Table 7, Table 8). We used all three definitions of documentation. In all documentation subgroups, lower $\hat{V}_T$ were associated with increasing patient height (PBW), highest quadrants on chest x-ray, and lowest P_aO_2/F_IO_2 ($p<0.00009$, Table 8, Supp Tables 5 and 6). Chest x-ray quadrants at study entry were associated with lower $\hat{V}_T$ in the documentation entry and end subgroups, but not in the documentation both subgroup ($p<0.00009$, Table 8, Supp Tables 5 and 6). ICU admission weight was associated with lower $\hat{V}_T$ in the documentation end subgroup only. PBW was associated with lower $\hat{V}_T$ in all versions of the ARDS non-documented and control non-documented subgroups ($p<0.00009$, Table 8, Supp Tables 5 and 6). No other factors were correlated with lower $\hat{V}_T$ in the end and both versions of the ARDS non-documented and control non-document subgroups. Chest x-ray quadrants at study entry and lowest P_aO_2/F_IO_2 were associated with lower $\hat{V}_T$ in the entry version of ARDS non-documented subgroup ($p<0.00009$, Supp Tables 5 and 6).

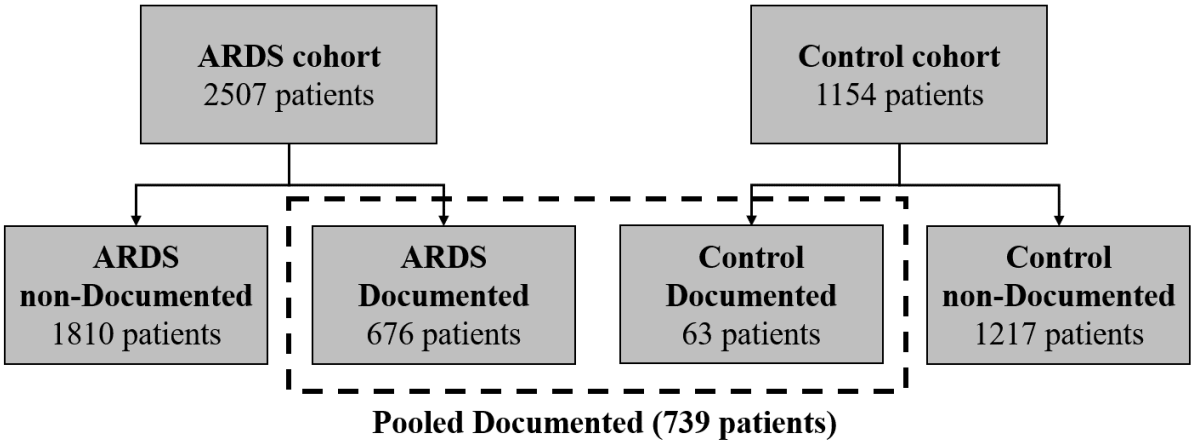


Figure 8: Cohort and subgroup definitions using the both definition of documentation

Table 8: Predictors of lowest standardized tidal volume (mL/kg PBW) in non-documented subgroups (β-coefficient [95% CI])

Factor	ARDS non-documented univariable	Control non-documented univariable
Predicted body weight	**-4.0*** **[-4.7, -3.2]**	**-6.8*** **[-7.8, -5.8]**
P_aO_2/F_IO_2 ratio		
Entry	0.37 [-0.11, 0.85]	0.25 [-0.27, 0.77]
End	0.35 [-0.57, 1.3]	-0.43 [-1.4, 0.51]
Lowest	0.86 [0.33, 1.4]	0.43 [-0.14, 1.0]
P_{plat}		
Entry	-0.95 [-1.8, 0.33]	-0.21 [-1.3, 0.85]
End	-0.95 [-2.0, 0.06]	0.06 [-1.0, 1.2]
Highest	-1.1 [-2.1, -0.15]	-0.28 [-1.3, 0.80]
Chest imaging quadrants		
Entry	0.0 [-0.30, 0.30]	-0.13 [-0.56, 0.29]

End	-0.34 [-0.93, 0.25]	-0.23 [-0.88. 0.43]
Highest	-0.51 [-1.1, 0.04]	-0.56 [-1.0, -0.09]
SOFA		
Entry	0.11 [-0.85, 1.1]	-0.47 [-1.3, 0.33]
End	-0.13 [-1.1, 0.84]	0.31 [-0.75, 1.4]
Highest	-0.18 [-1.0, 0.65]	-0.47 [-1.3, 0.39]
ICU admission weight	-0.33 [-1.3, 0.65]	-0.70 [-2.1. 0.70]
Study Age	-1.53 [-2.9, -0.16]	-1.6 [-3.0, -0.22]
Region		
Modality	0.25 [-0.27, 0.77]	0.03 [-0.58, 0.65]

[*] ***p* < 0.00009**

Empty cells indicate category was not used due to data being unavailable or not relevant.

3.3.5 Multivariable analysis

Significant factors from the univariable analyses were included in multivariable regressions comprised of all possible linear combinations of the factors and appropriate interaction terms. Due to the limited data availability of chest x-ray quadrant data (Supp Tables 3 and 4) and its covariance with lowest P_aO_2/F_IO_2, the factors included in the multivariable analysis were lowest P_aO_2/F_IO_2, PBW, and documentation both. We chose documentation both rather than entry or end because it was the strictest version of documentation and thus, the closest to our previous analysis (Chapter 2), which required a documented diagnosis of ARDS by an attending physician in the patient's chart. The documentation question at study entry was not specifically about ARDS, but about hypoxemia with ARDS as one of many selectable answers.

The documentation question at the end was more specific, but phrased in a reflective nature that may not reflect the physician's recognition state during the disease course.

Seven models were constructed using all combinations of PBW, documentation, and lowest P_aO_2/F_IO_2 as independent variables and a lowest P_aO_2/F_IO_2 Documentation interaction term (Table 9). In each model, the continuous variables were scaled between 0 and 1. AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) were calculated for each model to select the "best" model. AIC and BIC were calculated using the python package statsmodels (version 0.6.1).

Table 9: Multivariable models of lowest standardized tidal volume (mL/kg PBW) in ARDS cohort

Model	AIC	BIC
$\hat{V}_T$ ~ PBW	9868	9880
$\hat{V}_T$ ~ lowest_PF	10110	10122
$\hat{V}_T$ ~ Documentation	10142	10154
$\hat{V}_T$ ~ PBW + lowest_PF	9803	9820
$\hat{V}_T$ ~ PBW + Documentation	9840	9858
$\hat{V}_T$ ~ PBW+ lowest_PF +Documentation	**9786**	**9809**
$\hat{V}_T$ ~ PBW + lowest_PF + Documentation + Documentation:lowest_PF	9788	9817

AIC: Akaike Information Criterion for goodness of fit
BIC: Bayesian Information Criterion for goodness of fit

In the ARDS cohort, the multivariable regression model that included PBW, lowest P_aO_2/F_IO_2, and documentation as independent variables with no interaction terms resulted in the lowest AIC and BIC (Table 9). In this model, all independent variables were significantly correlated with $\hat{V}_T$ ($p < 0.00009$). Of these variables, PBW had the greatest effect on $\hat{V}_T$ (β -4.1, 95% CI -4.5 – -3.6). For the control cohort, only PBW was associated with $\hat{V}_T$, and therefore no multivariable analysis was performed.

3.3.6 Sensitivity analyses

As a sensitivity analysis, we restricted the cohort to only patients that were on ventilator modes in which the tidal volumes given were controlled by the ventilator (n=407 for ARDS, n=213 for control) and repeated all analyses. With the exception of the study end documentation subgroup, the only factor significantly associated with $\hat{V}_T$ was PBW in all other cohorts and subgroups (Supp Table 6). In the study end documentation subgroup, PBW and highest chest x-ray quadrants were correlated with $\hat{V}_T$ (Supp Table 6).

3.4 Discussion

In order to test the external validity of our findings in Chapter 2, we repeated our methods on the larger, international LUNG SAFE dataset. The secondary analysis corroborated all of our major conclusions from the Chicago-based assessment. First, as expected, we find that hypoxemia severity and ARDS documentation are associated with lower standardized tidal volumes in the ARDS cohort, but not in the control cohort. We also confirm the relationship between hypoxemia severity and ARDS documentation. These results support prior evidence that ARDS under-recognition is a barrier to LTVV use (9,18–21,24,27,33,34,39,40) and more hypoxemic patients are easier to recognize (9,27). Second, we confirm our unexpected result of taller heights (higher PBW) with lower standardized tidal volumes in both the ARDS and control cohorts. The reproducibility of this result in an international cohort further reinforces our previous theory of clinicians opting for a simpler heuristic when estimating tidal volumes for

ventilated patients. Overall, this secondary analysis provides evidence that the conclusions of our previous analysis are generalizable to other sites and conditions, particularly that PBW should be considered when estimating LTVV use.

The results of this chapter differed from our Chicago hospital analysis in two cases. First, hypoxemia severity was still associated with lower standardized tidal volumes in all documentation subgroups, which was not the case in the Chicago hospitals. There are a few possible explanations for this difference. First, our Chicago hospital analysis could be underpowered to capture this relationship, as it had significantly less ARDS patients (2507 vs 361). Second, the relationship between hypoxemia severity and standardized tidal volumes could be stronger in certain ventilator modalities. Our Chicago hospital analysis was restricted to volume assist controlled patients only. While the relationship between hypoxemia severity and standardized tidal volumes was not present in the VAC subgroup sensitivity analysis, the VAC subgroup is smaller than our Chicago cohort. Third, the same best fit multivariable model was selected in both the Chicago hospital and the LUNG SAFE datasets, but the strength of the associations for each variable differed. Hypoxemia severity and documentation maintained a significant association with standardized tidal volumes in the LUNG SAFE model, which was not the case for the Chicago hospital dataset. It is likely that this is also the result of the Chicago hospital analysis being underpowered.

Finally, this analysis has its own unique limitations. First, the LUNG SAFE dataset is not a complete medical record pull, as the Chicago hospital dataset was. Patients only have a single data collection per day around 10 am on a subset of their length of stay. It is possible that changes in tidal volumes or other important variables were missed in the interim. Second, while

we found no relationship between region and tidal volumes, regional differences in tidal volume effectors could still exist. By combining all regions together, it is possible that some effectors balanced each other out, resulting in no association with tidal volume selection.

Lastly, there are two additional analyses that were performed in the Chicago hospital analysis that were not included in the LUNG SAFE assessment. First, we did not perform a 5-95% sensitivity analysis to account for outliers in PBW. However, the LUNG SAFE dataset has already undergone quality control screening for outliers, and thus the presence of outliers is less likely to be an issue. Second, we did not evaluate the most common tidal volumes (non-standardized) in the LUNG SAFE cohorts, which would have further informed our hypothesis of unintentional LTVV use as the result of a default tidal volume.

CHAPTER 4: Models of ARDS Recognition

Portions of the work in this chapter was published with contributions from Adam R. Pah, Hanyu Shi, Sanjay Mehrotra, Stephen D. Persell, Shayna Weiner, Richard G. Wunderink, Luís A. Nunes Amaral, and Curtis H. Weiss.

All portions of the work in this chapter labeled as 'LUNG SAFE' are in preparation for publication with contributions from Luís A. Nunes Amaral, Curtis H. Weiss, and the LUNG SAFE consortium.

4.1 Introduction

A hallmark of healthcare quality improvement is the consistent measurement of an outcome (ex: number of infections, checklist use, etc.). In the case of LTVV use for ARDS, measurement of an outcome is challenging for multiple reasons. First, delivering LTVV is a two-step process requiring the recognition of ARDS, and then the selection and adjustment tidal volumes based on patient response. Both steps in this process can be affected by patient characteristics, as we and others have demonstrated (9,16,18,20,21,23,24,26–28,34). Second, while previous studies have employed a LTVV threshold or physician documentation of ARDS as surrogates for physician recognition of ARDS, these proxies can have limitations.

The gold standard for measuring physician recognition of ARDS would be to directly ask physicians if a patient has ARDS. There are advantages and disadvantages to this approach. On one hand, it mitigates the issue of subjective reporting by asking a clinician directly about a specific patient. Furthermore, when paired with patient care data collection, the evaluation of potential effectors of clinician recognition is more robust than one can achieve with a traditional survey. Conversely, there are some key limitations in this methodology for evaluating clinician recognition of ARDS. First, this approach is labor and resource intense as well as disruptive to

clinical practice, making it an infeasible solution for widespread implementation. Second, this approach intensifies the issue of the observer effect, which is largely unavoidable with prospective data collection that includes clinical judgement questions. Asking a question specifically about ARDS can introduce the idea that ARDS is a focus of the data collection, even if clinicians were not previously aware. This knowledge in turn can make them more likely to diagnose ARDS than they would otherwise. Third, this approach primes clinicians. Once a clinician has collected all the data necessary to diagnose ARDS for a study, they will potentially integrate that process into their everyday practice, leading to an inflated measured ARDS recognition rate.

An alternative method is to collect physician documentation of ARDS or LTVV delivery from electronic health records (EHR). While this approach is more scalable, it suffers from the drawback that physicians may recognize ARDS but not document it in their notes, or choose not to deliver LTVV despite this recognition. Furthermore, as we demonstrated in previous chapters, tidal volume selection can be affected by patient characteristics, such as height, that are a result of being mechanically ventilated for hypoxemia rather than an ARDS diagnosis.

In order to try to overcome the limitations of these approaches, we sought to use data science methods on EHR data and build an estimate of physician recognition of ARDS that could be widely implemented. We use tidal volume selection as a proxy for physician decision-making behavior and build two models of physician recognition of ARDS. In these models, we account for the effectors of tidal volume selection discussed in previous chapters. Given this standardization, our approach allows for the comparison of clinician recognition in our two rather different datasets.

4.2 Data Used in These Analyses

4.2.1 Chicago hospitals

In the Chicago hospitals, documentation was assessed by manual chart review of attending physicians' notes. A patient was considered to be documented if any attending caring for them discussed the possibility of ARDS or ALI (Acute Lung Injury, former name for ARDS) in one of their notes.

4.2.2 LUNG SAFE

Site investigators were asked about the possible presence of ARDS in patients at two time points: study entry and study end. At study entry, site investigators were asked to select all potential sources of the patient's hypoxemia from a list that included ARDS. At study end, site investigators were asked if the patient ever had ARDS during their hospital course. A patient was considered documented in our analysis if the site investigator answered positively at both time points. As part of a substudy, all site investigators were offered additional training on chest x-ray interpretation for diagnosis of ARDS.

4.3 Models of Recognition

We used two approaches to characterize physician recognition of ARDS. To this end, we split the two main cohorts (ARDS and control) into three major subgroups: 1) ARDS non-documented, 2) Control non-documented, and 3) Pooled documented (Figures 5, 8). All patients in the pooled documented subgroup met the criteria for documentation, which was dependent on the dataset. All patients in the non-documented subgroups do not meet these

criteria. Our two approaches are based on the assumption that the physician behaviors observed in the ARDS non-documented subgroup represent a mixture of patient-care scenarios in which patients are either recognized by their physician as having ARDS or not recognized as having ARDS. If a patient in the ARDS non-documented subgroup was recognized by their physician as having ARDS, we assume the physician tidal volume selection would be the same as the tidal volume selection seen in the pooled documented subgroup. If a patient in the ARDS non-documented subgroup was not recognized as having ARDS, we assume the physician tidal volume selection would be the same as for control non-documented subgroup. Therefore, the non-documented ARDS subgroup patients can be viewed as a mixture of the pooled documented subgroup and the non-documented control subgroup.

4.3.1 Naïve Bayes

We used a Naïve Bayes model for classifying patients in the non-documented ARDS subgroup as either recognized or unrecognized by their care teams. We used multivariate kernel density estimation (KDE) to characterize the PBW vs $\hat{V}_T$ clusters for the pooled documented and non-documented control subgroups (Figures 9, 11, 13). Classifying a patient in the non-documented ARDS subgroup as recognized or unrecognized was based on the following conditional probabilities leveraging Bayes Theorem:

$$\frac{P(documented|PBW,\hat{V}_T)}{P(control|PBW,\hat{V}_T)} = \frac{P\left(PBW,\hat{V}_T\middle|documented\right) * P(documented)}{P\left(PBW,\hat{V}_T\middle|control\right) * P(control)}$$

In the absence of a reasonable prior for *P(documented)* and *P(control)*, we assign each term 0.5, assuming equal probability of belonging or not belonging to each subgroup. We were able to define a boundary in the PBW vs $\hat{V}_T$ space where *P(documented | PBW,* $\hat{V}_T$*) = P(control | PBW,* $\hat{V}_T$*)* (Figures 9,11,13, black line). Below this boundary, *P(documented | PBW,* $\hat{V}_T$*)* is

greater than $P(control \mid PBW, \hat{V}_T)$ and the patient was classified as 'recognized'. Above this boundary, $P(documented \mid PBW, \hat{V}_T)$ is less than $P(control \mid PBW, \hat{V}_T)$ and the patient was classified as 'unrecognized'. Due to the size discrepancy between the non-documented control and pooled documented subgroups, we bootstrapped (100 iterations) the "non-documented" control subgroup and repeated this analysis to produce confidence bands (Figures 10, 12, 14).

4.3.1.1 Chicago hospital results

The KDE clusters for the pooled documented and control non-documented subgroups as well as the estimated probability equality line are shown in Figure 9. The peaks of male and female PBW (gender neutral height) frequency (Figure 9, bottom panel) align with the two peaks in the pooled documented subgroup (Figure 9, middle panel). Physician recognition of ARDS calculated for each ARDS severity category was: mild, 26%; moderate, 32%; severe, 57% (Table 10).

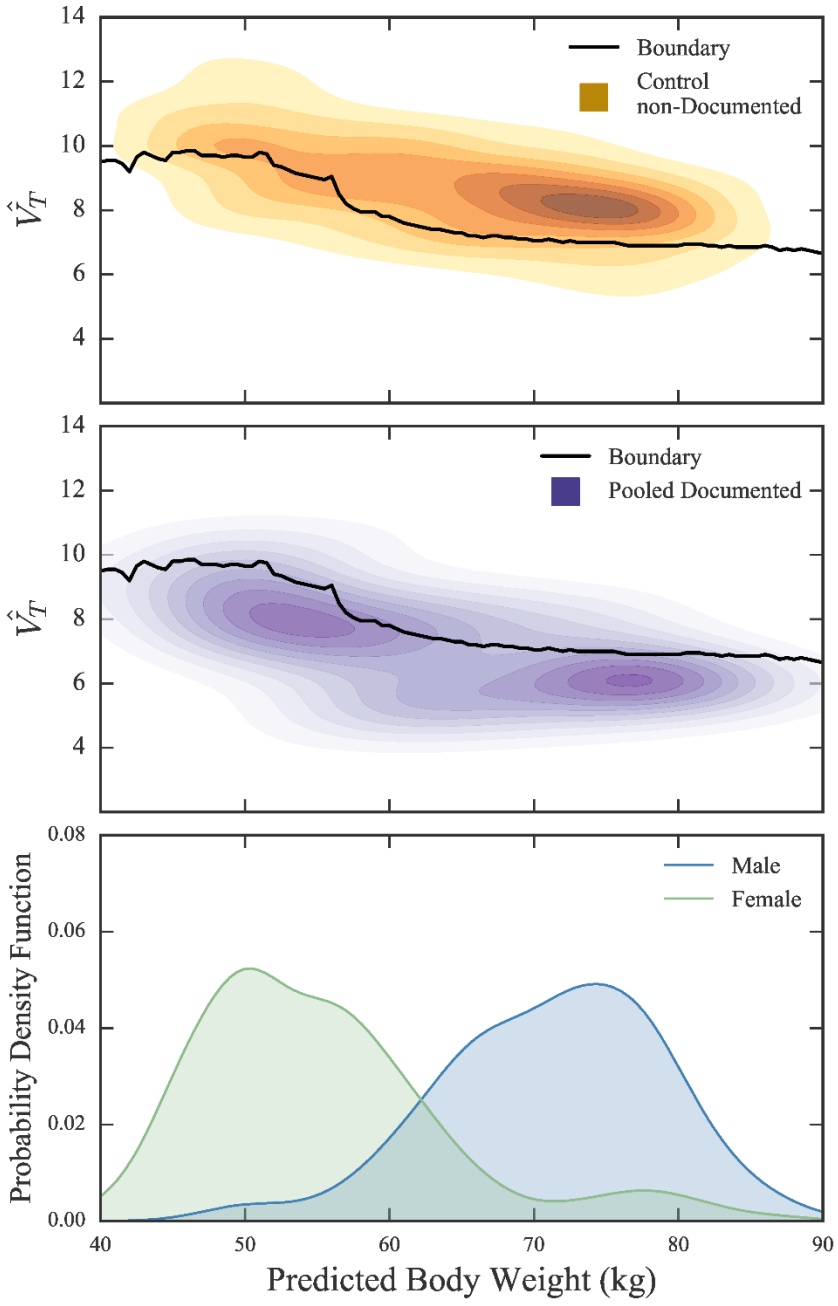


Figure 9: Kernel Density Estimation for control non-documented and pooled documented patients in Chicago hospitals.
Heatmaps of kernel density estimated probability density for data from control non-documented (yellow, top panel) and documented (purple, middle panel) subgroups. Solid line shows

boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line). (Bottom panel) Normalized gender frequency across PBW for combined patient population of documented and control non-documented. Male and female peaks align with high density regions in above heatmaps.

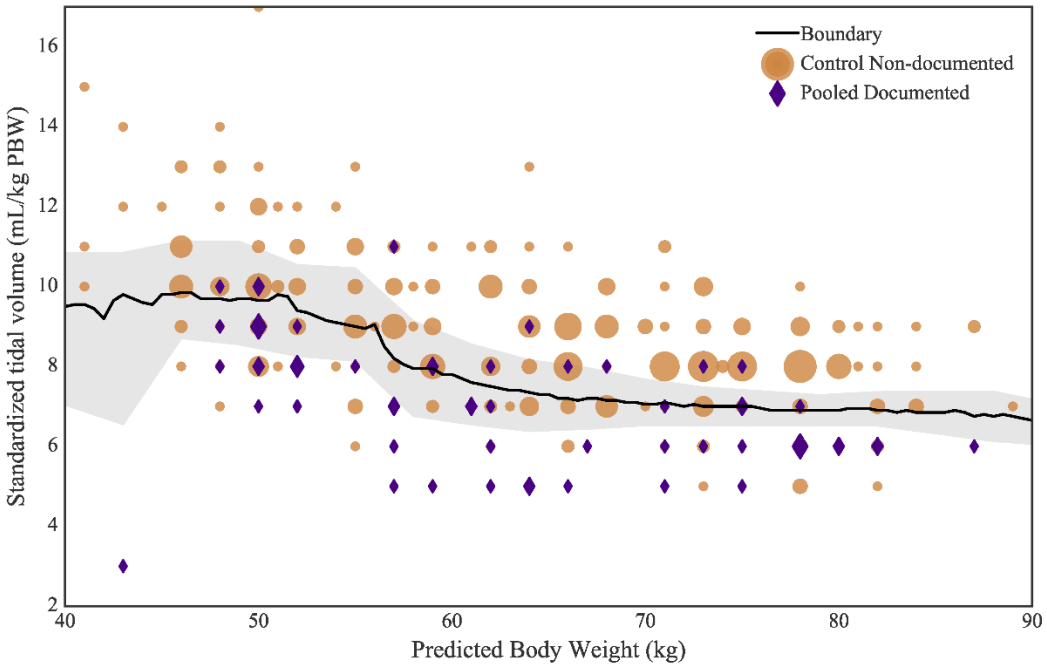


Figure 10: Naïve Bayes boundary between recognized and unrecognized regions with 95% confidence intervals from bootstrapping
Scatter plot shows pooled documented patients (purple diamonds) and control non-documented patients (tan circles). Size of marker represents number of data points. Solid line shows boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line) with 95% confidence bands from bootstrapped data (shaded region).

Table 10: Rates of physician recognition of ARDS by hypoxemia severity in Chicago hospitals

Severity	**ARDS Documented**		**Recognition**	
	n	%	Approach #1: Naïve Bayes (%)	Approach #2: Mixture Model (% [99% CI])
Mild $200 < P_aO_2/F_IO_2 \leq 300$	5	6	26	22 [9, 42]
Moderate	8	7	32	34

$100 < P_aO_2/F_IO_2 \leq 200$				[19, 49]
Severe $P_aO_2/F_IO_2 \leq 100$	24	30	57	67 [41, 100]

4.3.1.2 LUNG SAFE results

The KDE clusters for the pooled documented and control non-documented subgroups as well as the estimated probability equality line are shown in Figure 11. Physician recognition of ARDS calculated for each ARDS severity category was: mild, 54%; moderate, 64%; severe, 82% (Table 11).

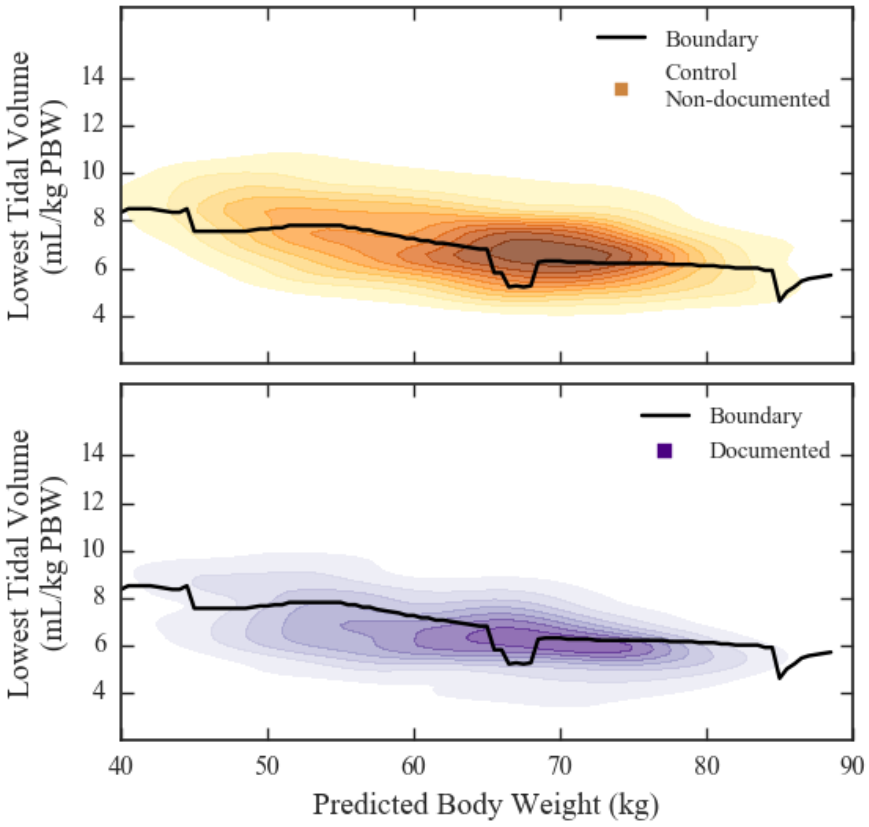


Figure 11: Kernel Density Estimation for control non-documented and pooled documented patients in LUNG SAFE.
Heatmaps of kernel density estimated probability density for data from control non-documented (yellow, top panel) and documented (purple, bottom panel) subgroups. Solid line shows boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line).

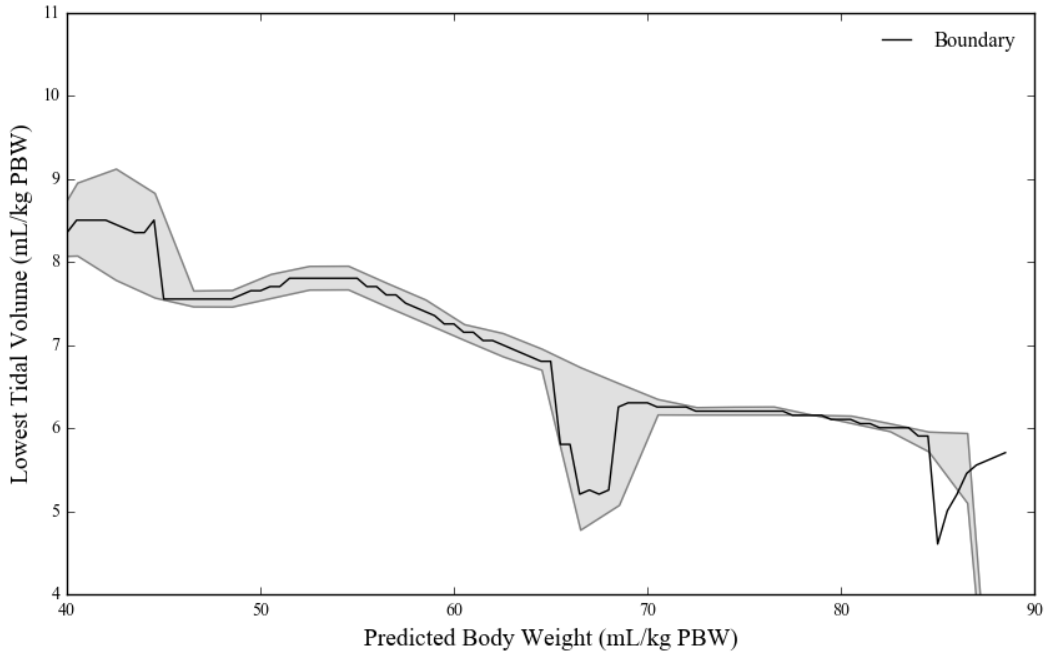


Figure 12: Naïve Bayes boundary between recognized and unrecognized regions with 95% confidence intervals from bootstrapping – LUNG SAFE cohort.
Solid line shows boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line) with 95% confidence bands from bootstrapped data (shaded region).

Table 11: Rates of physician recognition of ARDS by hypoxemia severity in LUNG SAFE

Severity	ARDS	Recognition

	Documented		Naïve Bayes (%)	LUNG SAFE study (9)
	n	%		(% [95% CI])
Mild $200 < P_aO_2/F_IO_2 \leq 300$	92	24	54	51.3 [47.5, 55.5]
Moderate $100 < P_aO_2/F_IO_2 \leq 200$	347	40	64	65.3 [62.4, 68.1]
Severe $P_aO_2/F_IO_2 \leq 100$	353	70	82	78.5 [74.8, 81.8]

For the VAC subgroup, KDE clusters for the pooled documented and control non-documented subgroups as well as the estimated probability equality line are shown in Figure 13. The overall documentation and recognition rates are lower for the VAC subgroup than the full cohort (Table 12). Physician recognition of ARDS calculated for each ARDS severity category was: mild, 48%; moderate, 57%; severe, 65% (Table 12).

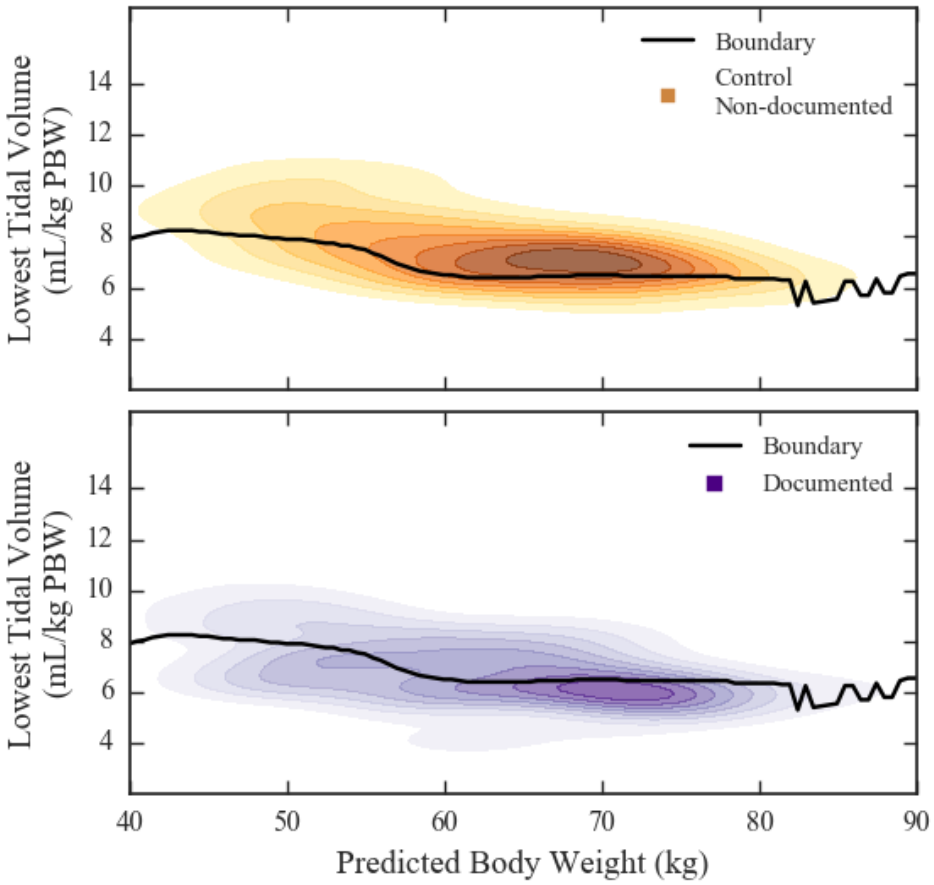


Figure 13: Kernel Density Estimation for control non-documented and pooled documented patients in LUNG SAFE (VAC subgroup)
Heatmaps of kernel density estimated probability density for data from control non-documented (yellow, top panel) and documented (purple, bottom panel) subgroups. Solid line shows boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line).

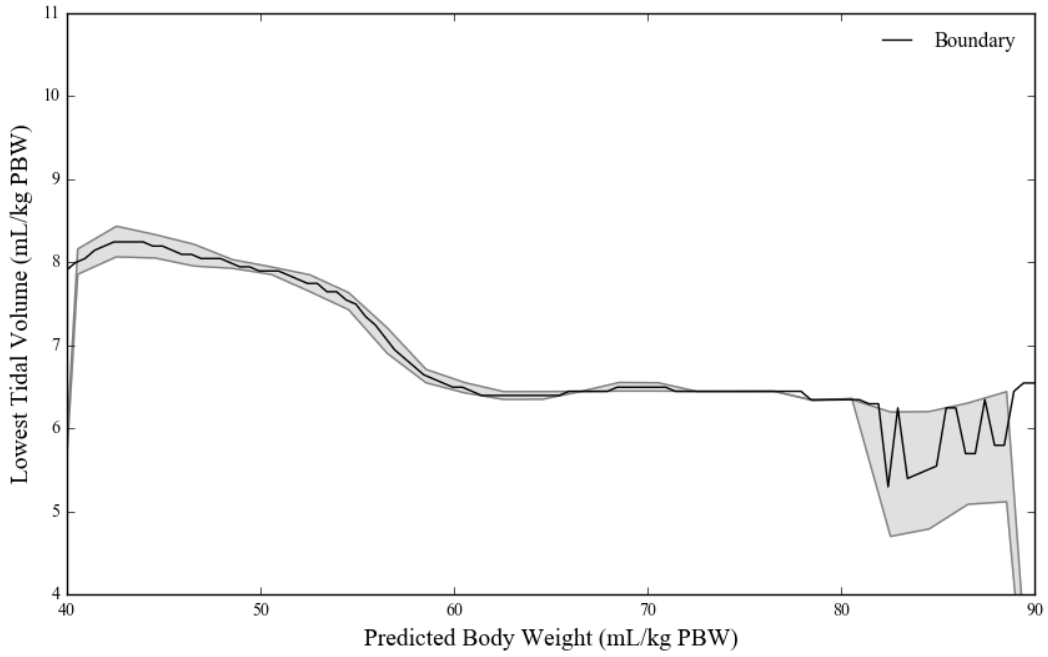


Figure 14: Naïve Bayes boundary between recognized and unrecognized regions with 95% confidence intervals from bootstrapping – LUNG SAFE cohort (VAC subgroup)
Solid line shows boundary separating region with unequal probability of belonging to documented (below line) and non-documented control (above line) with 95% confidence bands from bootstrapped data (shaded region).

Table 12: Rates of physician recognition of ARDS by hypoxemia severity in LUNG SAFE VAC subgroup

Severity	**ARDS Documented**		**Recognition** Naïve Bayes (%)
	n	%	
Mild $200 < P_aO_2/F_IO_2 \leq 300$	18	29	48
Moderate $100 < P_aO_2/F_IO_2 \leq 200$	53	42	57
Severe $P_aO_2/F_IO_2 \leq 100$	69	60	65

4.3.2 Mixture Model

In the second model, we incorporate $\hat{V}_T$, hypoxemia severity (lowest P_aO_2/F_IO_2), and PBW with the goal of calculating the fraction of recognized patients in each Berlin Definition ARDS severity category (mild, moderate, and severe).[5] To calculate physician recognition of ARDS, we estimated the fraction of patients recognized by physicians in each severity category ($f^i_{recognition}$) from the following set of equations:

$$P_{ARDS}(\hat{V}_T, PBW\ data \mid severity) = f^i_{recognition}\ P_{diagnosed\ ARDS}(\hat{V}_T, PBW\ data) + (1 - f^i_{recognition})\ P_{non-ARDS}(\hat{V}_T, PBW\ data \mid severity)$$

where *severity* can take the values "mild," "moderate," or "severe," as set forth in the Berlin Definition (7) and we defined the difference between the probability density functions as the L1 norm:

$$\Delta = \sum |P_{ARDS} - f_i * P_{diagnosed\ ARDS} + (1 - f_i)\ P_{non-ARDS}|$$

where the sum extends over all bins for values of $\hat{V}_T$ and PBW.

We determined the optimal value of $f^i_{recognition}$ by minimizing Δ. Since the corresponding optimization problem is formulated as a linear programming problem, we used *CPLEX* (version 12) as a solver. To determine the uncertainty in our estimates of $f^i_{recognition}$, we used bootstrapping to generate 1000 samples for P_{ARDS} ($\hat{V}_T$, PBW | severity) and repeated the optimization for the bootstrapped samples. As a result, we generated distributions for the optimal value of $f^i_{recognition}$ for each hypoxemia severity category and tested the null hypothesis that

these data were drawn from the same distributions with a Kolmogorov–Smirnov test (Python package *scikit-learn* (version 0.18.1)). The threshold was $p < 0.003$ (0.01/3).

4.3.2.1 Chicago hospitals results

This approach yielded a mean (99% confidence interval) physician recognition of ARDS: 22% (9%-42%) for mild; 34% (19%-49%) for moderate; and 67% (41%-100%) for severe (Table 10, Figure 15). All three recognition distributions were significantly different from each other ($p < 0.003$) when compared via a Kolmogorov–Smirnov test.

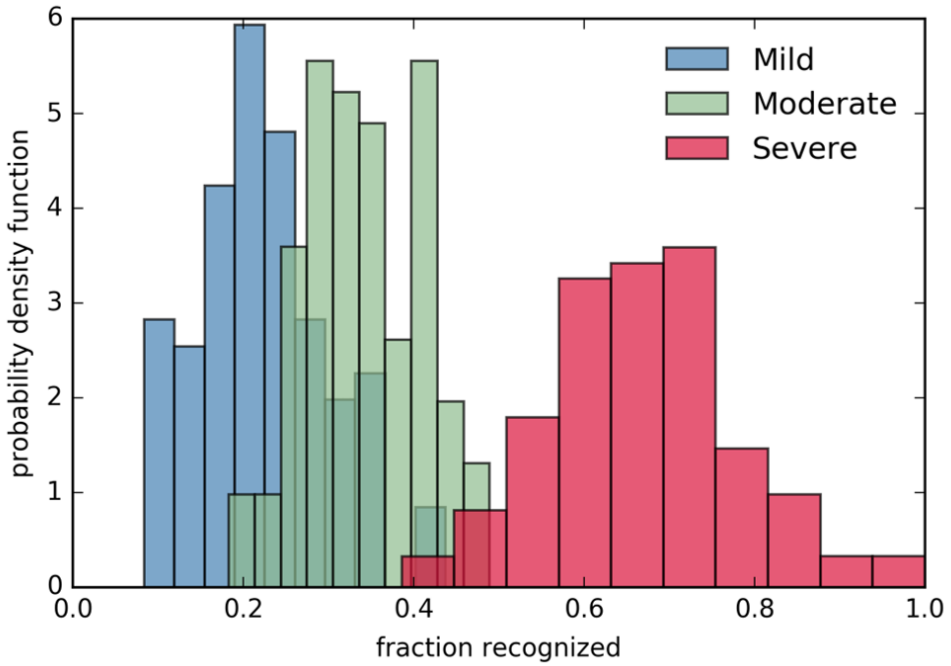


Figure 15: Distributions of $f^{i}_{recognition}$ from CPLEX analysis of bootstrapped data

4.3.2.2 LUNG SAFE results

Due to computational limitations of the LUNG SAFE consortium, this model was not able to be repeated on the LUNG SAFE dataset.

4.4 Discussion

Our prior analysis shows that hypoxemia severity and patient height (PBW) are significant drivers of tidal volume selection in both the Chicago hospital and LUNG SAFE cohort. In this chapter, we developed two ARDS recognition models that account for these factors. These models allow us to compare ARDS recognition rates in the two cohorts and provide insights into the effects of sources of potential biases.

First, our models are able to capture the previously reported association between hypoxemia severity and ARDS recognition. In both datasets, the estimated recognition rates increase with increasing hypoxemia severity. Furthermore, the rates of severe recognition in both cohorts are similar to each other, with the Chicago hospital cohort to the LUNG SAFE VAC subgroup severe recognition rates being closest. This similarity is expected given that the Chicago hospital cohort was restricted to patients on volume assist control ventilator modes. However, the documentation rates between the cohorts are rather different, providing evidence that documentation alone is a limited ARDS recognition metric.

Second, our analysis allows us to evaluate the effects of the observer effect and priming on ARDS recognition. The Chicago hospital dataset was pulled from the electronic health record with no contact with any clinicians, whereas the LUNG SAFE data collection required data entry and assessment by a site investigator. The LUNG SAFE protocol has the potential to introduce observer effect and priming biases, which we would expect to see as an increase in ARDS

recognition. We see an increase in ARDS recognition in the LUNG SAFE cohort as compared to the Chicago hospital cohort, particularly in the mild and moderate hypoxemia categories. We would expect these categories to be preferentially affected as compared to severe hypoxemia because patients with milder hypoxemia are harder to recognize at baseline (9,27). Thus, we can conclude that there is an effect that is inflating ARDS recognition rates in the LUNG SAFE cohort and the question becomes whether it is the observer effect, priming, or both.

We believe that priming is the primary source of ARDS recognition increase in the LUNG SAFE cohort as opposed to the observer effect. Study age, which measures the enrollment date of a patient relative to their particular study site, showed no association with tidal volumes in the LUNG SAFE cohort. If the observer effect was responsible for the increase in ARDS recognition, we would expect to see some association of tidal volumes with study age, either positive or negative. If there were a negative effect, one could postulate that it represents an initial additional focus on ARDS recognition, with decay as the study progressed. A positive effect could be interpreted as an increasing clinician awareness as the study continues. However, we see neither, suggesting that priming as a more plausible source. All participating clinicians were offered additional training on the radiological diagnosis of ARDS as part of a substudy. Such training would give clinicians additional awareness about ARDS and how to diagnose it, leading to an overall increase in ARDS recognition, which we see. The authors of the initial LUNG SAFE analysis acknowledge this as a limitation of their estimate of ARDS recognition and that it could potentially represent a best case estimate (9).

There are a few limitations to our analysis. First, we did not collect what proportion of physicians elected to participate in the training substudy, which would inform the strength of our

above conclusion regarding priming vs observer effects. However, the terms of the secondary analysis agreement stipulate that we are not permitted to analyze data on the study site level, so additional assessment of the observer effect would be rather limited. Additionally, we were not able to repeat the mixture model on the LUNG SAFE dataset, which includes both hypoxemia severity and patient height which is an improvement from the Naïve Bayes approach. Thus, the mixture model had the possibility of producing different results in the LUNG SAFE dataset, given that the LUNG SAFE dataset showed stronger associations between hypoxemia severity and tidal volumes than were found in the Chicago hospital analysis. This limitation is mitigated by the fact that in the Chicago hospital analysis, both the Naïve Bayes and mixture model approaches yielded similar recognition estimates and the possibility that the Chicago hospital analysis was simply too underpowered to capture the hypoxemia severity effects. Finally, we do not account for the other effectors of ARDS recognition reported in the initial analysis (pneumonia or pancreatitis as the inciting risk factor, younger patient age, nurse-to-patient ratios, and physician-to-patient ratios). This exclusion could also contribute to the differences in estimated recognition rates between the two datasets.

CHAPTER 5: Quality of care performance metrics

The work in this chapter is in preparation for publication with contributions from Adam R. Pah, Luís A. Nunes Amaral, and Curtis H. Weiss.

5.1 Introduction

Audit and feedback is a common approach to changing healthcare practices that has been shown to have a positive impact, whether on its own or included as part of a multifaceted intervention (41). In the case of increasing LTVV use for patients with ARDS, there has been one study that evaluated audit and feedback as an interventional strategy. In 2005, Wolthuis et al. investigated the utility of providing group feedback to ICU physicians and nurses on standardized tidal volumes being delivered in their units (42). Comparing pre and post-intervention standardized tidal volumes, they observed an overall decrease for both ARDS and non-ARDS patients that was sustained 6 and 12 months after the intervention (42). Their goal was to lower standardized tidal volumes below 8.0 mL/kg PBW, which they do achieve, but the authors also note that standardized tidal volumes under 6.0 mL/kg PBW are still rarely used. In this intervention, feedback was provided as a group on a whole unit basis.

Audit and feedback is most effective when there is a specific target and action plan (41). Yet, individual clinician statistics on LTVV use have not been used in an intervention strategy, potentially due to the complex nature of ARDS diagnosis and LTVV implementation. However, individual statistics that adjust for different environments are a mainstay in other fields, such as sports. Baseball (43) and hockey (44) both have extensive repertoires of metrics that account for factors such as stadium size and difficulty of schedules. It stands to reason that if the contributing factors can be quantified, the same could be done for clinicians. In this chapter, we present our

method for an ARDS recognition metric for the individual clinician that accounts for relative diagnostic difficulty of the clinician's cared-for patient population.

5.2 Data Used in these Analyses

We have previously described the development of the ARDS cohort used in this chapter, which includes 361 patients who met the Berlin Definition of ARDS via independent clinician review and were admitted to an ICU at one academic and three community hospitals in the Chicago region between June 24, 2013 and December 31, 2013 (45). All patient data was obtained from the electronic health records serving the participating hospitals. We defined study entry as the start of ARDS and study end was defined as the earlier of extubation, death, or ICU discharge. We recorded gender, height, and all P_aO_2/F_IO_2, tidal volumes, and clinician notes between ICU admission and study end where available (see Supp Tables 2,3, and 4 for data availability).

5.3 Clinician Recognition Calculation

For each clinician, we sought to calculate LTVV utilization in a manner that would account for the variable difficulty of each clinician's cared for patient cohort. The influence of patient hypoxemia severity and height on tidal volume delivery has been reported both in this specific patient cohort (45) and in prior studies (9,16,18,21,23,24,26,33–35). Therefore, we constructed a recognition metric which compares an individual clinician's observed ARDS recognition (using our Naïve Bayes recognition model from Chapter 4, Figure 16A) to that clinician's expected ARDS recognition given their specific patient cohort (Figure 16B). We make the assumption that ARDS recognition is the major barrier to LTVV delivery because

96.4% of clinicians reported “strong” or “very strong” belief in the evidence of LTVV use for patients with ARDS in the survey. Figure 16C shows three hypothetical clinicians and their patient populations as examples of how the observed and expected recognitions can vary. Clinicians were paired with patients in the above ARDS cohort that they cared for (46) and only the data that occurred during those that specific clinician’s patient contact was used in the recognition metric calculation.

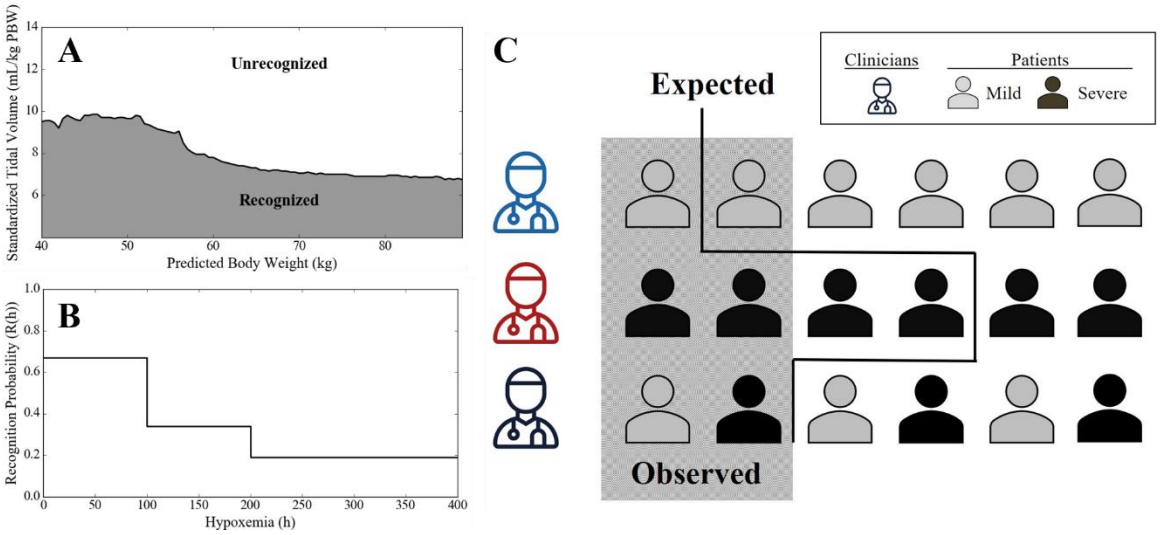


Figure 16: ARDS recognition metric that compares observed recognition to expected recognition
A) Model used to calculate observed recognition based on the standardized tidal volume and predicted body weight space. Patients are considered recognized below the boundary line and unrecognized above. B) Stepwise function used for calculation of expected recognition. The probability of recognition varies with hypoxemia severity. C) Three example clinicians and cared-for patient populations. All physicians are observed recognizing two patients, but have different expected recognition rates.

5.3.1. Observed Recognition

Previously, we developed a model of physician recognition of ARDS, which accounts for the effect of patient height on tidal volume delivery. Using a comparison of tidal volume delivery in ARDS and control hypoxemic patients, this model divides the predicted body weight (PBW)

vs standardized tidal volume (mL/kg PBW) space into “recognized” and “not recognized” regions (Fig 16A). Mapping each clinician’s patient population to the space, we calculated their observed recognition (N_{obs}) as the number of patients in the “recognized” region.

5.3.2. Expected Recognition

To establish a baseline expected recognition rate for each clinician, we calculated the number of patients recognized if the clinician was performing at the clinician population average, using the following equation:

$$N_{\exp}(\{h_1, h_2, \ldots h_{N_j}\}) = floor\left[\sum_{i=1}^{N_j} R(h_i)\right] \quad \text{[Eq 1]}$$

where:

h_i: hypoxemia of patient i

i: hypoxemia severity category (mild, moderate, or severe) according to the Berlin Definition (7)

N_{exp}: number of patients expected to be recognized

$R(h_i)$: recognition rate (Fig 16 B)

N_j: number of patients cared for by physician j

The recognition rates ($R(h_i)$) in Eq 1 are for the whole ARDS cohort by hypoxemia severity, which we estimated via mixture model in our previous chapter 4; 22% for mild, 34% for moderate, and 67% for severe. Expected recognition is rounded down to the nearest patient to account for the binary nature of ARDS recognition.

5.3.3. Recognition Metric

In order to estimate the relative likelihood of the observed and expected recognition scenarios, we simulated each clinician's patient population. Each patient in a clinician's patient population was treated as an independent event with a recognition probability equal to the recognition rate ($R(h_i)$) appropriate for their hypoxemia severity (Fig 16B). Each patient was classified as either recognized or not recognized at the end of the iteration according to this recognition probability. This process was simulated 1000 times to produce a probability distribution for each potential value of recognized patients for each physician (0 to N_j). The recognition metric (R) was calculated as the difference between cumulative likelihoods of the observed number of recognized patients (N_{obs}) and the expected number of recognized patients (N_{exp}) (Eq 2). The cumulative likelihood was used to ensure that clinicians recognizing more patients than expected would have positive values, while clinicians recognizing less patients would have negative values. Clinicians performing at the expected level would be graded at a 0.

$$R = P(\leq N_{obs}) - P(\leq N_{exp}) \quad \text{[Eq 2]}$$

5.4 Metric Robustness Evaluation

We used univariable ordinary least squares (OLS) regression to assess the robustness of our recognition metric to key independent variables including predicted body weight, hypoxemia (lowest P_aO_2/F_IO_2), total number of patients treated, and mortality proportion within each clinician's treated cohort. For predicted body weight, we used summary statistics of the clinician's cared for population (mean, median, proportions in the central, single standard

deviation, and second standard deviation ranges) and for hypoxemia, we used the proportion of the patient population meeting severe hypoxemia criteria ($P_aO_2/F_IO_2 \leq 100$).

For all clinician types, our metric showed no correlation with PBW, hypoxemia, or mortality proportion. In respiratory therapists, there was a small positive relationship between recognition and total number of patients treated (β=0.015, p<0.00007, Figure 17).

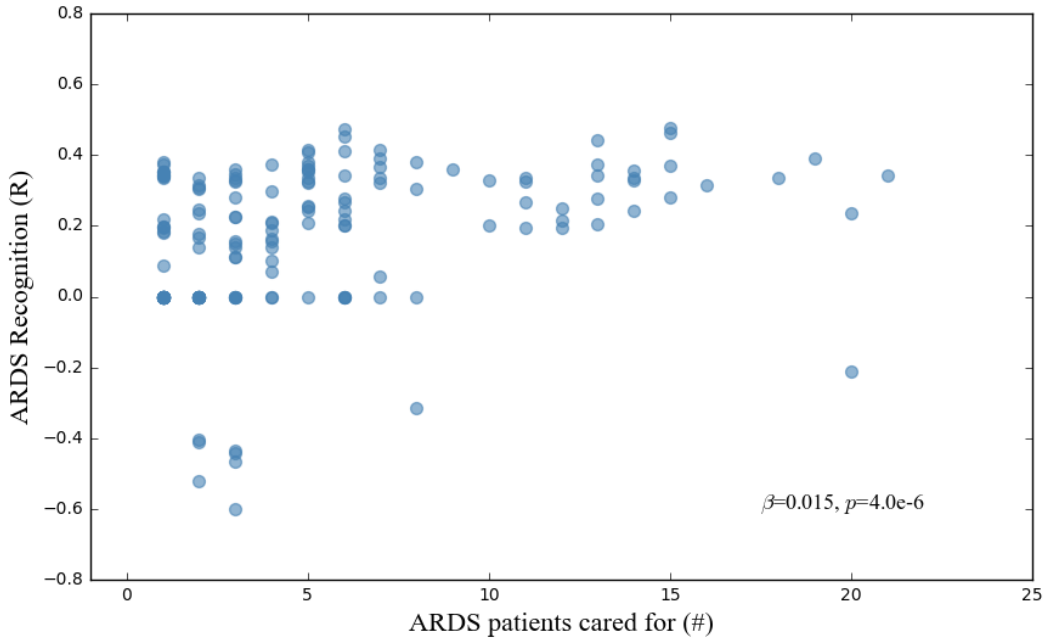


Figure 17: Respiratory therapists who cared for more ARDS patients had a higher rate of ARDS recognition.
Each marker represents a single respiratory therapist who cared for ARDS patients in our cohort.

5.5 Demographic associations

To evaluate associations between clinician recognition and clinician characteristics, we used OLS regression with our recognition metric as the dependent variable and demographic characteristics as independent variables. Demographic univariable analysis was performed first, as demographics have been previously shown to affect network connections (homophily principle) (47). Demographic variables included: ICU team (MD/RN only), age, gender, year of

training completion (ordinal and before/after ARDSnet), day/night shift (RN/RT only), and number of physical ICUs worked in (RT only).

For physicians, pulmonary and critical care (PCCM) team membership showed a significant association with higher recognition ($\beta=0.63$, $p<0.00007$, Figure 18). For respiratory therapists, working in a greater number of physical ICUs was associated with higher recognition rates ($\beta=0.040$, $p<0.00007$, Fig 19). Nurses showed no correlation between any demographic variables and recognition.

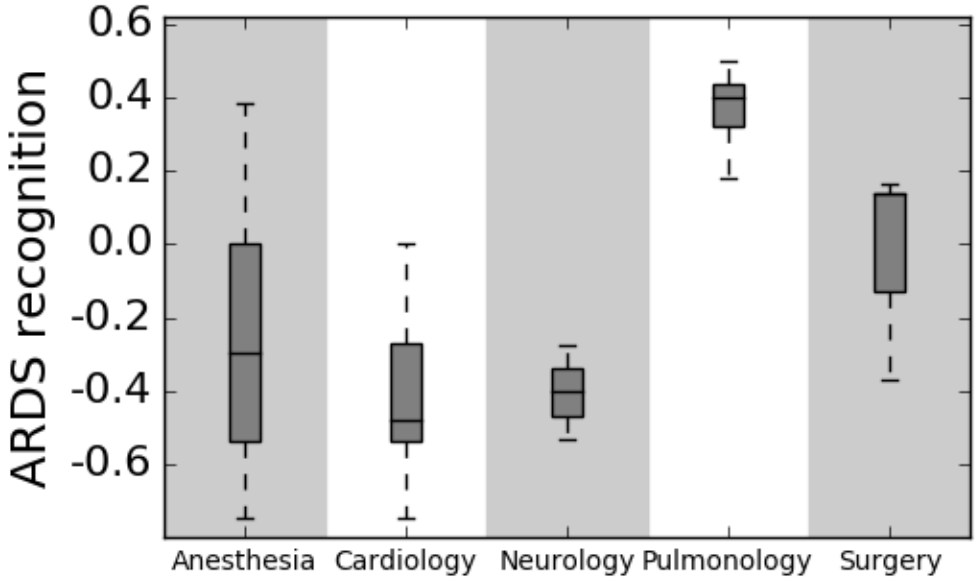


Figure 18: Attending physicians ARDS Recognition (R) for different ICU care teams

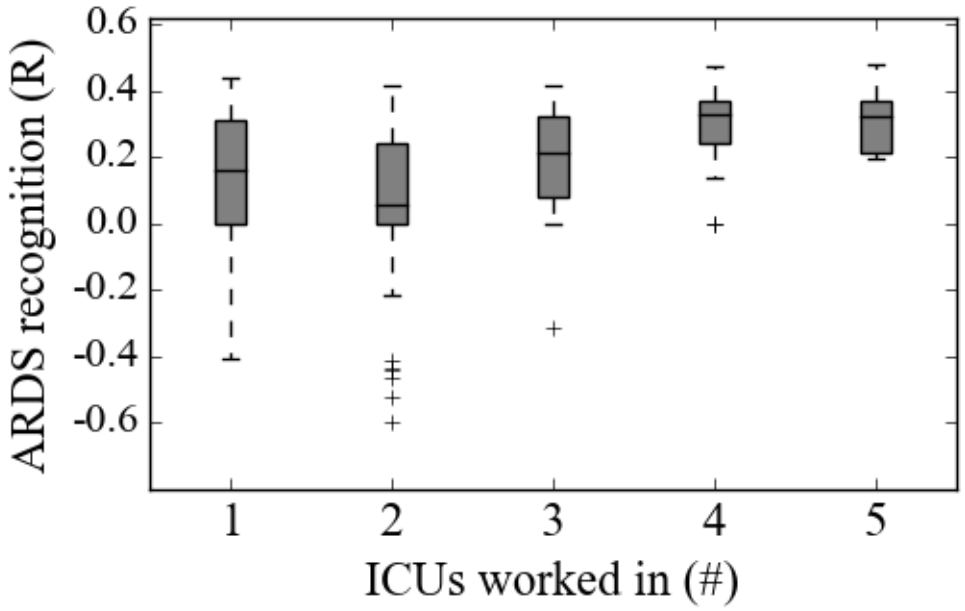


Figure 19: Respiratory therapists who worked in more ICUs had higher rates of ARDS recognition

5.5.1 Sensitivity Analyses

All robustness and demographic regressions were repeated using two alternative recognition measures previously used in the literature. First, the proportion of worked shifts during which the clinician delivered LTVV (defined at ≤ 6.5 mL/kg PBW) and second, the proportion of patients that a clinician cared for that received LTVV at any point during their disease course. All results were consistent with our recognition metric.

5.5.2 Statistical Significance

We used $\alpha = 0.01$ instead of 0.05 to ensure the statistical strength of our findings (31) and applied the Bonferroni correction for multiple hypotheses. For each clinician type, there were 134 to 140 comparisons in this thesis work where our recognition metric was the dependent

variable, thus we set $p < 0.00007$ (0.01/140) as the threshold for statistical significance for these analyses.

5.6 Discussion

In previous chapters, we quantify the impact of effectors of tidal volume selection and develop models for estimating ARDS recognition on a population level. Having identified ARDS recognition as the primary barrier to LTVV use, we build an ARDS recognition metric that allows for measurement at the individual clinician level. With this metric, we assess the impact of clinician demographic factors on ARDS recognition and establish a few important findings.

First, we find that ICU team membership predicts ARDS recognition, specifically that those physicians belonging to the pulmonology and critical care team outperform their peers. This result is logical given that ARDS is a pulmonary condition and therefore, those on the pulmonology and critical care team have the most training with regards to this specific syndrome. One potential confounding factor could be amount of exposure to patients with ARDS, which would prime pulmonologists. However, in this cohort, it is not the pulmonology and critical care team that cares for the most ARDS patients, but instead the surgical team. Furthermore, we did not find an association between total patients cared for and ARDS recognition for individual physicians. Finally, the hypothesis that training background is the etiology of this difference is further supported by the fact that the lowest performing team is cardiology. The cardiology critical care team is the only ICU care team which does not have additional intensivist training; the rest traditionally undergo additional dedicated intensivist

fellowship training. These results suggest the presence of a local team-based culture around ARDS and associated ventilator management

Second, this concept of a local team-based culture is reinforced with the associations found in the respiratory therapists and nurses. Respiratory therapists have increasing ARDS recognition scores with increasing number of ICUs worked in. This result is consistent with the local team-based culture etiology. Working in many different ICUs would provide respiratory therapists with more potential exposure to different teams and the opportunity to sample from different ideologies. An alternative explanation for this association could be the presence of a physical ICU systems barrier or facilitator. However, this explanation is unlikely because physician ICU teams are not assigned to a physical ICU and furthermore, we find no associations between ARDS recognition and nurse ICU teams, which are assigned to a physical ICU.

Limitations of this work are focused on a lack of systems knowledge. First, we do not know how respiratory therapists are scheduled or assigned to patients. We know that RTs are not assigned to a physical ICU in the way that nurses are and can work in many different ones. However, there is a possibility that we are instead capturing a measure of seniority, interpersonal popularity, or clinical performance. Second, we do not know if physician ICU teams are employing different tools that may affect their ability to recognize ARDS. For example, specific LTVV ventilator protocols have been shown to improve the use of LTVV in the past (18) and if one team has one and the others do not, that could affect the results. This limitation is mitigated by the fact that ICU physician teams are not expected to work in isolation and have ready access to other specialty services through consults.

CHAPTER 6: Network Analysis

The work in this chapter is in preparation for publication with contributions from Adam R. Pah, Luís A. Nunes Amaral, and Curtis H. Weiss.

6.1 Introduction

A network is defined as a collection of nodes that are connected in some fashion (47). There are many systems that are crucial to our everyday lives that can be thought of as networks: transportation, telephones, and even metabolism. The connections within networks can serve as routes of transmission and exchange for a variety of things, such as physical goods or information. In this same vein, the spread of new ideas, commonly referred to as "diffusion of innovation", can also be thought of as a type of transmission (1,48). To this end, communication and social networks have been examined in implementation science as both potential barriers/facilitators of innovation spread, but also as route for interventions that promote adoption. However, as mentioned previously, implementation science has focused on qualitative methods quantitative methods and that trend extends to the integration of network science.

The impact of clinician interpersonal networks has been limited. The major reason for this low impact is that when networks are obtained, they are often not used for intervention development. A 2012 review that examined 62 studies on social networks of healthcare professionals between 1950 and 2011 revealed that 61 studies only visualized and described the network (49). Only one study went on to use the results of the social network analysis to inform the development of an intervention to change practice; Anderson et al. used social network analysis to identify "educationally influential" individuals to target for the increase of personalized electronic order sets (50). However, Anderson et al is not as isolated as the 2012 review would suggest, but instead is an example of a more common approach that try to leverage

interpersonal networks in intervention design. The 2012 review required studies to build and describe a network in order to be included, but more often, networks are not built but assumed. Instead, typically studies only attempt to identify opinion leaders by surveys or asking leadership and then implementation interventions revolve around those opinion leaders. The theory behind this approach is that opinion leaders are well-respected and well-positioned within their own communities and therefore best situated to enact change.

While not fully leveraging the information contained in the network, the targeting of opinion leaders has had some success promoting the uptake of evidence-based practices in medicine (Figure 20). Twenty-two studies have used opinion leader targeting over the last forty years and some common patterns have emerged (50–69). The preferred method of identifying opinion leaders is via survey (51–54,56–60,62–65,69). The studies are pretty evenly split between inpatient and outpatient settings, with the fields of OBGYN and cardiology being particularly common. There are two clusters of studies where the same protocol was tested in different fields yielding the same results: 1) all publications by Stross and 2) Majumbar 2006-2008 and McAlister 2009 (on which Majumbar was an author). Almost all of the studies have used patient outcomes as the measure of success, with three opting for clinician-focused assessments (50,53,60), such as the use of electronic order sets and clinician knowledge assessments. The majority of studies report an improvement with the use of opinion leader targeting (Figure 20), which the majority comparing against no intervention as a control (50,52,54,56,60–64,66–68). Seven studies included opinion leader targeting as part of a larger, multifaceted quality improvement intervention (53,59,64,66–69).

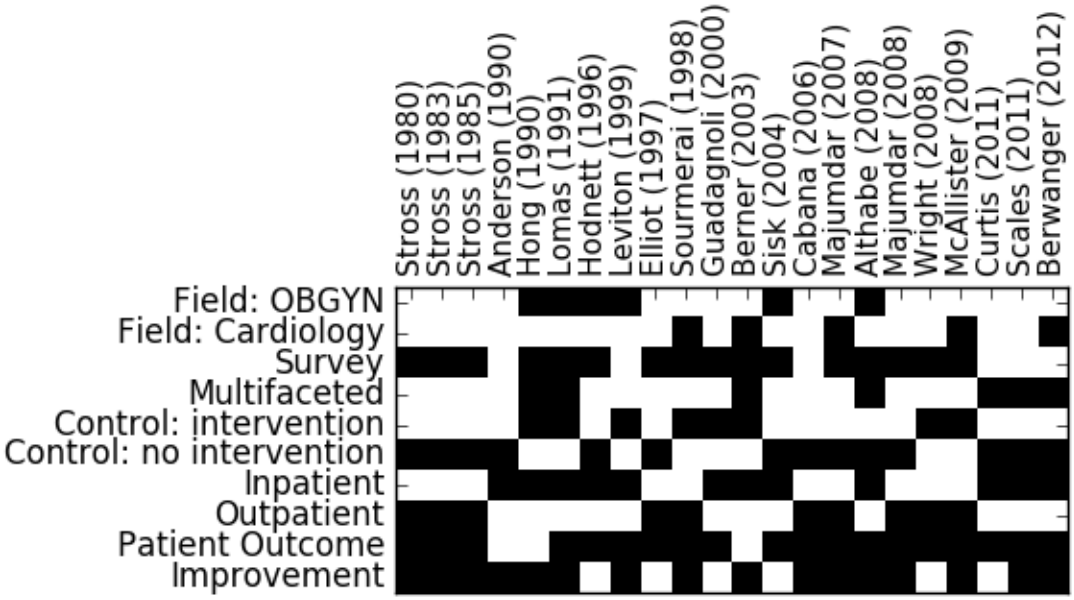


Figure 20: Studies using opinion leader targeting as an intervention to increase use of evidence-based practices.

Despite these advances, there are still limitations to the opinion leader targeting approach and room for improvement as far as integrating social network analysis into the design of implementation interventions. First, opinion leaders are often compared to a control condition of no intervention and thus it is difficult to parse out the specific impact of opinion leaders versus simply instituting an intervention at all. Second, the overall gain of opinion leader targeted interventions is relatively modest. In a 2011 Cochrane review of 18 opinion leader focused interventions, the median risk difference for opinion leader intervention groups versus their controls was 0.12, representing a 12% increase in evidence-based practice compliance (49). Third, it is difficult to assess what the etiology of this limited success may be, as the particular role and involvement of opinion leaders is often not described in detail or left up to the discretion of each individual opinion leader(49). Finally, as mentioned previously, the identification of an opinion leader is rather limited approach to social network analysis as it focuses on only one

aspect of the information flow surrounding patient care, so it is unclear how much influence the opinion leader themselves actually has.

There is evidence to support performing a thorough social network analysis, as network structures and conditions that form the network can influence the spread of innovation. First, the theory of structural holes postulates that new information or ideas will be accepted more readily in networks where one's neighbors are not as well connected (Figure 21B) (47). Conversely, networks that are highly cohesive will form an echo chamber effect and make the introduction of a new norm very difficult (Figure 21A) (47). We see evidence for this in the use of evidence-based practices by physicians in studies out of Italy examining both self-reported and observed evidence-based practice use (70,71). Second, a physician's position within a interaction network has previously been tied to their propensity to use evidence-based medicine, with variation based on the number of their connections (72) and which opinion leader they are connected to (73). Finally, one must consider the principle of homophily, in which people preferentially form ties with those that are most similar to themselves (47). Considering this, opinion leader interventions may always be limited to the particular group that that leader belongs to (gender, race, training background, etc), but it is difficult to assess that if no further analysis is completed beyond identification. By electing to only identify an opinion leader, the analysis is simplified, but one may miss these important other influential factors.

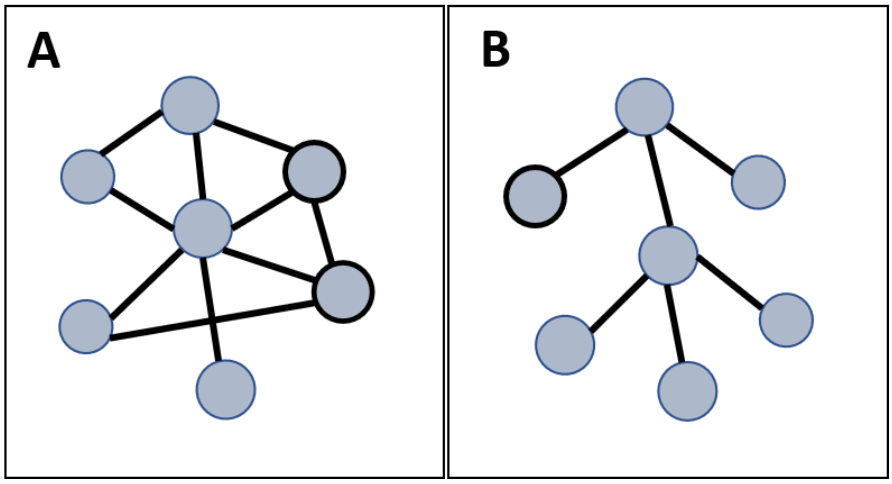


Figure 21: Examples of a tightly connected network (A) and one with structural holes (B)

In this chapter, we explore the potential effects of network factors on the use of LTVV for patients with ARDS. In this specific physician population, we have evidence to suggest that physician-physician interactions play a role in the adoption of innovations. In previous work at our academic site, knowledge of the availability of a new lab test was released to two physicians rather than being advertised publicly and the orders for this new lab test were tracked over the next 244 days (74). A persuasion agent-based model was able to very closely replicate the experimentally obtained results (Figure 22), suggesting that a peer-to-peer contact and conversion process was taking place. This analysis was conducted on a low burden (easier to adopt) innovation in a single ICU, specifically using shared work shifts as a means of contact. In this chapter, we expand on this prior analysis by examining a more complex innovation (LTVV) across multiple ICUs as well as multiple contact types. Specifically, we will assess potential associations between clinician position within interaction networks and use of LTVV for ARDS patients and compare the effect of these associations to that of other potential adoption drivers.

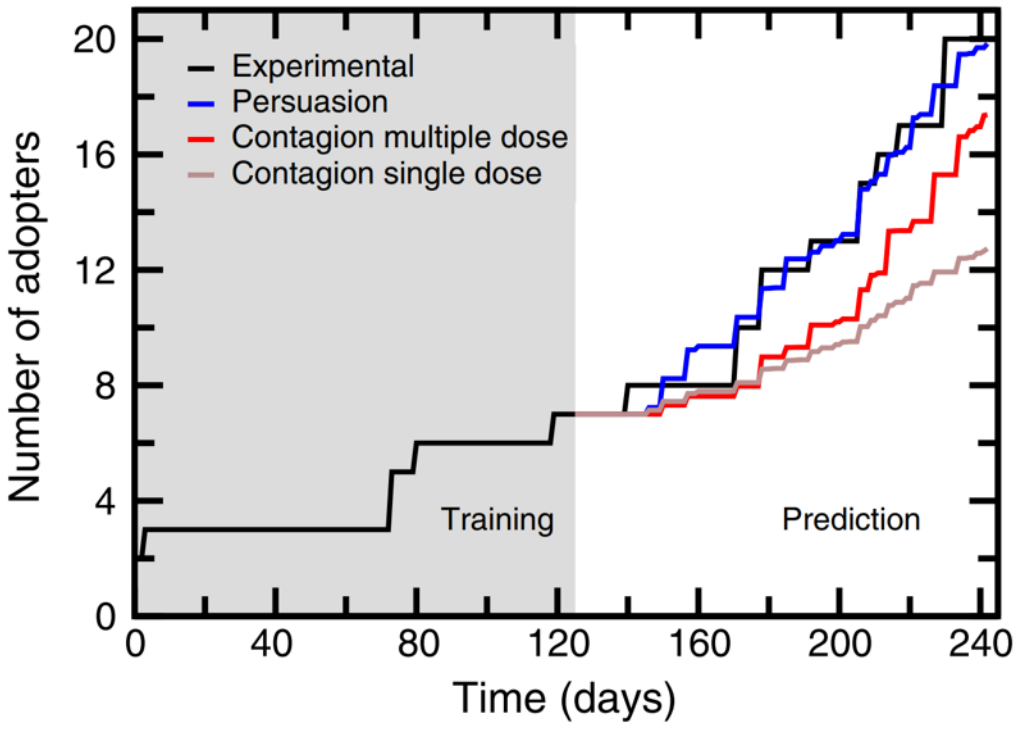


Figure 22: Persuasion agent-based model accurately predicts physician adoption of new lab test. Originally published in Weiss Poncela-Casasnovas et al (74). Included here with permission from the authors

6.2 Data Used in These Analysis

We have previously described the survey used in this chapter (46), which includes all physicians, fellows, ICU nurses, and respiratory therapists that cared for the ARDS patient cohort described above. The survey was administered between October 2014 and June 2015 and had a 69.3% response rate (83 physicians, 307 nurses, 77 respiratory therapists) (46). The survey included questions on attitudes towards innovation in general and LTVV, barriers and facilitators to LTVV use, relationships with other clinicians in the ICU, and clinician demographics.

6.3 Network Creation

We built two categories of networks: formal and informal. For the formal networks, only attending physicians were included as nodes. Physicians were connected if they both wrote a note on the same patient on the same day. These formal networks represent the documented flow of patient care through the hospital (Figure 23).

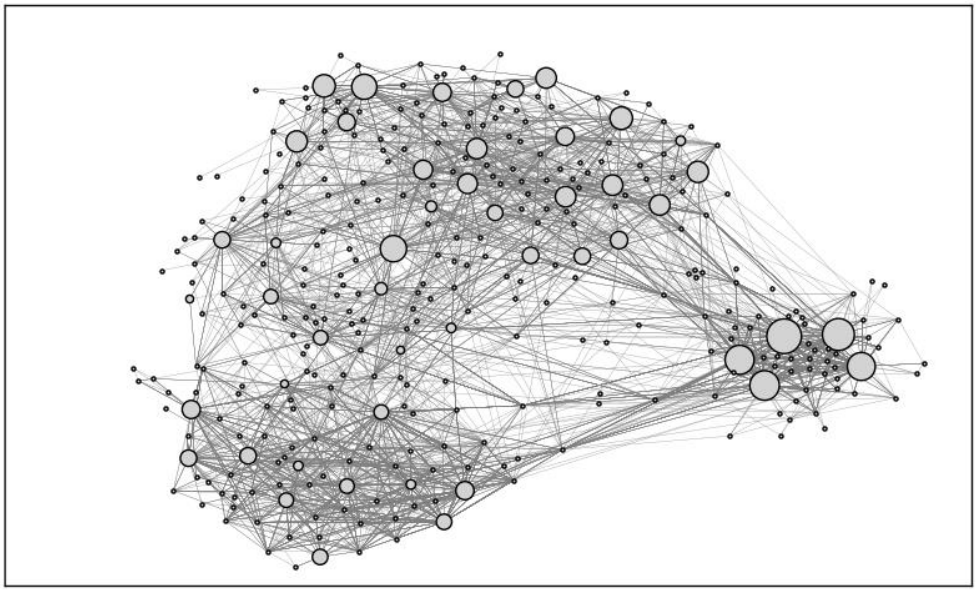


Figure 23: Formal physician interaction network
Each circle indicates an individual physician. Individuals are connected if they authored a note on the same patient on the same day. Size of marker represents number of ARDS patients cared for. Marker position is kept constant across network visualizations.

Informal networks were built using the survey results and included physicians, nurses, and respiratory therapists as nodes, but only a single node type in each network (physician only, nurse only, RT only). Clinicians were connected using the four connection questions:

1) Please write down the names of up to five critical care physicians with whom you work in your ICU whose input you regularly seek to help you make good clinical decisions based on the best available evidence.

2) Please write down the names of up to five critical care physicians with whom you work in your ICU who regularly seek your input to help them make good clinical decisions based on the best available evidence.

3) Please write down the names of up to five critical care physicians with whom you work in your ICU who you consider to be your friends.

4) Please write down the names of up to three critical care physicians with whom you work in your ICU who you think tend to be the first to use new therapies or diagnostic tests.

Questions 1 and 2 were used to build a professional connections network; question 3 was used for the friendship network (Figure 24); question 4 was used for the innovation network (Figure 25). Connections were included even if they were not bidirectional, but directed and undirected versions of all networks were created. Questions 1 and 2 also had a frequency component, which was used to build weighted and unweighted versions of the professional network. Due to the phrasing of the questions, only within-ICU ties were included for physician and nurse informal networks.

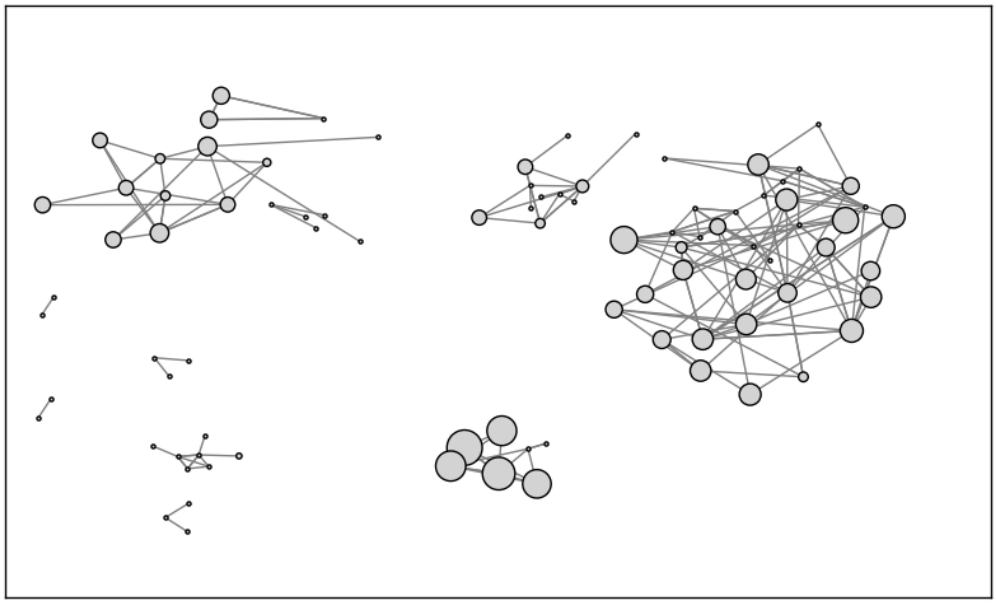


Figure 24: Physician friendship interaction network
Each circle indicates an individual physician. Individuals are connected if they were named on the survey friendship question. Size of marker represents number of ARDS patients cared for. Marker position is kept constant across network visualizations.

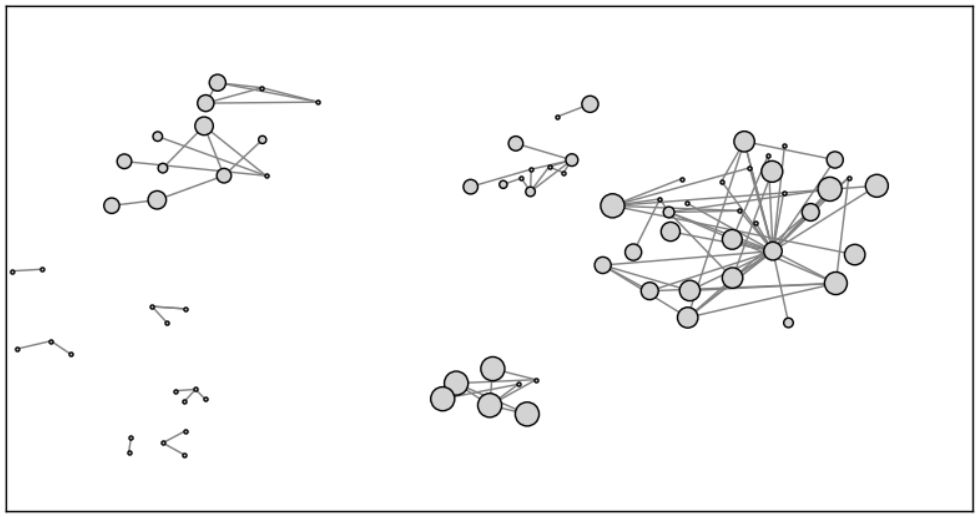


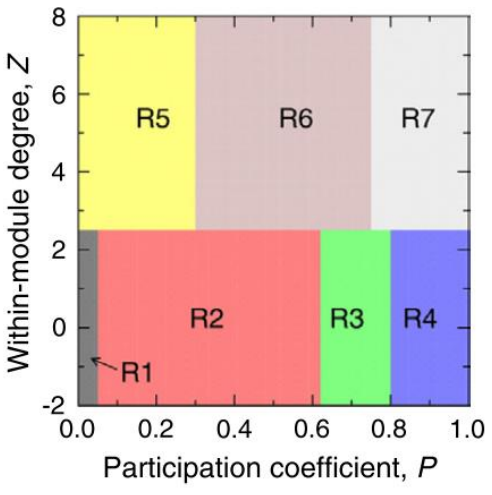
Figure 25: Physician innovation interaction network
Each circle indicates an individual physician. Individuals are connected if they were named on the survey innovation question. Size of marker represents number of ARDS patients cared for. Marker position is kept constant across network visualizations.

6.4 Network Characterization

Using graph theory, we quantified different aspects of a node's position within a network. For each node in every network version, we calculated 8 node network characteristics: betweenness, closeness, degree, katz centrality, k-shell embeddedness, participation, role, and community membership (Table 13). All centrality characteristics (betweenness, closeness, degree, and katz) were calculated using the Networkx Python package (version 1.11), except embeddedness which was calculated manually (75). Participation, role, and community membership were calculated with netcarto (v 1.15). All characteristics were normalized for the number of nodes in the network, except community, which was treated as a categorical variable.

Table 13: Node network-related characteristics

Node Characteristic	Description	Calculation
Betweenness (also called 'brokerage')	Node placement on paths between other nodes	$x_i = \frac{1}{n^2}\sum_{st}\frac{n_{st}^i}{g_{st}}$ x_i: betweenness of node i n: number of nodes in network n_{st}^i: number of geodesic paths from s to t that pass through i. g_{st}: number of geodesic paths between s and t
Closeness	Distance from all other nodes in the network	$x_i = \frac{n-1}{\sum_{st} g_{st}}$ x_i: closeness of node i n: number of nodes in network g_{st}: number of geodesic paths between s and t
Degree	Number of connections to other nodes. Can be calculated as in and out degree for directed networks.	$x_i = \sum_j A_{ij}$ x_i: degree of node i A_{ij}: adjacency matrix of node i
Katz Centrality	Measure of centrality that includes not only a node's	$x_i = \alpha\sum_j A_{ij}x_j + \beta$

	degree, but the degree of its immediate neighbors as well.	x_i: Katz centrality of node i A_{ij}: adjacency matrix of node i α, β: positive weighting constants
K-shell embeddedness	Measures the hierarchy of a node within a network. K-shell embeddedness is the maximal subgraph of the network having minimal degree of at least k, but not k+1	Process: - prune all nodes with degree ≤ k - in new graph, prune all nodes with degree ≤ k - iteratively prune until no nodes exist with degree ≤ k - all nodes pruned have a k-shell embeddedness of k.
Community	A group of nodes that are more connected than would be expected by random chance.	Maximization of modularity as defined by: $M \equiv \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - (\frac{d_s}{2L})^2\right]$ N_M: number of communities L: number of links in network l_s: number of links in community s d_s: sum of degrees of nodes in community s
Participation	Measure of connections node has to communities other than its own	$P_i = 1 - \sum_{s=1}^{N_M} (\frac{k_{is}}{k_i})^2$ P_i: participation of node i N_M: number of communities k_{is}: links to node i in community s k_i: total degree of node i
Role* (76)	There are 7 distinct roles depending on the location of a node within the participation/in-community degree z-score space. They include: ultra-peripheral (R1), peripheral (R2), non-hub connector (R3), non-hub kinless (R4), provincial hub (R5), connector hub (R6), and kinless hub (R7).	

* Figure originally published in Guimerá et al. (76) Reproduced here with author permission.

6.5 Association between network position and ARDS recognition

Significant demographic variables were included as a fixed effect in multivariable OLS regressions with node network characteristics as an additional independent variable. Each node network characteristic was evaluated in a separate regression. No node network variables for any clinician or network type showed any association with recognition.

In physicians, the ICU team membership appeared to be the dominant variable. In Figure 26, the clusters of tightly connected nodes correspond to ICU teams.

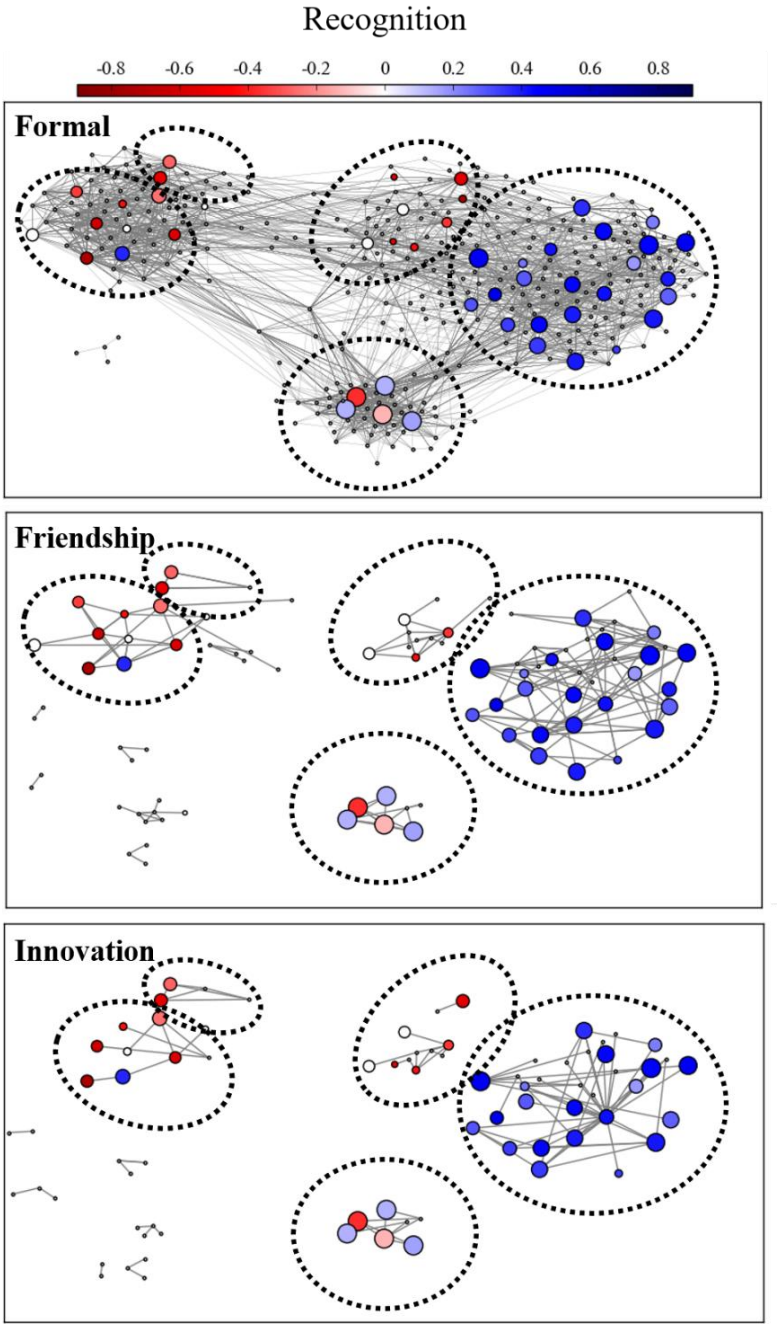


Figure 26: Physician ARDS recognition clusters by ICU team across different interaction networks

Each circle indicates an individual physician. Size of marker represents number of ARDS patients cared for. Marker position is kept constant across network visualizations. ARDS

recognition is represented via color Markers are colored by adjusted ARDS recognition rate (colorbar). Dotted circles indicate ICU teams.

6.5.1 Sensitivity Analyses

All network characteristic regressions were repeated using two alternative recognition measures previously used in the literature. First, the proportion of worked shifts during which the clinician delivered LTVV (defined at ≤ 6.5 mL/kg PBW) and second, the proportion of patients that a clinician cared for that received LTVV at any point during their disease course. All results were consistent with our recognition metric.

6.6 Discussion

In this chapter, we explored the potential influence of a clinician's position within interaction networks on their ability to integrate evidence-based practices into their work. Previous literature suggests that the structures of interaction networks can enhance or inhibit the diffusion of innovations (70–72) and that these networks can be leveraged for adoption interventions through the targeting of opinion leaders (52–69). Our analysis has allowed us to evaluate the applicability of this prior research to our specific clinical environment and reach a few important conclusions.

First, an individual clinician's position within the interaction networks does not have an association with their ability to recognize ARDS. For physicians, their ICU team membership (i.e. training background) has a much stronger effect and once this is accounted for, individual network-based characteristics show no association. This finding is consistent with prior literature that shows that physicians tend to form tightly knit communities that do not promote the

integration of new ideas (77). Instead, as the structural hole theory states, these dense communities will instead encourage the status quo, which is what we observe in our data. The dominance of the local culture effect is further supported by the results of the formal network analysis, which allows for contact between different ICU teams and still shows no association between ARDS recognition and metrics such as the participation coefficient that would capture exposure to physicians from different teams.

Second, this lack of association does not vary with the type of network evaluated. Valente et al describes ten different ways to identify opinion leaders (78) and a variety of these have been used in prior opinion leader targeting interventions (50–69). To address this, we used multiple types of contact (professional, friendship, innovation, formal work) and built a variety of possible networks (directed/undirected, weighted/unweighted). Even with this variety, we see no association between network-based characteristics and ARDS recognition. This result aligns with the prior literature findings that opinion leader targeting interventions have variable success in different situations and even when they are successful, the improvement is only moderate (49). Our analysis suggests that this mitigation of success may be due to the effects of local culture and which group the opinion leader belongs to. If the opinion leader belongs to the majority, the success of an opinion leader focused intervention will likely be greater than if they are somehow more isolated.

There are limitations to this approach. First, the majority of the networks were built using self-reported interactions, which are potentially biased by subjective reporting. However, this mitigated by the fact that the results do not change between directed and undirected networks or when we use the formal network for physicians. Moreover, this survey-based approach is simply

the state of the field at the moment and was employed in the majority of prior studies that identified opinion leaders (51–54,56–60,62–65,69). Second, the informal physician networks assessed are small and therefore, the analysis may be underpowered. However, the networks described here are relatively large on the scale of hospitals and ICUs and therefore represent a dataset which would have particularly good chances of showing an association if one existed. Furthermore, the dominance of team membership is also found in the formal network, which is larger, making the network size less likely to be a contributing factor. Finally, our assessment of associations between network-related characteristics and ARDS recognition tested for unidirectional relationships only. It is possible that there are relationships between network position and the absolute magnitude of ARDS recognition.

CHAPTER 7: Survey Analysis

The work in this chapter is in preparation for publication with contributions from Adam R. Pah, Luís A. Nunes Amaral, and Curtis H. Weiss.

7.1 Introduction

There have been three main survey studies that have specifically examined the barriers and facilitators of LTVV for ARDS patient (32,33,46). Each one has expanded on its predecessor(s) and brought new insights to this implementation challenge.

Rubenfeld et al. collected their data in 2004, soon after the ARMA trial, and had the goal of capturing the wisdom gained from the initial introduction of LTVV for ARDS patients into the clinical care system (33). The survey was distributed specifically to nurses and respiratory therapists that had participated in the ARMA trial, as identified by research coordinators at each site. The survey instrument consisted of ten coded questions about specific barriers to LTVV use and three open-ended response items requesting feedback in general, on the most common error witnessed, and recommendations for future implementation. The barriers were ranked by average impact reported and percent of respondents ranking the barrier as important.

For barriers to the initiation of LTVV, respondents identified the most important barriers as physician unwillingness to relinquish control of the ventilator, physician under-recognition of ARDS, and physician perceptions of LTVV contraindications. For barriers to the continuation of LTVV, respondents identified care team concerns for patient comfort, including tachypnea, hypercapnia, acidosis, and hypoxemia.

In the free response items, respondents frequently commented on sedation use and rapid decrease of the tidal volume as challenges. They also reported issues of clinicians using dry weight instead of PBW and focusing on P_{plat} as the target instead of tidal volume. Their

recommendations included the use of specific ventilator protocols, clinician education, and quantitative tools for assessing patient discomfort.

While the study was an important first step toward assessing the implementation environment, the authors acknowledge that significant limitations included that participants were not asked how often these barriers changed practice, the participant pool was restricted to trial participants only, and there was no assessment of provider experience, knowledge, or actual practice.

A year later, Dennison et al. built on this first survey by issuing it to physicians, nurses, and respiratory therapists and including knowledge assessment items (32). The goal of this study was two-fold. First, expand the survey instrument by adding in questions and organizing into subscales of attitudes, behaviors, knowledge (barriers), ICU organization, and knowledge (test). Second, evaluate differences in responses between participant types (profession and level of experience). The authors note that physicians report the least amount of barriers to LTVV use and higher knowledge test scores when compared with nurses or RTs.

Experience also appeared to play a role. When subdivided into interns, residents, fellows, and attendings, interns reported the most issues with barriers and performed the worst on the knowledge test, while fellows and attendings had opposite results. This pattern was maintained in the nurses, when they were divided into categories of those with more or less than 10 years of experience. For specific barriers, the authors noted that a minority (42%) of participants report that teams discussed tidal volumes in terms of mL/kg PBW and recommend that having PBW readily calculated and available in clinical flow would be helpful. For limitations, the authors

acknowledge that the study was conducted at a single site and disproportionately internal medicine respondents.

A decade later, Weiss et al. added to these studies by being the first to correlate survey responses with actual LTVV use (46). Distributed to attending physicians, fellows, nurses, and respiratory therapists at four Chicago hospitals, the survey results confirmed Dennison's findings that physicians reported less barriers than nurses or respiratory therapists. In fact, physicians exhibited strong support of LTVV use for patients with ARDS with 96.4% reporting that they believed the evidence for LTVV was 'strong' or 'very strong' and 80.7% disagreed that they would only give LTVV if they were certain that their patient had ARDS. The LTVV use metric employed was the percent of eligible ARDS patients that a clinician initiated LTVV on during a 6 month period a year prior to the survey distribution.

There were no significant correlations found between LTVV initiation and physician item responses. For nurses and respiratory therapists, the only question that showed a correlation with LTVV initiation was "What percentage of your patients with ARDS have contraindications to receiving low tidal volume ventilation?" and the two groups reported opposite associations (RNs positive and RTs negative). The authors note that the overall rate of LTVV use was small and that the delay between the patient data and survey collections could potentially contribute to these null results.

In this chapter, I report a secondary analysis on the dataset of Weiss et al with the goal of quantifying the effects of the clinician demographic factors discussed in Chapter 5. With the data available, I compare the reported barriers, attitudes, and experiences between demographic groups that have diverging ARDS recognition rates. In contrast to Dennison et al, I demonstrate

that those who report more barriers actually recognize ARDS more often and discuss the potential etiologies and implications of this result.

7.2 Methods

In order to evaluate any association between reported attitudes and experiences and our recognition metric, the rest of the survey questions (non-demographic, non-network) were filtered for those that showed a maximum range of responses (Appendix C). A Kruskal-Wallis H-test was used to evaluate differences in recognition between categories of survey answer (Python Scipy package version 0.18.1).

Furthermore, clinicians were split according to significant demographic variables (PCCM vs not for physicians, high (>4) and low (≤4) number of ICUs worked in for RTs) and their responses from the same filtered question pool were assessed for differences between demographic groups using a Mann-Whitney U test (Python Scipy package version 0.18.1). There were 20 questions for physicians evaluated, thus the significance threshold was $p < 0.0005$ (0.01/20). For RTs, there were 12 questions evaluated and the threshold was set at $p<0.0008$ (0.01/12).

7.3 Results

No survey questions showed a significant trend between specific answers and clinician recognition.

The only question that showed a difference between PCCM and non-PCCM physicians was: “How long does it usually take from the time a patient clinically develops ARDS to the time you receive all the information needed to make a diagnosis of ARDS?”. Answers included:

< 6 hours, 6-12 hours, 12-24 hours, 24-48 hours, and >48 hours. For those taking care of ARDS patients in our cohort, only PCCM physicians reported times over 12 hours and only 2 (0.08%) non-PCCM physicians on service reported times over 6 hours (Figure 27). For RTs, no questions showed a significant difference between high and low number of ICUs, but all RTs who answered 'Disagree' to "It is easy to initiate and administer LTVV" performed above expectation (Figure 29).

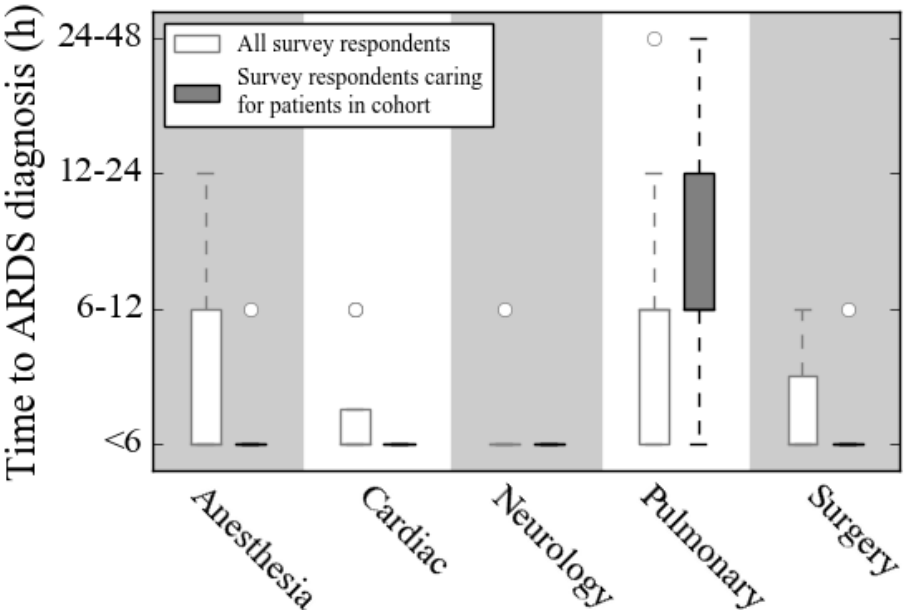


Figure 27: Physician reported time to diagnosis by ICU care team
ICU average reported times to receipt of all information necessary to make an ARDS diagnosis. White bars represent all survey responders while dark bars are restricted to only physicians who took care of patients in our cohort.

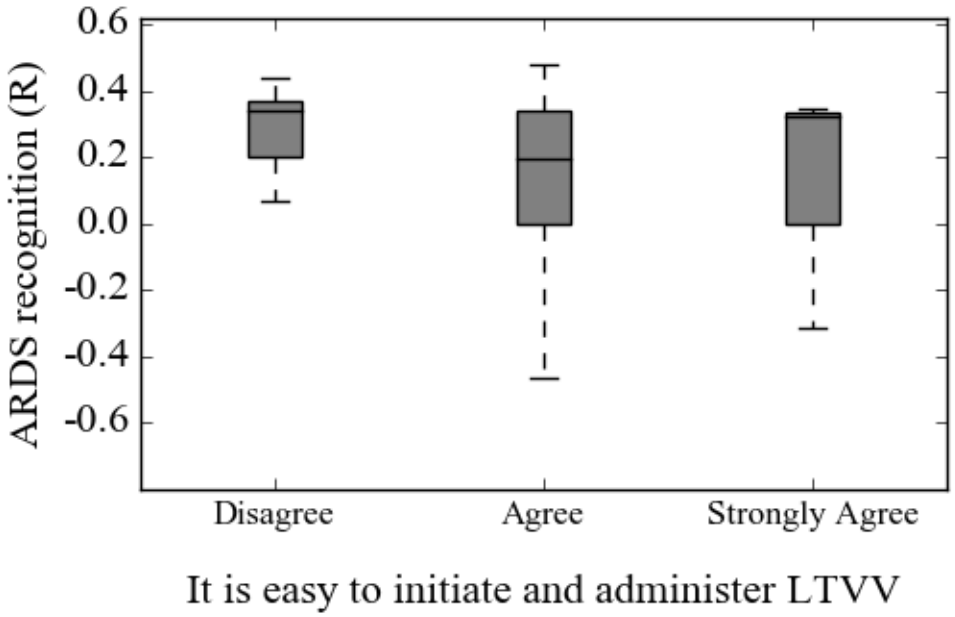


Figure 28: Respiratory therapist ARDS recognition rates and responses to ease of LTVV administration question

7.4 Discussion

In this chapter, we evaluate reported barriers, attitudes, and experiences in order to assess potential drivers of the local culture division we observed previously. It is important to delve into the specific barriers as the type of difference observed would have an effect on potential intervention design. For example, if a systems barrier exists, that may require an organizational restructuring, whereas a difference in attitudes would most benefit from an intervention focused on clinician education and engagement. The results of our analysis provide evidence to support our prior assumption of ARDS recognition as a major barrier to LTVV use. Furthermore, our findings have important implications for the assessment of implementation barriers in future studies.

First, the survey results suggest that ARDS recognition is a more significant barrier than systems or attitudes. The only question that top performing physicians answer differently than

their peers focuses on delays related to the synthesis of all clinical data points necessary to make the diagnosis of ARDS. When asked about issues with availability of each individual data point (lab values, imaging, etc), there is no difference observed in the answers, implying that it is not the result of a difference in workplace environment. Furthermore, we see no difference in reported attitudes from top performers toward the benefits or appropriateness of LTVV use for patients with ARDS. These results imply that the process of making the diagnosis is particularly challenging, which is consistent with the fact that the physician's primary role in LTVV delivery is the diagnosis of ARDS. The actual delivery of LTVV usually is the responsibility of the respiratory therapist. To this end, we see that respiratory therapists who disagree with the idea that LTVV delivery is easy all have above average ARDS recognition rates.

Both of these findings speak to a possibility of disproportionate engagement. For both physicians and respiratory therapists, those that perform better are reporting more difficulties. Those that recognize ARDS less often report no issues with the process, implying that perhaps they are not actually attempting the process. If a clinician does not diagnose or treat a particular condition, they would report no difficulties doing so because they don't experience those difficulties. Furthermore, while there is a survey question that asks about the providers' experience with not making an ARDS diagnosis promptly, there is no difference in the answers of top performers. This finding is still consistent with the theory of disproportionate engagement, because providers actually making the diagnosis may make it promptly and lack of a diagnosis is not necessarily the same as a delayed diagnosis.

These results have important implications for how barriers to evidence-based practice use are assessed. As described above, prior approaches have focused on barriers that the majority of

providers report as important. Our analysis suggests that this method may be confounded by differing levels of clinician engagement and barriers reported by a minority of provider may be more reflective of real-world experiences. Thus, provider engagement should be included as an influential factor in the analysis of potential barriers to implementation.

Limitations of this analysis focus on specific survey items. As with prior surveys, our analysis of the magnitude of each barrier is limited. We did not ask respondents to rank barriers with respect to each other, so it is possible that the survey captures a heterogenous experience under a single answer. Furthermore, while the survey included questions about how often physicians experienced barriers, the answers were not specific time frames, but more general options like ‘frequently’ or ‘rarely’, which can have variable definitions. These limitations are mitigated by the fact that the question with differences between provider groups actually does utilize specific time frames, asking the respondents quantify the delay in terms of hours.

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Appendix A: Supplementary Information

Supp Table 1: Demographics of cohorts and subgroups from Chicago hospital dataset

Factor	ARDS n=361	ARDS non-documented n=317	Control n=388	Control non-documented n=371	Pooled Documented n=60
Women (n [%])	153 [42]	135 [42]	158 [41]	150 [40]	26 [45]
Height (in) (median [SD])	67.0 [4.4]	67.0 [4.4]	67.0 [4.2]	67.0 [4.2]	66.0 [4.5]
Predicted Body Weight (kg) (median [SD])	63.9 [11.8]	63.9 [11.7]	63.9 [11.4]	65.9 [11.4]	61.5 [11.8]
P_aO_2/F_IO_2 ratio (lowest)					
mild (median [SD])	243 [29.6]	245 [29.6]	240 [28.4]	240 [28.4]	234 [29.2]
moderate (median [SD])	142 [29.4]	141.2 [29.2]	150 [28.7]	150 [28.6]	135 [30.4]
severe (median [SD])	67.5 [16.7]	68.4 [16.3]	72.5 [20.4]	74.0 [19.4]	60.0 [20.2]
P_{plat} (highest) (cm H2O) (median [SD])	25.0 [7.0]	24.0 [6.7]	22.0 [5.9]	22.0 [5.4]	30.0 [7.6]
ICU admission weight (kg) (median [SD])	80.0 [26.1]	81.1 [26.6]	84.0 [24.4]	84.0 [24.6]	77.2 [22]
Bilateral Infiltrates (n [%])	-	-	173 [50.7]	178 [50.7]	57 [95]
Admitting ICU (n [%])					
Medical	127 [35]	104 [33]			
Surgical	43 [12]	42 [13]			
Neuro	37 [10]	33 [10]	-	-	-
Cardiac	64 [18]	65 [20]			
Mixed	80 [22]	73 [23]			

Supp Table 2: Data availability for Chicago hospital dataset

Factor	ARDS n=361	Control n=388	Pooled Documented n=60	ARDS non-documented n=317	Control non-documented n=371
P_aO_2/F_IO_2 ratio (lowest)	281	388	54	244	371
P_{plat} (highest)	272	350	53	235	334
ICU admission weight	298	386	56	259	369
Bilateral Infiltrates	-	341	60	-	325
Admitting ICU	361	0	-	361	-

Supp Table 3: Data availability for LUNG SAFE full cohort

	ARDS				Control				Documented		
	All	Non-documented			All	Non-documented					
Factor		Both	End	Entry		Both	End	Entry	Both	End	Entry
Predicted Body Weight	2584	899	991	1774	1193	887	903	1107	760	1768	896
P_aO_2/F_IO_2											
Entry	2584	899	991	1774	1190	885	901	1104	760	1767	896
End	1621	531	594	1098	642	469	476	597	483	1124	568
Lowest	2584	899	991	1774	1192	887	903	1106	760	1767	896
Documentation											
Entry	2584	899	991	1774	1193	887	903	1107			
End	2507	899	991	1718	1155	887	903	1076			
Both											
Chest imaging quadrants											
Entry	2527	871	961	1726	1011	740	754	932	750	1715	880
End	1261	412	461	860	496	364	374	453	375	875	444
Both	2566	889	981	1761	1133	840	854	1052	754	1754	886
SOFA score											
Entry	1493	473	527	1016	624	461	468	577	449	1049	524
End	966	338	370	653	373	271	275	343	299	649	343
Highest	1888	601	669	1266	781	565	573	724	582	1337	679
ICU admission weight	2554	888	980	1750	1173	875	890	1090	753	1743	887
Study Age		899	991	1774		887	903	1107	760	1768	896
Region	2584				1193						
Modality	2445	818	907	1664	1119	824	839	1037	732	1705	863

Supp Table 4: Data availability for LUNG SAFE VAC subgroup

	ARDS				Control				Documented		
		Non-documented				Non-documented					
Factors	All	Both	End	Entry	All	Both	End	Entry	Both	End	Entry
Predicted Body Weight	399	126	132	271	203	154	155	184	139	301	147
P_aO_2/F_IO_2											
Entry	399	126	132	271	203	154	155	184	139	301	147
End	248	68	73	167	103	74	74	91	87	195	93
Lowest	399	126	132	271	203	154	155	184	139	301	147
Documentation											
Entry	399	126	132	271	203	154	155	184			
End	385	126	132	258	203	154	155	184			
Both											
Chest imaging quadrants											
Entry	393	123	129	265	169	125	126	152	137	293	145
End	215	62	67	145	102	80	81	92	73	160	80
Highest	398	125	131	270	191	144	145	173	138	299	146
SOFA score											
Entry	224	63	69	147	106	74	74	92	84	174	91
End	132	45	49	87	47	33	33	40	47	91	52
Highest	260	76	82	172	122	88	88	108	95	200	102
ICU admission weight	396	126	132	270	201	152	153	182	137	298	145
Study Age		126	132	271		154	155	184	139	301	147
Region	399				203						

Supp Table 5: Predictors of lowest $\hat{V}_T$ (mL/kg PBW) in LUNG SAFE documentation variation subgroups, all modalities (β-coefficient [95% CI])

	ARDS Non-documented		**Control Non-documented**		**Documented**	
Factors	End	Entry	End	Entry	End	Entry
Predicted Body Weight	**-4*** **[-4.69, -3.31]**	**-4.21*** **[-4.77, -3.65]**	**-7.62*** **[-8.66, -6.58]**	**-6.86*** **[-7.74, -5.98]**	**-5.27*** **[-5.9, -4.65]**	**-5.82*** **[-6.7, -4.94]**
P_aO_2/F_iO_2						
Entry	0.35 [-0.11, 0.81]	0.52 [0.18, 0.86]	0.25 [-0.3, 0.81]	0.18 [-0.3, 0.66]	0.49 [0.13, 0.85]	0.74 [0.21, 1.28]
End	0.23 [-0.61, 1.08]	0.31 [-0.3, 0.91]	-0.65 [-1.73, 0.43]	-0.44 [-1.28, 0.39]	-0.26 [-0.79, 0.27]	-0.46 [-1.29, 0.37]
Lowest	0.87 [0.37, 1.37]	**1.08*** **[0.69, 1.46]**	0.46 [-0.16, 1.07]	0.44 [-0.07, 0.95]	**1.1*** **[0.69, 1.51]**	**1.46*** **[0.87, 2.05]**
Chest imaging quadrants						
Entry	-0.03 [-0.32, 0.25]	-0.39 [-0.59, -0.19]	-0.19 [-0.65, 0.26]	-0.34 [-0.71, 0.02]	**-0.89*** **[-1.17, -0.62]**	**-0.88*** **[-1.3, -0.46]**
End	-0.29 [-0.84, 0.26]	-0.74 [-1.12, -0.35]	-0.43 [-1.2, 0.34]	-0.53 [-1.1, 0.03]	-0.73 [-1.1, -0.37]	-0.66 [-1.22, -0.1]
Highest	-0.61 [-1.13, -0.09]	**-1.17*** **[-1.55, -0.78]**	-0.62 [-1.12, -0.11]	-0.69 [-1.1, -0.29]	**-1.46*** **[-1.82, -1.09]**	**-1.64*** **[-2.22, -1.07]**
SOFA score						
Entry	0.03 [-0.85, 0.9]	0.07 [-0.61, 0.75]	-0.4 [-1.32, 0.51]	0.13 [-0.57, 0.83]	0.49 [-0.11, 1.08]	0.5 [-0.4, 1.4]
End	-0.04	-0.09	0.35	0.85	0.47	0.52

	[-0.96, 0.88]	[-0.79, 0.6]	[-0.72, 1.43]	[-0.06, 1.76]	[-0.18, 1.12]	[-0.36, 1.4]
Highest	-0.25 [-1.01, 0.51]	-0.43 [-1.04, 0.18]	-0.36 [-1.32, 0.6]	0.08 [-0.65, 0.82]	0.07 [-0.5, 0.64]	0.18 [-0.65, 1.01]
ICU admission weight	-0.33 [-1.26, 0.61]	-0.9 [-1.77, -0.04]	-0.41 [-1.9, 1.07]	-0.52 [-1.78, 0.74]	**-1.9*** **[-2.81, -0.98]**	-2.21 [-3.64, -0.78]
Study Age	-1.26 [-2.6, 0.07]	-0.98 [-2.1, 0.14]	-1.43 [-2.89, 0.03]	-1.56 [-2.8, -0.33]	-0.08 [-0.9, 0.75]	0.66 [-0.51, 1.82]
modality	0.26 [-0.23, 0.76]	0.3 [-0.09, 0.69]	0.16 [-0.49, 0.81]	-0.04 [-0.58, 0.49]	-0.21 [-0.62, 0.21]	-0.2 [-0.83, 0.43]

* ***p* < 0.00009**

Empty cells indicate category was not used due to data being unavailable or not relevant.

Supp Table 6: Predictors of lowest $\hat{V}_T$ (mL/kg PBW) in LUNG SAFE documentation variation subgroups, VAC subgroup (β-coefficient [95% CI])

	ARDS Non-documented		Control Non-documented		Documented	
Factors	End	Entry	End	Entry	End	Entry
PBW	**-2.8***	**-4.11***	**-6.22***	**-8.67***	**-7.17***	**-4.96***
	[-3.63, -1.96]	**[-4.87, -3.35]**	**[-7.48, -4.96]**	**[-10.08, -7.25]**	**[-8.2, -6.13]**	**[-6.18, -3.75]**
P_aO_2/F_iO_2						
Entry	0.81	0.9	0.38	0.2	0.76	0.65
	[-0.07, 1.7]	[0.26, 1.54]	[-0.5, 1.27]	[-0.7, 1.11]	[0.04, 1.48]	[-0.31, 1.61]
End	0.6	0.91	-0.67	-0.91	0.36	0.05
	[-0.75, 1.95]	[-0.26, 2.08]	[-2.48, 1.15]	[-2.81, 0.98]	[-0.78, 1.49]	[-1.3, 1.39]
Lowest	0.92	0.99	0.18	0.23	0.95	0.8
	[-0.02, 1.85]	[0.29, 1.7]	[-0.74, 1.1]	[-0.72, 1.18]	[0.14, 1.77]	[-0.28, 1.88]
Chest imaging quadrants						
Entry	0.11	-0.21	0.18	-0.21	-1.09	-0.87
	[-0.48, 0.71]	[-0.6, 0.18]	[-0.52, 0.88]	[-0.93, 0.51]	[-1.65, -0.52]	[-1.68, -0.07]
End	-0.71	-0.86	-0.04	-0.11	-1.23	-1.46
	[-2.03, 0.61]	[-1.59, -0.13]	[-0.96, 0.89]	[-0.99, 0.77]	[-1.89, -0.57]	[-2.5, -0.42]
Highest	-0.03	-0.5	0.04	-0.26	**-1.67***	-1.71
	[-0.87, 0.82]	[-1.06, 0.06]	[-0.75, 0.82]	[-1.07, 0.54]	**[-2.39, -0.96]**	[-2.74, -0.68]
SOFA score						
Entry	0.32	-0.05	-1.51	-1.02	0.08	0.3
	[-0.84, 1.47]	[-1.06, 0.96]	[-3.13, 0.1]	[-2.45, 0.41]	[-0.92, 1.09]	[-1.07, 1.68]

End	-0.3 [-1.8, 1.2]	-0.65 [-1.81, 0.51]	0.71 [-1.45, 2.87]	0.61 [-1.3, 2.52]	-0.18 [-1.5, 1.13]	0.79 [-1.01, 2.6]
Highest	-0.34 [-1.51, 0.83]	-0.48 [-1.4, 0.43]	-0.85 [-2.28, 0.58]	-0.67 [-1.96, 0.62]	-0.57 [-1.57, 0.43]	-0.61 [-2.12, 0.9]
ICU admission weight	-0.04 [-1.53, 1.45]	-0.83 [-2.02, 0.35]	-0.39 [-2.32, 1.55]	-0.83 [-2.85, 1.19]	-1.05 [-2.38, 0.28]	0.3 [-1.5, 2.1]
Study Age	-0.28 [-1.83, 1.27]	-0.56 [-1.7, 0.58]	-0.76 [-2.61, 1.09]	-0.88 [-2.68, 0.91]	-1 [-2.72, 0.72]	-0.64 [-2.91, 1.63]

* ***p* < 0.00009**

Empty cells indicate category was not used due to data being unavailable or not relevant.

Appendix B: LUNG SAFE Case Report Form

Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE – ['LUNG-SAFE']

BASELINE DATA COLLECTION FORM - Study Day 1

Date of fulfillment of criteria for severe respiratory failure (from screening form):_____

Date of Hospital Admission: _ _ / _ _ / 201 _ _ _ : _ _ (24 h clock)

Height (first documented at ICU admission): _____ □ inch□ cm

Weight (first documented at ICU admission): _____ □ lbs □ kg

Admission Source:
□ Other hospital (ICU) □ Other hospital (Ward) □ ER/ambulance
□ Operating Room □ Study Hospital (Ward) □ Study Hospital (Other ICU) □ Other, please specify _____

If patient transferred from another hospital and/or ICU:
What was date of Admission to that Hospital: _____
If patient transferred from external ICU, what was date of ICU Admission: _____

Reason for transfer: □ ICU Bed Unavailability □ Need for more advanced support
□ Need for specialty medical input □ Other (please be precise):_____

Co-morbidities (check all that Apply):
□ COPD
□ Diabetes Mellitus
□ Chronic Renal Failure
□ Active Neoplasm
□ Hematologic neoplasm
□ Immunosuppression
□ Heart failure: NYHA classes III-IV
□ Chronic liver failure (Child-Pugh Class C)
□ Home Ventilation

ARDS Risk Factor (check all that apply):

	Direct		**Indirect**
	Pneumonia		Non-pulmonary sepsis
	Aspiration of gastric contents		Major trauma

	Inhalational injury		Pancreatitis
	Pulmonary contusion		Severe burns
	Pulmonary vasculitis		Non-cardiogenic shock
	Drowning		Drug overdose
			Multiple transfusions/transfusion-associated acute lung injury (TRALI)
	OTHER (Specify):		
	NONE		

Date of the insult: _ _ / _ _ / _ _ _ _ OR Not Known ☐

Can hypoxemia be entirely explained by cardiac failure?
☐ Yes ☐ No

Did you use any of these method to rule out the cardiac origin of the disease? (check all that apply):

	Echocardiography
	Pulmonary artery catheter
	Transpulmonary thermodilution (e.g., PiCCO)
	Other (specify):
	None:

What is/are the cause(s) of the patient's acute hypoxemic respiratory failure (check all that apply)?
☐ Pneumonia
☐ Cardiac Failure
☐ Asthma
☐ ARDS
☐ COPD
☐ Unknown
☐ Other _____

Are there new or worsening respiratory symptoms within the last week?
☐ Yes ☐ No

DAILY DATA COLLECTION FOR PATIENTS WITH SEVERE RESPIRATORY FAILURE[1]

Day_____ Date of this form_____

Is the patient in the ICU on this date? □ YES □ NO*
* If "NO" please complete the discharge/Death forms

ARTERIAL BLOOD GAS	Units	Value
pH:		
PaO_2:		
$PaCO_2$:		
FiO_2:		
Arterial blood gas not available		☐
SpO2		

CHEST X-RAY (CXR) / CT SCAN	
Chest x-ray (CXR) / CT scan not available	☐
Bilateral opacities on the CXR/CT scan	**Yes** ☐ **No** ☐
Number of involved quadrants:	**1**☐ 2 ☐ 3 ☐ 4☐

Mechanical Ventilation *(Please record ventilatory settings as close as possible to the ABG)*:

☐ Invasive ☐ Non-invasive ☐ Only O_2 ☐ None
Modailty
☐ *Volume A/C*
☐ *PC/BIPAP/APRV*
☐ *SIMV*
☐ *PRVC*
☐ *PSV*
☐ *NAVA*
☐ *HFO*
☐ *CPAP*
☐ *T-Tube*
☐ Other

[1] Data is collected at at 10am on Days 1,2,3,5,7 inclusive, Day 10, 14, 21, 28 until ICU discharge/death.

Ventilatory settings:	
Respiratory Rate (set)	
Respiratory Rate (Total)	
Tidal Volume (ml)	
PEEP (cmH_2O)	
Plateau Pressure available?	**Yes ☐ No ☐**
Plateau Pressure (cmH_2O)	
Peak Inspiratory Pressure (PIP) (cmH_2O)	
Mean Airway Pressure (MAP) (cmH_2O)	
Is the patient triggering the Ventilator?	**Yes ☐ No ☐**
Oxygen flow (for t-tube or O2 therapy)	

Adjunctive Measures/Therapies (in the last 24 hours – check all that apply)

	Prone positioning *		CT scan
	Recruitment maneuvers		Alveolar surfactant
	Extracorporeal membrane oxygenation (If yes: V-V or A-V or V-A)		Lung Ultrasound
	High dose corticosteroids		Renal Replacement Therapy
	Almitrine besylate		Tracheostomy
	Continuous Sedation		Inhaled vasodilators
	Oesophageal pressure monitoring**		Neutrophil Elastase Therapy
	Continuous Neuromuscular Blocking Agents		
	Pulmonary Artery Catheter	Mean pulmonary arterial pressure:_____	
	None of the above		

Sequential Organ Failure Assessment (SOFA) Score (worst value over last 24hrs)

SOFA Score	Units	Value	NOT AVAILABLE
Estimated Glasgow Coma Scale			□
Mean Arterial Pressure	mmHg		□
Vasopressors used? Yes/No			
Dopamine infusion			□
Dobutamine infusion			□
Noradrenaline infusion			□
Adrenaline infusion			□
Platelet Count($\times 10^3/mm^3$)			□
Total Bilirubin	µmol/L mg/dL		□
Creatinine (mg/dL)			□
OR Creatinine (µmol/L)			□
OR Urine Output (mL/day)			□

*** For Patients Receiving prone position:**

	Units	Supine (before pronation)	Prone
pH:	--------		
PaO_2:			
$PaCO_2$:			
PEEP	cmH_2O		
Plateau pressure	cmH_2O	☐	
Duration of the session	hours		

**** For Patients receiving Oesophageal pressure measurement:**
Why was esophageal pressure used?
☐ To measure chest wall elastance
☐ To facilitate PEEP titration
☐ To assess the Work of breathing
☐ To assess synchrony
☐ Other:_____

OUTCOME AND ICU DISCHARGE/DEATH

OUTCOMES AT ICU DISCHARGE/DEATH

ICU (or day 90) Outcome (whichever event comes first)
□ Alive □ Dead

Date of ICU discharge/Death: _ _ / _ _ / _ _ _ _

For patients without severe respiratory failure only this section is necessary

Discharged to:
□ Other ICU □ Hospital Ward □ Intermediate Care Unit □ Hospital Discharge

Did the patient develop additional risk factors for ARDS (in addition to those indicated in the "STUDY DATA-BASELINE" form) (check all that apply):

	Direct		**Indirect**
	Pneumonia		Non-pulmonary sepsis
	Aspiration of gastric contents		Major trauma
	Inhalational injury		Pancreatitis
	Pulmonary contusion		Severe burns
	Pulmonary vasculitis		Non-cardiogenic shock
	Drowning		Drug overdose
			Multiple transfusions/transfusion-associated acute lung injury (TRALI)
	OTHER (Specify):		

Could patient hypoxemia be entirely explained by cardiac failure?
☐ Yes ☐ No

Did you use any of these method to rule out the cardiac origin of the disease? (check all that apply):

	Echocardiography
	Pulmonary artery catheter
	Transpulmonary thermodilution (e.g., PiCCO)
	Other (specify):
	None:

Did the patient have ARDS at any stage of their ICU stay?
☐ Yes ☐ No

Respiratory status at ICU Discharge (Check all that apply):
□ Tracheostomy □ Invasive ventilation □ Non-invasive ventilation □ CPAP
□ Oxygen therapy □ No oxygen therapy

Date of liberation from MV: _ _ / _ _ / _ _ _ _

If patient did not survive:
What was the most important factor leading to ICU Death (Check one)?
- □ Respiratory Failure
- □ Cardiovascular Failure [i.e. Unresponsive Shock]
- □ Renal Failure
- □ Hepatic Failure
- □ Coagulation Failure
- □ Neurologic Failure

Limitations in Care
Was there a decision to withhold a life sustaining measure at any time during the ICU stay? □ Yes □ No

Was there a decision to withdraw a life sustaining measure at any time during the ICU stay? □ Yes □ No

Date of decision to withhold/withdraw life sustaining measures: _ _ / _ _ / _ _ _ _

Did the patient undergo an autopsy (i.e. post mortem) examination
□ Yes □ No

If an Autopsy was performed, what did lung histology demonstrate [Check all that apply]
□ Pneumonia
□ Diffuse Alveolar Damage
□ Pulmonary Oedema
□ Atelectasis
□ Alveolar Haemorrhage
□ No lung pathology
□ Other (Specify) _____

DISCHARGE/DEATH

ADDITIONAL DISCHARGE FORM FOR PATIENT WITHOUT RISK FACTORS FOR ARDS

This form is required only for patients with "none" selected as risk factor for ARDS

Was a broncho-alveolar lavage (BAL) fluid analysis performed? ☐ Yes ☐ No

If yes, please provide

- Day BAL performed*: _ _ / _ _ / _ _ _ _
- Cytological analysis:

Macroscopic aspect: ☐ normal ☐ bloody or pink ☐ lactescent

Number of cells: _ _ _ _ _ _ / mL

Macrophages: _ _ % lymphocytes: _ _ % neutrophils: _ _ %

mast cells: _ _ % eosinophils: _ _ % siderophages: _ _ % other cells: _ _ %

- Microbiological analyses performed (check all that apply):
  - ☐ Bacterial culture
  - ☐ *Pneumocystis jiroveci* stain or PCR
  - ☐ Fungal analysis
  - ☐ Viral PCRs

  Positive result(s): _ _ _ _ _

*if several BAL were performed: results of the nearest to the ARDS diagnosis

Were immunological tests performed? ☐ Yes ☐ No

If yes, please check if the result is positive:

☐ antinuclear antibodies

☐ Antisynthetase antibodies

☐ Anti-CCP antibody

☐ ANCA

☐ Rheumatoid factor

☐ Other: _ _ _ _

Was the patient taking pneumotoxic medications* before the development of ARDS? ☐ Yes ☐ No

If yes, provide name of the drugs (check all that apply)

☐ Amiodarone

☐ Methotrexate

☐ Hydrochlorothiazide

☐ Tyrosine kinase inhibitors

☐ Chemotherapy agents: _ _ _ _ _ _ _ _

☐ Other: _ _ _ _ _ _ _ _ _

* see www.pneumotox.com for more information

Was a final etiology for ARDS obtained? ☐ Yes ☐ No

If yes, specify: _

Was a chest CT-scan performed? ☐ Yes ☐ No

If yes, day chest CT-scan performed: _ _ / _ _ / _ _ _ _

If yes, provide CT-scan patterns present (check all that apply):

☐ *Honeycombing*

☐ *Ground class attenuation*

☐ *Traction bronchiectasis*

☐ *Interlobular septal thickening*

☐ *Air space consolidation including atelectasis*

☐ *Other* Specify: _

*if several CT were performed: results of the nearest to the ARDS diagnosis

DISCHARGE/DEATH

HOSPITAL OUTCOME

Hospital (or 90 day) Outcome (whichever event occurs first)

□ Alive □ Dead

Date of hospital discharge: _ _ / _ _ / _ _ _ _

Appendix C: Weiss et al Physician Survey

This survey asks questions about your current ICU practice. For each of these questions, please think about your responses in the context of the ICU <u>where you spend most of your time</u> (i.e., not including working part-time or moonlighting in other ICUs).

Please indicate your response by placing an "X" in the appropriate box.

<u>Part 1</u>

The first group of questions refers to how you use <u>daily sedation interruption</u> (sometimes called daily sedation holidays) for your intubated patients.

1. What percentage of your intubated patients are appropriate for daily sedation interruption based on the best available evidence?

0 ☐	5 ☐	10 ☐	15 ☐	20 ☐	25 ☐	30 ☐	35 ☐	40 ☐	45 ☐	50 ☐	55 ☐	60 ☐	65 ☐	70 ☐	75 ☐	80 ☐	85 ☐	90 ☐	95 ☐	100 ☐

2. How strong do you believe the evidence is that your intubated patients will benefit from daily sedation interruption?

Very strong	Strong	Neither strong nor weak	Weak	Very weak
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

3. In your opinion, how large is the clinical benefit of daily sedation interruption?

Very large	Large	Moderate	Small	Very small
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

4. What percentage of your intubated patients have contraindications to receiving daily sedation interruption?

0 ☐	5 ☐	10 ☐	15 ☐	20 ☐	25 ☐	30 ☐	35 ☐	40 ☐	45 ☐	50 ☐	55 ☐	60 ☐	65 ☐	70 ☐	75 ☐	80 ☐	85 ☐	90 ☐	95 ☐	100 ☐

5. Please state your level of agreement or disagreement with the following statement:

I will only order/administer sedation interruption if I am <u>certain</u> my intubated patient is an appropriate candidate.

Strongly agree ☐ 1	Agree ☐ 2	Disagree ☐ 3	Strongly disagree ☐ 4

<u>Part 2</u>

The next group of questions refers to how you use <u>spontaneous breathing trials (SBTs)</u> for your intubated patients who are eligible for liberation from mechanical ventilation (sometimes called “weaning”).

6. How long would you wait to perform an SBT once a patient first appears clinically ready to attempt one?

No wait (immediate SBT) ☐ 5	12 hours ☐ 4	One day ☐ 3	Two days ☐ 2	Three or more days ☐ 1

7. Please state your level of agreement or disagreement with the following statement:

I will order/administer an SBT even if I think I might have to re-intubate a patient after weaning and extubation.

Strongly agree	Agree	Disagree	Strongly disagree

☐ 4	☐ 3	☐ 2	☐ 1

Part 3

The next group of questions refers to how you use low tidal volume ventilation (LTVV, sometimes called lung protective ventilation) for your patients with acute respiratory distress syndrome (ARDS).

8. What percentage of your patients with ARDS warrant treatment with LTVV based on the best available evidence?

0 ☐	5 ☐	10 ☐	15 ☐	20 ☐	25 ☐	30 ☐	35 ☐	40 ☐	45 ☐	50 ☐	55 ☐	60 ☐	65 ☐	70 ☐	75 ☐	80 ☐	85 ☐	90 ☐	95 ☐	100 ☐

9. How strong do you believe the evidence is that your patients with ARDS will benefit from LTVV?

Very strong ☐ 5	Strong ☐ 4	Neither strong nor weak ☐ 3	Weak ☐ 2	Very weak ☐ 1

10. In your opinion, how large is the benefit of LTVV in reducing mortality for your ARDS patients?

Very large ☐ 5	Large ☐ 4	Moderate ☐ 3	Small ☐ 2	Very small ☐ 1

11. What percentage of your patients with ARDS have contraindications to receiving LTVV?

0 ☐	5 ☐	10 ☐	15 ☐	20 ☐	25 ☐	30 ☐	35 ☐	40 ☐	45 ☐	50 ☐	55 ☐	60 ☐	65 ☐	70 ☐	75 ☐	80 ☐	85 ☐	90 ☐	95 ☐	100 ☐

12. Please state your level of agreement or disagreement with the following statement:

I will only order/administer LTVV if I am <u>certain</u> my patient has ARDS.

Strongly agree	Agree	Disagree	Strongly disagree
☐ 1	☐ 2	☐ 3	☐ 4

<u>Part 4</u>

The next questions ask about other aspects of your practice. They do not refer <u>only</u> to patients with ARDS or those eligible for liberation from mechanical ventilation.

13. I am bothered if I have to re-intubate a patient after weaning and extubation.

Very much	Quite a bit	Somewhat	A little bit	Not at all
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

14. If I start a patient on <u>empirical</u> antibiotics, I will continue them until I am <u>certain</u> the patient does not have an infection.

Always	Usually	Sometimes	Rarely	Never
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

15. It feels like I made a mistake if I have to re-intubate a patient after weaning and extubation.

Strongly agree	Agree	Disagree	Strongly disagree
☐ 1	☐ 2	☐ 3	☐ 4

16. If I start a patient on empirical antibiotics, I will discontinue them after about 48 hours if there is no clear evidence of infection (e.g., negative blood cultures, no pulmonary infiltrate, etc.).

Always	Usually	Sometimes	Rarely	Never
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Part 5

The next two questions ask about how you view new therapies and diagnostic tests.

	Always	Usually	Sometimes	Rarely	Never
17. I wait until a new therapy or diagnostic test has been used for a while by other people before changing my own practice	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. If a new therapy or diagnostic test looks beneficial, I will use it even if more studies are needed to know with certainty that it is better than the current standard of care	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Part 6

Next, we want you to tell us about factors in the ICU where you usually practice that may contribute to delays in prompt diagnosis or treatment.

First, we are going to ask you about patients who may be eligible for daily sedation interruption.

Please state your level of agreement or disagreement with the following statements:

	Strongly agree	Agree	Disagree	Strongly disagree
19. It is easy for me to obtain all the information I need to determine whether a patient is eligible for daily sedation interruption.	☐ 4	☐ 3	☐ 2	☐ 1
20. It is easy to make sure a patient is scheduled to receive or has received daily sedation interruption.	☐ 4	☐ 3	☐ 2	☐ 1
21. It is easy to order daily sedation interruption.	☐ 4	☐ 3	☐ 2	☐ 1

22. How long does it usually take from the time a patient becomes clinically ready for daily sedation interruption to the time you identify or are notified they are ready for daily sedation interruption?

Less than 6 hours	6 to just under 12 hours	12 to just under 24 hours	24 to just under 48 hours	More than 48 hours
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

For questions 23 to 26, please describe how often the following issues delay patients receiving daily sedation interruption:

	Very frequently	Frequently	Sometimes	Rarely	Never
23. Providers placing too much emphasis on relative contraindications to daily sedation interruption.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Delay in you being notified that a patient is eligible for daily sedation interruption.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Not promptly recognizing that a patient is eligible for daily sedation interruption even when all data are available and the criteria appear to be met.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. The time from ordering daily sedation interruption to your patient receiving it.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Now we are going to ask you about patients who may be eligible for a spontaneous breathing trial (SBT).

Please state your level of agreement or disagreement with the following statements:

	Strongly agree	Agree	Disagree	Strongly disagree
27. It is easy for me to obtain all the information I need to determine whether a patient is eligible for an SBT.	☐ 4	☐ 3	☐ 2	☐ 1
28. It is easy to make sure a patient is scheduled to receive or has received an SBT.	☐ 4	☐ 3	☐ 2	☐ 1
29. It is easy to order an SBT.	☐ 4	☐ 3	☐ 2	☐ 1

30. How long does it usually take from the time a patient becomes clinically ready for an SBT to the time you identify or are notified they are ready for an SBT?

Less than 6 hours	6 to just under 12 hours	12 to just under 24 hours	24 to just under 48 hours	More than 48 hours
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

For questions 31 to 34, please describe how often the following issues delay patients receiving an SBT:

	Very frequently	Frequently	Sometimes	Rarely	Never
31. Providers placing too much emphasis on relative contraindications to an SBT.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Delay in you being notified that a patient is eligible for an SBT.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Not promptly recognizing that a patient is eligible for an SBT even when all data are available and the criteria appear to be met.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. The time from ordering an SBT to your patient receiving it.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Part 7

Now we are going to ask you about patients who may have ARDS.

Please state your level of agreement or disagreement with the following statements:

	Strongly agree	Agree	Disagree	Strongly disagree
35. It is easy for me to obtain all the information I need to determine whether a patient has ARDS.	☐ 4	☐ 3	☐ 2	☐ 1
36. It is easy to make sure a patient is receiving LTVV.	☐ 4	☐ 3	☐ 2	☐ 1
37. It is easy to order LTVV.	☐ 4	☐ 3	☐ 2	☐ 1

38. How long does it usually take from the time a patient clinically develops ARDS to the time you receive all the information needed to make a diagnosis of ARDS?

Less than 6 hours	6 to just under 12 hours	12 to just under 24 hours	24 to just under 48 hours	More than 48 hours
☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

For questions 39 to 43, please describe how often the following issues delay the diagnosis of ARDS and/or the decision to treat a patient with LTVV:

	Very frequently	Frequently	Sometimes	Rarely	Never
39. Obtaining a chest radiograph and being notified of the results.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
40. Obtaining an arterial blood gas and being notified of the results.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
41. Finding time to review all the patient's records and decide whether to make a diagnosis of ARDS.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
42. Not promptly recognizing that a patient has ARDS even when all data are available and the criteria appear to be met.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
43. The time from ordering LTVV to your patient receiving it.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Part 8

Now we are going to ask questions about communication in your ICU.

	Very high quality	High quality	Average	Low quality	Very low quality
44. Rate the quality of collaboration you have with nurses in your ICU.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
45. Rate the quality of collaboration you have with respiratory therapists in your ICU.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Part 9

We want to know how physicians talk to each other to share information and to get advice. We are asking this information for research purposes only; this information is critical to understand professional network structure and dynamics, and to design future interventions to improve the care of mechanically ventilated patients. Remember, all information you give us is confidential.

46. Please write down the names of up to five critical care physicians with whom you work in your ICU whose input you regularly seek to help you make good clinical decisions based on the best available evidence. Also, please indicate how often you seek their input by placing an X in the appropriate box.

Name of colleague (First and last name)	Several times per week	Once per week	Few times per month	Once per month	Less than once per month
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

47. Please write down the names of up to five critical care physicians with whom you work in your ICU who regularly seek your input to help them make good clinical decisions based on the best available evidence. Also, please indicate how often they seek your input by placing an "X" in the appropriate box.

Name of colleague (First and last name)	Several times per week	Once per week	Few times per month	Once per month	Less than once per month
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

48. Please write down the names of up to three critical care physicians with whom you work in your ICU who you think tend to be the first to use new therapies or diagnostic tests.

Name of colleague (First and last name)

49. Please write down the names of <u>up to five</u> critical care physicians with whom you work in your ICU who you consider to be your friends.

Name of colleague (First and last name)

Part 10

50. What is your age?

Under 25	25-34	35-44	45-54	55-64	65 or older
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

51. What is your gender?

Male	Female
☐ 1	☐ 2

52. What was your position from July 1, 2013 until June 30, 2014?

Attending physician	Fellow	Nurse	Respiratory therapist
☐ 1	☐ 2	☐ 3	☐ 4

53. From July 2013 until June 2014, were you working in the same ICU as you are currently?

Yes	No
☐ 1	☐ 2

54. What year did you complete your fellowship training?

Still in training	2009-2014	2004-2008	1999-2003	1994-1998	1989-1993	1984-1988	1983 or earlier
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8