

# Chapter 18

## Trend Analysis: Evolution of Tidal Volume Over Time for Patients Receiving Invasive Mechanical Ventilation

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### Learning Objectives

Learn the importance of trend analysis

- To understand epidemiological changes in health and delivery of healthcare.
- To assess the implementation of new evidence into clinical practice.
- Assess real world effectiveness of discoveries (interrupted time series design; difference in differences, regression discontinuity).

Learn methods of performing trend analysis

- Cochrane-Armitage test for trend.
- Differences Logistic/linear regression analysis with time as an independent variable.

Addressing changes in aspects of the study population over time with relation to the main dependent and independent variables

- Adjustment/confounding.
- Interaction of covariates with time and outcomes.

Refining the research question

- Addressing limitations in the data.

## 18.1 Introduction

Healthcare is a dynamic field that is constantly evolving in response to changes in disease epidemiology, population demographics, and new discoveries. Epidemiologic changes in disease prevalence and outcomes have important implications for determining healthcare resource allocation. For example, identifying trends that show increasing utilization of invasive mechanical ventilation may

suggest local or societal needs for more intensive care unit beds, critical care nurses and physicians, and mechanical ventilators. Additionally, changes in healthcare outcomes over time can provide insight into the adoption of new scientific knowledge and identify targets for quality improvement where implementation of evidence has been slow or where results from tightly-controlled trials are not realized in the “real world”. Trend analyses utilize statistical methods in an attempt to quantify changes to better understand the evolution of health and healthcare delivery.

To highlight the uses of trend analysis, we present a study evaluating how scientific evidence supporting treatment of one condition may be generalized by healthcare professionals to other conditions in which the treatment is untested. We investigated adoption of evidence supporting lower tidal volumes during mechanical ventilation for patients admitted to the medical intensive care unit (MICU) compared to the cardiac care unit (CCU).

Critically ill patients can develop severe difficulty breathing and may require the assistance of a breathing machine (ventilator) through a process called invasive mechanical ventilation. Patients may require invasive mechanical ventilation for a wide variety of conditions such as pneumonia, asthma, and heart failure. In some cases, the lungs fall victim to massive inflammation triggered by severe systemic diseases such as infection, trauma, or aspiration. The inflammation leads to leakage of fluid into the lungs (pulmonary edema) in a condition called the acute respiratory distress syndrome (ARDS). ARDS is defined by four criteria [1]:

1. Acute in nature
2. Bilateral infiltrates on chest x-ray
3. Not caused by heart failure (as heart failure can also cause pulmonary edema)
4. Severe hypoxia defined by the partial pressure of arterial oxygen to fraction of inspired oxygen (P/F) ratio

Regardless of the cause of respiratory failure, many patients receiving invasive mechanical ventilation develop ARDS.

Mechanical Ventilators are most often set to deliver one volume of air for each breath (i.e. tidal volume). Too much air delivered during each breath can cause over-stretch and injury to already impaired lungs, resulting in yet further damage by the systemic release of inflammatory chemicals. In the setting of ARDS, large tidal volumes cause already inflamed lungs to release more inflammatory chemicals that can cause further lung damage but also damage to other organs. Based on the theory that lower tidal volumes may act to protect the lungs and other organs by decreasing lung over-distention and release of inflammatory chemicals during invasive mechanical ventilation, a landmark study demonstrated that use of lower tidal volumes for patients receiving invasive mechanical ventilation with ARDS resulted in an absolute mortality reduction of 8.8 % [2]. Since then, several studies have demonstrated improvements in mortality over time for patients with ARDS [3–6] as well as a reduction in the tidal volumes used in all patients in MICUs [3, 7].

Because the definition of ARDS strictly excludes patients with heart failure, patients with heart failure have been excluded from studies evaluating effects and

epidemiology of tidal volume reduction. In order to fill current knowledge gaps regarding tidal volume selection among patients with heart failure, we sought to use trend analysis to explore temporal changes in tidal volumes among patients with heart failure as compared to patients with ARDS. In order to address difficulties with identifying the indication for mechanical ventilation in electronic health records, we adjusted our analytic plan to focus on trends in tidal volume selection in CCUs (where heart failure is the most common cause of invasive mechanical ventilation) as compared to MICUs (where most patients with ARDS receive care).

## 18.2 Study Dataset

In this case study we used the Medical Information Mart for Intensive Care II (MIMIC-II) database version 3 [8], which contains de-identified, granular patient-level information for 48,018 patients across 57,995 ICU hospitalizations at a single academic center from 2002 to 2011. The MIMIC II Clinical Database is a relational database that contains individual values for a variety of patient variables such as lab results, vital signs, and billing codes.

## 18.3 Study Pre-processing

We identified patients in MIMIC-II who received invasive mechanical ventilation. We excluded patients <18 years of age; pediatric critical care practices and the physiology of pediatric patients differ from adult patients. While we initially sought to compare patients with ARDS to patients with heart failure, accurate identification of specific indications for mechanical ventilation in electronic health records was difficult and subject to misclassification. Thus, we selected patients admitted to the MICU as a surrogate for patients with ARDS [3, 7] and patients admitted to the CCU as a surrogate for patients with heart failure. We excluded patients whose initial ICU service was a surgical ICU as the majority of patients would likely have been receiving invasive mechanical ventilation for routine post-operative care. For patients who were admitted to multiple different intensive care units (ICU) during a single hospitalization, we based inclusion/exclusion criteria on the initial ICU admission. We further excluded patients who had missing data on tidal volume.

## 18.4 Study Methods

Our primary outcome was average tidal volume ordered by clinicians during assist-control ventilation. We used the Cochran-Armitage test for trends to evaluate changes over time in the percentage of patients in each unit who required

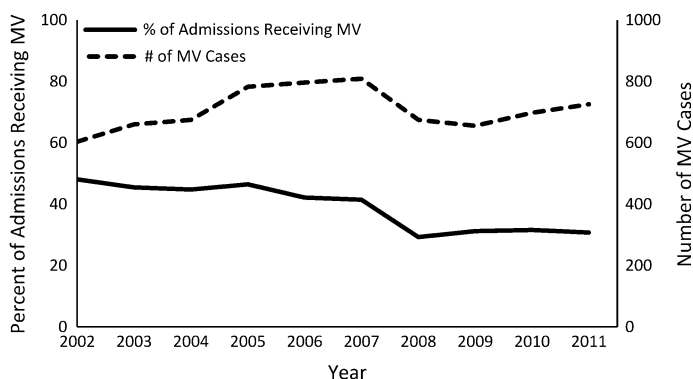
invasive mechanical ventilation. We calculated the average tidal volume for the entire period of assisted invasive mechanical ventilation for each patient and then calculated the average of tidal volumes for the MICU and CCU each year. In order to assess for a temporal trend in tidal volume, we performed multivariable linear regression (see Sect. 5.2 in Chap. 5 on Data Analysis for details) stratified by ICU type. Analyses for trends in tidal volume change over time included a dependent (outcome) variable of tidal volume and independent variable (exposure) of time (year of intensive care admission). Year of admission is a common time variable chosen for trend analysis. Smaller sample sizes can result in large amounts of noise and fluctuations when analyzing shorter time frames such as ‘month’. We chose multivariable linear regression because tidal volume is a continuous variable and because regression techniques allowed for adjustment of effect estimates for possible confounders of the relationship between time and tidal volume. We adjusted for patient age and gender as both could affect tidal volume selection. To determine differences in tidal volume trends between the MICU and CCU, we included an interaction term between time and patient location in regression models. In order to determine if variability in average tidal volumes had changed over time, we compared the coefficient of variation (standard deviation normalized to the sample mean) at the beginning of the study to the end of the study, in each unit [9]. All testing was done at an alpha level = 0.05.

All studies were deemed exempt by the Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess. All statistical testing was performed with SAS 9.4 (Cary, NC).

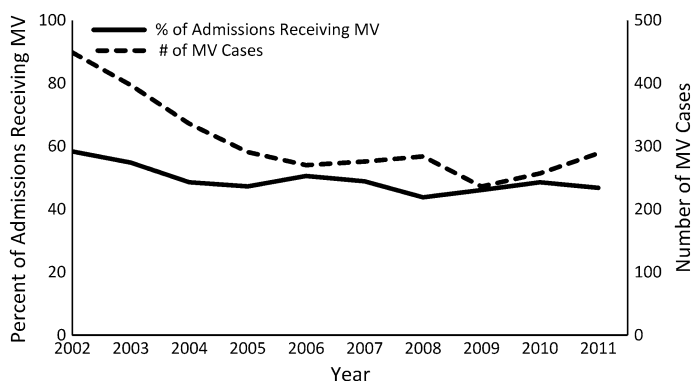
## 18.5 Study Analysis

We identified 7083 patients receiving invasive mechanical ventilation in the MICU and 3085 patients in the CCU from 2002 to 2011. The number of patients receiving invasive mechanical ventilation in the MICU fluctuated during the study period, but the net change was consistent with a 20.2 % increase in mechanical ventilation between 2002 and 2011. The percentage of MICU patients who received invasive mechanical ventilation decreased from 48.1 % in 2002 to 30.8 % in 2011 ( $p < 0.0001$  for trend) (Fig. 18.1). Thus, the driver of increasing mechanical ventilation utilization was a rising MICU census rather than a greater likelihood of using mechanical ventilation among MICU patients. In contrast to trends in the MICU, mechanical ventilation in the CCU declined by 35.6 %, with trends driven by a lower CCU census and a reduction in the proportion of patients receiving invasive mechanical ventilation decreased (from 58.4 % in 2002 to 46.8 % in 2011) ( $p < 0.0001$  for trend) (Fig. 18.2).

Average tidal volumes in the CCU decreased by 24.4 % over the study period, from 661 mL (SD = 132 mL) in 2002 to 500 mL (SD = 59) in 2011 ( $p < 0.0001$ ).

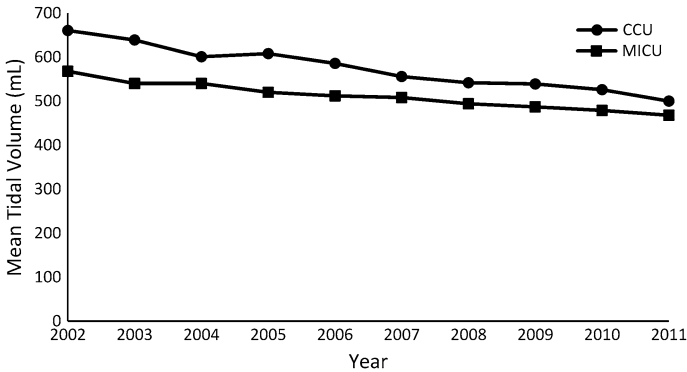


**Fig. 18.1** Percent of all admissions (*left y-axis*) and number of cases (*right y-axis*) receiving invasive mechanical ventilation in the MICU. *MV*—invasive mechanical ventilation, *MICU*—medical intensive care unit



**Fig. 18.2** Percent of all admissions (*left y-axis*) and number of cases (*right y-axis*) receiving invasive mechanical ventilation in the CCU. *MV*—invasive mechanical ventilation, *CCU*—cardiac care unit

Tidal volume in the MICU decreased by 17.6 %, from 568 mL (SD = 121 mL) in 2002 to 468 mL (SD = 65 mL) in 2011 ( $p < 0.0001$ ) (Fig. 18.3). During each year of the study period, the CCU used higher tidal volumes than the MICU ( $p < 0.0001$  for comparison between units for each year). After adjusting for age and gender, tidal volume in the CCU decreased by an average of 18 mL per year (95 % CI 16–19 mL,  $p < 0.0001$ ) while tidal volumes in the MICU decreased by 11 mL per year (95 % CI 10–11,  $p < 0.0001$ ). The decrease in tidal volume in the CCU was greater than the decrease in the MICU ( $p_{\text{interaction}} < 0.0001$ ). Additionally, the coefficient of variation decreased in both units during the study period (MICU: 20.0 % in 2002 to 11.8 % in 2011,  $p < 0.0001$ ; CCU: 21.3 % in 2002 to 13.9 % in 2011,  $p < 0.0001$ ).



**Fig. 18.3** Average tidal volume in the MICU and CCU per year. For each year, the average tidal volume was higher in the CCU,  $p < 0.0001$  for comparison for each year. The decrease (slope) of the change in tidal volume was greater for the CCU,  $p < 0.001$ . *MICU*—medical intensive care unit. *CCU*—cardiac care unit

## 18.6 Study Conclusions

While there is strong evidence indicating survival benefits for lower tidal volumes in patients with non-cardiogenic pulmonary edema (ARDS) [2] there is little evidence for its use in patients with cardiogenic pulmonary edema (heart failure). Using the MIMIC-II database, we identified a decrease in rates of invasive mechanical ventilation in both the MICU and CCU, despite an increase in the actual number of invasive mechanical ventilation cases in the MICU. Tidal volumes decreased in both ICUs over the course of the study period. Interestingly, tidal volumes decreased at a faster rate in the CCU as compared to the MICU, with tidal volumes nearly equivalent in the MICU and CCU by 2011. The more rapid rate of tidal volume decline in the CCU occurred despite little evidence supporting use of low tidal volumes for patients with cardiogenic pulmonary edema or heart failure. In addition to declining tidal volumes, variability in tidal volume selection also declined over time, demonstrating an evolving tendency towards greater uniformity in tidal volume selection. Our findings demonstrate a generalization of the evidence for ARDS towards the treatment of patients previously excluded from studies investigating tidal volumes during mechanical ventilation.

## 18.7 Next Steps

Our analysis has several limitations. First, many factors affect tidal volume choice in ICUs including patient height, respiratory drive, and acid/base status. If these unmeasured factors were to have changed over time in our study population, they would be potential confounders of our observation that tidal volumes have been set

lower over time. Including covariates related to these factors in the regression analysis could reduce possible confounding. For the purposes of this case study, we limited our covariates to demographic characteristics, but others could be added to the model in future analyses. Second, our primary outcome variable is mean tidal volume. We did not look at changes in tidal volumes during a patient's hospitalization, an analysis that may also be performed in future studies. Third, tidal volumes are generally normalized to the ideal body weight, as normal lung size correlates with ideal body weight. We did not have ideal body weights available in MIMIC-II.

The next step from this study would be determine associations between changes in tidal volume and changes in clinical outcomes. Studies attempting to assess the association of changing tidal volumes with clinical outcomes would need to be vigilant to measure multiple potentially confounding variables that may have been co-linear secular trends along with decreasing tidal volumes. Additionally, we used patients admitted to the MICU as a surrogate for patients with ARDS and to the CCU as a surrogate for patients with heart failure. In future studies we would hope to refine our search algorithms within EHR databases to be able to identify patients with ARDS and heart failure with minimal risk of misclassification bias. The strengths of EHR databases such as MIMIC-II lie in their unique granularity, providing a wealth of opportunities to measure clinical details such as pharmacy data, laboratory results, physician notes (via natural language processing), etc., that allow a greater ability to attenuate confounding.

## 18.8 Connections

Trend analyses assess health care changes over time. In our case study we used linear regression techniques to determine the association of time on a continuous variable (tidal volume). Regression methods allow researchers to account for confounding variables that may have changed over time along with exposures and outcomes of interest. However linear regression techniques are limited to data that have a linear relationship. For non-linear data, transformation techniques (e.g. log-transformation) can be used to convert a nonlinear distribution to a more linear relationship, higher-order polynomial regression, or spline regression may be used; alternatively Poisson regression may be used for count data.

Other techniques should be used for categorical outcomes. The Cochran-Armitage test for trends is a modified Pearson chi-squared test that allows for ordering of one of the variables (i.e. a time variable). Additionally multivariable logistic regression tools allow for trend analysis for categorical data with the potential for addition of possible confounders as covariates.

These analytic techniques can be applied broadly beyond our case study. The fundamental aspect of trend analyses stems from the fact that the main independent/exposure variable is time. With this concept, numerous conditions and treatments can be studied to see how their utilization changes over time such as

subgroups of patients receiving invasive mechanical ventilation [10], patients with tracheostomy [11], etc. Trend analysis is important to evaluate how well clinical trial findings have penetrated usual care by assessing changes in trends with relationship to new research findings or new guidelines. Additionally, trend analyses are critical for quality assessment in determining if certain interventions or process have significantly changed outcomes. As with all statistics, one must understand the assumptions involved in the types of tests being performed and ensure that the data meet those criteria.

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## Code Appendix

The code used in this case study is available from the GitHub repository accompanying this book: <https://github.com/MIT-LCP/critical-data-book>. Further information on the code is available from this website.

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