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_____ _____

Ogbonna C. Ogbu Date

Approval Sheet

The Association Between Tidal Volume and Ventilator-Associated Events in Adult ICU Patients

By

Ogbonna Chigozie Ogbu, MBBS

Master of Science
Clinical Research

_____

Greg S. Martin, MD, MSc
Advisor

_____

David J. Murphy, MD, PhD
Advisor

_____

Amita Manatunga, PhD
Committee Member

_____

John E. McGowan, Jr., MD
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

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By

Ogbonna Chigozie Ogbu

MBBS, University of Ibadan, 2005

Advisors:

Greg S. Martin, MD, MSc

David J. Murphy, MD, PhD

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Abstract

The Association Between Tidal Volume and Ventilator-Associated Events in Adult ICU Patients

By

Ogbonna Chigozie Ogbu, MBBS

Objective: Ventilator-associated events (VAE) are associated with an increased risk for mortality in adult ICU patients; however, there is still limited data regarding modifiable risk factors. Mechanical ventilation with a high tidal volume is associated with an increased risk for developing the acute respiratory distress syndrome and pneumonia which are both common causes of VAEs. The primary purpose of this study was to evaluate the association between tidal volume and VAE in adult ICU patients receiving invasive mechanical ventilation. In addition, the association between tidal volume and two broad categories of VAEs (infection-related and non-infection related VAEs) was also examined.

Study design: Nested matched case-control study

Study setting: Medical, surgical, coronary care and neurointensive care units at two academic teaching hospitals

Methods: Patients who received conventional invasive mechanical ventilation for more than 2 days were screened for VAE. VAE cases were matched to up to five controls based on admission ICU and the cases' duration of mechanical ventilation prior to VAE onset. Conditional logistic regression was used to estimate the association between mean tidal volume and VAE. Additional models examined the association between mean tidal volume and both infection-related and non-infection related VAEs independent of additional patient and clinical characteristics.

Results: A total of 190 VAE cases were identified and were successfully matched to 931 controls. Mean tidal volume was independently associated with the occurrence of ventilator-associated events when adjusted for the matching variables (adjusted OR, 1.21 per 1 ml/kg PBW; 95% CI, 1.11 – 1.33) and after controlling for 16 additional patient characteristics (adjusted OR, 1.23; 95% CI, 1.11 – 1.35). This association remained significant for non-infection-related VAEs (adjusted OR, 1.23; 95% CI, 1.09 – 1.38) and there was a trend towards significance for infection-related VAEs (adjusted OR, 1.22; 95% CI, 0.99 – 1.50). In the multivariable model, male sex and black race were also independent risk factors for VAE.

Conclusion: Invasive mechanical ventilation with a high tidal volume is independently associated with an increased risk of developing a VAE in adult ICU patients. More research is needed to determine if the use of low tidal volume ventilation decreases VAE rates.

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INTRODUCTION

Almost 800,000 patients are estimated to require invasive mechanical ventilation in the US every year.(1) Although it is potentially life-saving, mechanical ventilation is also associated with complications such as ventilator-associated pneumonia (VAP) and the acute respiratory distress syndrome (ARDS) leading to increased morbidity and mortality.(2, 3) Routine surveillance for the complications of mechanical ventilation is a key step in the process of designing and implementing effective prevention programs; however, surveillance for individual clinical conditions, such as VAP, is labor-intensive and is often unreliable.(4) In response to this challenge, the Centers for Disease Control and Prevention (CDC) introduced a new approach to surveillance that shifted the focus away from individual clinical conditions to a heterogeneous group of conditions called ventilator-associated events (VAE).(5)

A VAE is an episode that is characterized by a sustained period of worsening oxygenation in a mechanically ventilated patient whose gas exchange was previously stable or improving (Figure 1). Mechanically ventilated patients who experience VAEs have an increased risk for in-hospital mortality and other adverse clinical outcomes.(6-9). The increased morbidity and mortality seen in these patients has made VAE prevention an important quality improvement goal; however, there are still few studies that have identified modifiable risk factors for VAEs.(10)

One important area that is still poorly understood is whether ventilator settings, such as tidal volume, affect the risk of developing a VAE. While there is no consensus on the most appropriate tidal volume for mechanically ventilated patients, several studies have shown that a high tidal volume is associated with an increased risk for two of the most

common causes of VAEs – pneumonia and ARDS.(11, 12) This suggests that a high tidal volume may be a modifiable risk factor for ventilator-associated events.

The primary objective of this study was to examine the association between tidal volume and ventilator-associated events in adult ICU patients receiving invasive mechanical ventilation. We hypothesized that a high tidal volume is independently associated with an increased risk for developing a VAE among patients who have received invasive mechanical ventilation for more than 2 days. We also examined the association between tidal volume and the two broad categories of ventilator-associated events: infection-related VAEs and non-infection-related VAEs (Figure 2).

BACKGROUND

Surveillance for ventilator-associated events was introduced by the Centers for Disease Control and Prevention in 2013.(5) The current tiered VAE definition algorithm defines three types of events (Figure 1).(13) The first tier is called a ventilator-associated condition (VAC) and is defined by a sustained increase in the fraction of inspired oxygen (FiO_2) and/or positive end-expiratory pressure (PEEP) level of a patient whose FiO_2 and/or PEEP level has been stable or decreasing for at least two days. The second tier, called an infection-related ventilator-associated complication (IVAC), is a VAC that is determined to be due to an infectious cause (based on changes in a patient's temperature, white blood cell count and antibiotic use). The third tier, called possible ventilator-associated pneumonia (PVAP), is an IVAC that is determined to be due pneumonia (based on respiratory cultures). Consequently, VAEs can be divided into two broad groups based on cause: (a) non-infection-related VAEs, which consist of all ventilator-associated conditions that do not meet the definition of an infection-related ventilator associated condition, and (b) infection-related VAEs, which consists of infection-related ventilator-associated complications and possible ventilator-associated pneumonia (Figure 2).

Ventilator-associated events are associated with an increased risk of adverse patient outcomes. In a recent study, Klompas et al examined 20,356 consecutive episodes of mechanical ventilation over a five-year period and found that, compared to matched controls, patients with VAEs had twice the odds of in-hospital mortality (adjusted OR, 1.98; 95% CI, 1.60 – 2.44).(14) The study also found that VAEs were associated with a 3-day longer ventilator length of stay (95% CI, 2.96 – 3.29 days) and a 1.5-day longer

hospital LOS (95% CI, 1.37 – 1.55 days). Several recent studies have demonstrated similar findings.(6-9)

The surveillance definitions for ventilator-associated events were purposefully designed to capture a wide range of potentially preventable clinical conditions and complications. Two of the most frequently identified conditions are pneumonia and ARDS. In a study by Boyer and colleagues which prospectively evaluated 1209 patients who received mechanical ventilation for more than 2 days, 35 (52%) of the 67 VAE cases that were identified were determined to be caused by either pneumonia or ARDS.(15) In a larger single-center study by Lilly and colleagues, ARDS was determined to be associated with the majority (73%) of the 387 VAE cases that were identified over a three-year period.(16)

There have been several recent investigations into the association between processes of care in the ICU and ventilator-associated events. In a large multicenter quality improvement program, increased adherence to paired spontaneous awakening and spontaneous breathing trials was associated with a decrease in VAE rates over time.(17) In an analysis of 9603 consecutive episodes of mechanical ventilation, Klompas and colleagues found that a sedation regimen that included either a benzodiazepene or propofol was associated with an increased risk for VAE compared to a regimen that did not (HR 1.4, 95% CI 1.1 – 1.7 and HR 1.3, 95% CI 1.1 – 1.6 respectively).(18) In an effort to identify modifiable risk factors for VAE, Lewis and colleagues performed a case-control study which found that a mandatory mode of ventilation (adjusted OR, 3.4; 95% CI 1.6–8.0) and a positive fluid balance (adjusted OR, 1.2; 95% CI, 1.03–1.40) were independently associated with an increased risk for VAE.(19) Interestingly, Lewis and

colleagues did not observe an association between tidal volume and ventilator-associated events. However, the mean maximum tidal volume observed in the study was relatively low (less than 8 ml/kg of predicted body weight).

Tidal volume is an important determinant of patient outcomes during invasive mechanical ventilation.(11) This has been most clearly demonstrated in patients with ARDS; however, there is a growing body of evidence that suggests that it is true for all mechanically ventilated patients.(11, 20) The most recent evidence comes from an individual patient data meta-analysis that included studies of critically-ill patients who were mechanically ventilated in the ICU for more than 48 hours.(12) The study found that patients who were ventilated with tidal volumes ≤ 7 ml/kg PBW had a decreased odds of developing a composite outcome of pneumonia and ARDS compared to patients who received tidal volumes ≥ 10 ml/kg PBW (OR, 0.72; 95% CI, 0.52 – 0.98). Given that ARDS and pneumonia account for a significant proportion of VAEs, the results of the meta-analysis suggests that a high tidal volume could potentially increase a patient's risk for VAE. If true, this would support the use of low tidal volume ventilation as a strategy to reduce ventilator-associated events.

METHODS

Specific Aims

Aim 1: To estimate the association between mean tidal volume and ventilator-associated events in adult patients who have received invasive mechanical ventilation for more than 2 days.

Hypothesis: A high tidal volume is associated with an increased risk for ventilator-associated events in adult ICU patients who have received invasive mechanical ventilation for more than 2 days.

Aim 2a: To estimate the association between mean tidal volume and non-infection-related ventilator-associated events in adult patients who have received invasive mechanical ventilation for more than 2 days.

Hypothesis: A high tidal volume is associated with an increased risk for non-infection-related ventilator-associated events in adult ICU patients who have received invasive mechanical ventilation for more than 2 days.

Aim 2b: To estimate the association between mean tidal volume and infection-related ventilator-associated events in adult patients who have received invasive mechanical ventilation for more than 2 days.

Hypothesis: A high tidal volume is associated with an increased risk for infection-related ventilator-associated events in adult ICU patients who have received invasive mechanical ventilation for more than 2 days.

Study design and setting

A matched nested case-control study was performed using a cohort of ICU patients admitted to two teaching hospitals within a single university health system between January 1, 2013 and December 31, 2014.

Study participants

Patients admitted to any of the eight participating ICUs during the study period were screened for eligibility. Patients were eligible if they were older than 18 years and received conventional mechanical ventilation through an endotracheal tube or tracheostomy tube for more than 2 days. Patients for whom a predicted body weight could not be calculated (due to missing data on height) were excluded.(20) Only the first episode of mechanical ventilation was included if a patient was intubated more than once during the study period.

VAE case selection

All patients who were included in the study were screened for ventilator-associated events using mechanical ventilation data extracted from the electronic medical records (EMR). Ventilator-associated events were defined using the current CDC surveillance definition.(13) If a patients had more than one VAE during the study period, the first episode was used to define their VAE onset day.

For aim 2, patients with VAEs were further subdivided into two groups: infection-related VAEs and non-infection-related VAEs (Figure 2). All VAE cases who met the definition of an IVAC were classified as infection-related VAEs, while patients who met the definition for a VAC but did not meet the definition of an IVAC were classified as non-infection-related VAEs.

Control selection

Controls were selected from eligible patients who did not develop a VAE during the study period. Each VAE case was matched to 5 controls, where available, on the basis of their admission ICU and the duration of mechanical ventilation prior to the case's VAE onset day. All patients selected as controls had a ventilator length of stay that was at least one day longer than the duration of mechanical ventilation prior to their matched case's VAE onset day. Each control was then assigned a "match day" that corresponded to the VAE onset day of their matched case. Matching was performed using a Mayo Clinic SAS macro (gmatch).(21)

Primary Exposure

The primary exposure was mean tidal volume. This was calculated using the highest exhaled tidal volume on each day starting from the first day of mechanical ventilation until the VAE onset day in cases or the match day in controls. The absolute tidal volume (in milliliters) was obtained from the electronic medical record and then expressed as a relative tidal volume in ml/kg of predicted body weight. Predicted body weight was calculated based on the patient's height using the following formulas: for males, 50 + 0.91 × (height in centimeters - 152.4); for females, 45.5 + 0.91 × (height in centimeters - 152.4).(20)

Covariates

We recorded the patient's age, race, sex and height on day one of mechanical ventilation. Race was categorized into three groups: white, black or other/unknown. The Charlson Comorbidity Index (CCI) was calculated using ICD-9 codes that were based on discharge diagnoses.(22, 23) We also recorded the presence of any of the following specific

comorbidities within the CCI: congestive heart failure, moderate to severe liver disease, moderate to severe chronic kidney disease and chronic lung disease. The sequential organ failure assessment (SOFA) score was calculated using the variables recorded on day one of mechanical ventilation.(24)

We also recorded clinically relevant hospital exposures that occurred during the period from the day of intubation and until the VAC onset day in cases or from the day of intubation until the match day in controls. These included the use of intravenous opioid medications (fentanyl, hydromorphone or morphine), the use of any intravenous sedative medications (midazolam, lorazepam, propofol or dexmedetomidine) and the transfusion of any packed red blood cells, platelets or fresh frozen plasma during the defined exposure period.

Data Sources and Data cleaning

All data used in the study was extracted from the electronic medical record system (Cerner, Kansas City, MO) through a clinical data warehouse (MicroStrategy, Tysons Corner, VA). At both hospitals, the patient's tidal volume and height are entered manually into the electronic medical record (EMR) by the respiratory therapists and nursing staff respectively. To ensure the accuracy of these variables, the top and bottom 0.5% of all entries were manually reviewed. Consequently, tidal volume values less than 250 ml or greater than 1800 ml were determined to be outliers and excluded from the analysis (less than 0.5% of all documented entries). We also excluded height values that were less than 142.2 cm because a review of the EMR revealed that a height below this threshold frequently represented a vertical measurement of a patient with either bilateral lower extremity amputations or severe lower extremity contractures.

Statistical Analysis

Patient and clinical care characteristics of VAE cases and controls were summarized using means for continuous variables and proportions for categorical variables. The adjusted association between mean tidal volume and ventilator-associated events was estimated using conditional logistic regression to account for matching.

For aim 1, a bivariate analysis of the association between mean tidal volume and VAE, adjusted for the matching variables, was first performed. This model was then adjusted for the following 16 additional pre-specified patient and clinical care characteristics: age, sex, race, a history of congestive heart failure, moderate to severe liver disease, moderate to severe chronic kidney disease or chronic lung disease, Charlson Comorbidity Index, SOFA score, any use of intravenous opioid or sedative medications and any transfusion of packed red blood cells, platelets or fresh frozen plasma. Mean tidal volume was included as a continuous variable in both models. As a sensitivity analysis, we repeated the bivariate and multivariable analyses with mean tidal volume represented as a categorical variable based on quintiles.

For aim 2a, only non-infection-related VAE cases and their matched controls were included in the analysis. A bivariate analysis of the association between mean tidal volume and non-infection-related VAE was first performed. This model was then adjusted for 16 additional pre-specified patient and clinical care characteristics.

For aim 2b, only infection-related VAE cases and their matched controls were included in the analysis. A bivariate analysis of the association between mean tidal volume and infection-related VAE was performed and then the model was then adjusted

for 15 additional pre-specified patient characteristics. All IVAC cases received intravenous sedatives, as a result, this variable was excluded from the model.

All analyses were performed using SAS (version 9.4 Cary Corp., NC). A p-value less than 0.05 was considered statistically significant. This study was performed with the approval of the Institutional Review Board of Emory University.

RESULTS

A total of 2598 patients received invasive mechanical ventilation for more than 2 days during the study period (Figure 3). Two hundred and ninety-three patients (11%) were excluded because they did not have a valid height recorded in the electronic medical records. All of the 2305 patients who were eligible for the study were screened for ventilator-associated events. A total of 190 VAE cases were identified, and were successfully matched to a total of 931 controls. Of the 190 VAE cases, 133 were classified as non-infection-related VAEs, while the remaining 57 cases were classified as infection-related VAEs.

The demographic, anthropometric and clinical characteristics of VAE cases and their matched controls are shown in Table 1. Males accounted for 57% of VAE cases but only 48% of controls. The most common racial group among cases was white (48%), followed by black (33%), while the remainder were classified as other or unknown. Among controls, 50% were classified as black, 40% were classified as white, and 10% of patients were classified as other or unknown. There was no difference between the mean Charlson comorbidity index and the SOFA score on the day of intubation for cases and controls. VAE cases occurred most commonly in the medical ICUs (41%) while the fewest cases were seen in the coronary care units (4%). More than 90% of both cases and controls received an intravenous opioid or sedative medication. Mean tidal volume quintiles are shown in table 2.

The Association Between Mean Tidal Volume and Ventilator-Associated Events

Each increase in mean tidal volume of 1 ml/kg PBW increased the odds of ventilator-associated events by 21% (95% CI, 11% - 33%; p-value < 0.0001) when adjusted for

matching variables. This association remained significant after adjusting for 16 additional patient characteristics (adjusted OR, 1.23; 95% CI, 1.11 – 1.35) (Table 2). In the multivariable analysis, black patients had lower adjusted odds of developing a VAE when compared to white patients (adjusted OR, 0.65; 95% CI, 0.45 – 0.93). Also, male patients had higher adjusted odds of developing a VAE when compared to female patients (adjusted OR, 1.62; 95% CI, 1.14 – 2.31).

The results of the sensitivity analyses are shown in figures 3 and 4. In both of these models, mean tidal volume was included as categorical variable based on quintiles (Table 2). The reference group was the first quintile and it consisted of patients whose mean tidal volume was less than or equal to 7.4 ml/kg PBW. As shown in figure 3, when compared to the reference group, each subsequent quintile had higher adjusted odds of developing a VAE. The highest adjusted odds were seen when comparing the fifth quintile (mean tidal volume ≥ 10.1 ml/kg PBW) to the reference group (adjusted OR, 2.66; 95% CI, 1.57 – 4.49). This association remained significant after controlling for 16 additional patient characteristics (adjusted OR, 2.74; 95% CI, 1.58 – 4.75) (Figure 4).

The Association Between Mean Tidal Volume and Non-Infection-Related VAE

A total of 787 patients were included in this analysis (133 non-infection-related VAEs and 654 matched controls). The mean tidal volume was independently associated with non-infection-related VAE when adjusted for the matching variables (adjusted OR, 1.22 per 1 ml/kg PBW; 95% CI, 1.09 – 1.36; p-value = 0.0005). After controlling for 16 additional patient characteristics, the association remained significant (adjusted OR, 1.23; 95% CI, 1.09 – 1.38) (Table 3). The results of the multivariable analysis showed that

black patients had lower adjusted odds of developing a VAE when compared to white patients (adjusted OR, 0.62; 95% CI, 0.41 – 0.95).

The Association Between Mean Tidal Volume and Infection-Related VAE

A total of 334 patients were included in this analysis (57 non-infection-related VAEs and 277 matched controls). The mean tidal volume was independently associated with infection-related VAE when adjusted for the matching variables (adjusted OR, 1.20 per 1 ml/kg PBW; 95% CI, 1.01 – 1.43; p-value = 0.06). This association was not statistically significant after controlling for 15 additional patient characteristics (adjusted OR, 1.22; 95% CI, 0.99 – 1.50) (Table 2). In the multivariable analysis, male patients had higher adjusted odds of developing a VAE when compared to female patients (adjusted OR, 2.79; 95% CI, 1.34 – 5.82).

DISCUSSION

In this matched case-control study, a higher mean tidal volume was independently associated with an increased risk of developing a ventilator-associated event in adult ICU patients who had received invasive mechanical ventilation for more than 2 days. We also identified male sex and black race to be independent risk factors for VAEs.

Our study found that the odds of developing a VAE increased by 21% for every 1 ml/kg PBW increase in mean tidal volume after controlling for ICU admission and duration of mechanical ventilation. This association remained significant after adjusting for 16 additional patient characteristics. Further demonstrating that the highest risk was seen in patients who received the largest tidal volumes, the study found a greater than twofold increase in the odds of developing a VAE when comparing patients who received a mean tidal volume greater than or equal to 10.1 ml/kg to patients whose mean tidal volume was less than or equal to 7.4 ml/kg. In addition, when infection and non-infection-related VAEs were examined separately, a high mean tidal volume was found to be an independent risk factor for both categories of ventilator-associated events. This association remained statistically significant for non-infection-related VAEs after controlling for the prespecified patient characteristics; however, for infection-related VAEs, which accounted for only 30% of VAE cases, there was only a trend towards statistical significance.

The results of this study are consistent with prior studies that showed an association between the use of a high tidal volume during mechanical ventilation and the risk of developing ARDS. In a single-center retrospective cohort study performed by Gajic and colleagues, the odds of developing ARDS was increased by 29% for every 1 ml/kg PBW

increase in a patient's tidal volume on the first day of mechanical ventilation (adjusted OR, 1.29; 95% CI, 1.12 – 1.51).(25) A subsequent multi-center study by the same author showed that the use of an absolute tidal volume > 700 ml on day one of mechanical ventilation was associated with a greater than two-fold increase in the odds of developing ARDS (adjusted OR, 2.55; 95% CI, 1.67 – 3.89).(26)

However, the results of our study differed from a prior case-control study that showed no association between the mean maximum tidal volume and ventilator-associated events.(19) There are two possible reasons for this difference. First, our patient population was larger thereby increasing the power of our study. Second, in the prior study, the mean tidal volume in cases and controls was 7.7 ml/kg and 7.6 ml/kg PBW respectively, meaning that fewer patients were exposed to the potentially harmful high tidal volumes seen in our study (mean tidal volume of 9.2 ml/kg PBW and 8.7 ml/kg PBW for cases and controls respectively).

The association between mean tidal volume and ventilator-associated events can potentially be explained by the damaging effects of high tidal volumes on the lungs.(27) This process, referred to as volutrauma, has been demonstrated in animals and is thought to be due to overdistension of the lungs.(28) This overdistention can lead to disruption of the alveolar-capillary membrane leading to pulmonary edema. Volutrauma can also be associated with the release of inflammatory mediators in the lungs, termed biotrauma, leading to further lung damage.(27) The clinical sequelae of both volutrauma and biotrauma in mechanically ventilated patients can include a deterioration in oxygenation that can trigger a ventilator-associated event.

An additional finding in our study was that male patients had higher adjusted odds of developing a ventilator-associated event than female patients. This finding is consistent with the results of a large multicenter matched cohort study by Rello and colleagues which found an increased risk for ventilator-associated pneumonia in male patients when compared to female patients (adjusted OR, 1.58; 95% CI, 1.36 – 1.83).(29) Likewise, in our study, this association was only seen in the subset of patients who had infection-related VAEs (which would include patients with VAP) but not in patients who had non-infection-related VAEs.

Our study also found that black patients had lower adjusted odds of developing a ventilator-associated event when compared to white patients. This finding is consistent with studies that have shown that black patients have a decreased risk for developing ARDS when compared to white patients. A multi-center observational cohort study by Lemos-Filho et al found a 34% decrease in the odds of developing ARDS for black patient when compared to white patients.(30) This explanation would explain why, in our study the association was only seen in the subset of patients who had non-infection-related VAEs (which would include patients with ARDS) and not in patients who had infection-related VAEs.

An unexpected finding in this study was that patients whose race was classified as "other/unknown" had higher adjusted odds of developing infection-related VAEs when compared to white patients. This finding was only seen in the subset of patients with infection-related VAEs and not in patients with non-infection-related VAEs. A post-hoc analysis showed that this association was strongest in patients whose race was listed as

"unknown" in the electronic medical records (about 8% of the study population). The significance of this finding is unclear.

One of the strengths of this study was that the risk of misclassification of cases and controls was low because the case definition for ventilator-associated events is based on clear and objective criteria.(13, 31) This study was also nested within a defined cohort of patients which allowed all incident cases during the study period to be included in the analysis thereby reducing the risk of selection bias. The selection of controls was done independently of their exposure status further reducing the risk of selection bias. An additional strength was that mean tidal volume, which was the primary exposure, was measured prior to the onset of the ventilator-associated event in cases. This temporal relationship supports (but does not prove) a causal association between tidal volume and ventilator-associated events.

Our study has some limitations. A total of 293 (11%) mechanically ventilated patients were excluded from the study because they did not have a height recorded in the electronic medical record. However, the only significant difference between eligible and excluded patients was that the excluded patient patients were slightly less sick as evidenced by both a lower mean Charlson Comorbidity Index (CCI) and Sequential Organ Failure Assessment (SOFA) score. Of note, neither CCI nor SOFA have been found to be independently associated with the risk of developing a VAE.

A second limitation was that accurate data on the net fluid balance of patients within our study population was not available. This could potentially have been an important risk factor given that fluid overload is a known cause of ventilator-associated events.(32) A third limitation was that the study was carried out in only two centers, both of which

are large academic teaching hospitals within a single healthcare system, and this could limit the generalizability of our results to smaller community hospitals.

Our study is the first to show that a high tidal volume is independently associated with an increased risk for ventilator-associated events. The importance of this finding is two-fold. First, it provides further evidence of the potential harm associated with the use of a high tidal volume during mechanical ventilation. Second, it identifies a modifiable process of care that can serve as a target for quality improvement initiatives aimed at decreasing VAE rates.

In conclusion, our study found that in adult ICU patients who have received invasive mechanical ventilation for more than 2 days, exposure to a high tidal volume was independently associated with an increased risk of developing a ventilator-associated event. Although our findings are consistent with the current evidence regarding the harmful effects of a high tidal volume during mechanical ventilation, they still require confirmation. Future studies are needed to demonstrate whether the use of low tidal volume ventilation in critically ill patients leads to a decrease in VAE rates.

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TABLES AND FIGURES

Table 1. Characteristics of ventilator-associated event cases and their matched controls

Variable	VAE		Non-infection-related VAE		Infection-related VAE	
	Cases (n = 190)	Controls (n = 931)	Cases (n = 133)	Controls (n = 654)	Cases (n = 57)	Controls (n = 277)
Demographic and anthropometric characteristics						
Age, y, mean (SD)	56 (15)	58 (16)	57 (15)	58 (16)	55 (16)	57 (16)
Male sex, n (%)	109 (57%)	448 (48%)	72 (54)	315 (48)	37 (65%)	133 (48%)
Race, n (%)						
Black	69 (33%)	463 (50%)	51 (38%)	326 (50%)	18 (32%)	137 (50%)
White	91 (48%)	373 (40%)	69 (52%)	263 (40%)	22 (39%)	110 (38%)
Other/unknown	30 (16%)	95 (10%)	13 (10%)	65 (10%)	17 (30%)	30 (11%)
Height, cm, mean (SD)	170 (12)	170 (11)	169 (12)	169 (10)	171 (11)	171 (11)
Comorbidities and severity of illness						
Chronic lung disease, n (%)	63 (33%)	322 (35%)	49 (37%)	224 (34%)	14 (25%)	98 (35%)
Chronic liver disease, n (%)	68 (36%)	321 (34%)	54 (41%)	232 (35%)	14 (25%)	89 (32%)
Congestive heart failure, n (%)	30 (16%)	137 (15%)	22 (17%)	101 (15%)	8 (14%)	36 (13%)
Diabetes mellitus, n (%)	53 (28%)	321 (34%)	40 (30%)	230 (35%)	13 (23%)	91 (33%)
Chronic kidney disease, n (%)	90 (47%)	398 (43%)	67 (50%)	285 (44%)	23 (40%)	113 (41%)
Charlson comorbidity index, mean (SD)	5 (3)	5 (3)	6 (3)	5 (3)	4 (3)	5 (4)
Sequential organ failure assessment score, mean (SD)[a]	9 (3)	9 (4)	9 (3)	8 (4)	9 (3)	9 (3)
Clinical characteristics						
ICU type, n (%)						
Coronary care unit	7 (4%)	33 (4%)	6 (5%)	28 (4%)	1 (2%)	5 (2%)
Medical	78 (41%)	377 (40%)	59 (44%)	288 (44%)	19 (33%)	89 (32%)
Neurointensive care	60 (32%)	300 (32%)	36 (27%)	180 (28%)	24 (42%)	120 (43%)
Surgical	45 (24%)	221 (24%)	32 (24%)	158 (24%)	13 (23%)	63 (23%)
Tidal volume, ml/kg PBW, mean (SD)[b]	9.2 (1.9)	8.7 (1.6)	9.3 (1.9)	8.7 (1.6)	9.1 (1.9)	8.6 (1.6)
Transfusions, n (%)[c]						
Red blood cell transfusion	90 (47%)	394 (42%)	64 (48%)	274 (42%)	26 (46%)	120 (43%)
Fresh frozen plasma transfusion	38 (20%)	141 (15%)	25 (19%)	98 (15%)	13 (23%)	43 (16%)
Platelet transfusion	38 (20%)	153 (16%)	28 (21%)	103 (16%)	10 (18%)	50 (18%)
Infusions, n (%)						
Pressors on the day of intubation	103 (54%)	467 (50%)	73 (55%)	342 (52%)	30 (53%)	125 (45%)
Use of intravenous opioids[d]	187 (98%)	875 (94%)	131 (99%)	615 (94%)	56 (91%)	260 (94%)
Use of intravenous sedatives[e]	184 (97%)	859 (92%)	127 (95%)	602 (92%)	57 (100%)	257 (93%)

Definition of abbreviations: PBW = Predicted Body Weight; VAE = Ventilator-associated event;

a. Sequential organ failure assessment score calculated on the day of intubation
b. Mean of the highest recorded daily tidal volumes prior to the VAE onset day in cases or the match day in controls
c. Transfusion of at least one unit prior to VAE onset day in cases or match day in controls
d. Any use of intravenous fentanyl, morphine or hydromorphone prior to VAE onset day in cases or match day in controls
e. Any use of intravenous benzodiazepine, propofol or dexmedetomidine prior to VAE onset day in cases or match day in controls

Table 2. Distribution of mean tidal volume quintiles in the study population

Quintile	Number of Patients	Tidal Volume (ml/kg PBW)
First (reference group)	224	≤ 7.4
Second	224	7.5 – 8.2
Third	224	8.3 – 9.0
Fourth	224	9.1 – 10
Fifth	225	≥ 10.1

Definition of abbreviations: PBW = Predicted Body Weight

Table 3. Multivariable model of the association between mean tidal volume and ventilator-associated events

Variable	Odds Ratio (95% CI)	P-value
Tidal volume, ml/kg PBW[a]	**1.23 (1.11 – 1.35)**	**<0.0001**
Age, per 10 years	0.94 (0.84 – 1.05)	0.2984
Male sex	**1.62 (1.14 – 2.31)**	**0.0072**
Race		
White	Reference	-
Black	**0.65 (0.45 – 0.93)**	**0.0202**
Other/unknown	1.34 (0.82 – 2.21)	0.2446
Charlson comorbidity index	0.98 (0.91 – 1.04)	0.4334
Comorbidities		
Chronic lung disease	1.01 (0.71 – 1.43)	0.9708
Chronic liver disease	0.93 (0.62 – 1.42)	0.7450
Congestive heart failure	1.06 (0.68 – 1.68)	0.7876
Diabetes mellitus	0.84 (0.57 – 1.23)	0.3740
Chronic kidney disease	1.25 (0.83 – 1.89)	0.2909
Sequential organ failure assessment score[b]	1.01 (0.95 – 1.08)	0.7256
Red blood cell transfusion[c]	1.14 (0.79 – 1.66)	0.4876
Fresh frozen plasma transfusion[c]	1.36 (0.82 – 2.23)	0.2308
Platelet transfusion[c]	0.90 (0.55 – 1.46)	0.6619
Pressors on the day of intubation	1.04 (0.70 – 1.53)	0.8577
Use of intravenous opioids[d]	2.83 (0.82 – 9.78)	0.1012
Use of intravenous sedatives[e]	1.78 (0.69 – 4.57)	0.2308

Definition of abbreviations: PBW = Predicted Body Weight; VAE = Ventilator-associated event;

a. Mean of the highest recorded daily tidal volumes prior to the VAE onset day in cases or the match day in controls
b. Sequential organ failure assessment score calculated on the day of intubation
c. Transfusion of at least one unit prior to VAE onset day in cases or match day in controls
d. Any use of intravenous fentanyl, morphine or hydromorphone prior to VAE onset day in cases or match day in controls
e. Any use of IV midazolam, lorazepam, propofol or dexmedetomidine prior to VAE onset day in cases or match day in controls

Table 4. Multivariable model of the association between mean tidal volume and non-infection-related ventilator-associated events

Variable	Odds Ratio (95% CI)	P-value
Tidal volume, ml/kg PBW[a]	**1.23 (1.09 – 1.38)**	**0.0005**
Age, per 10 years	0.92 (0.80 – 1.05)	0.2182
Male sex	1.35 (0.88 – 2.05)	0.1665
Race		
White	Reference	-
Black	**0.62 (0.41 – 0.95)**	**0.0268**
Other/unknown	0.75 (0.38 – 1.49)	0.4075
Charlson comorbidity index	1.00 (0.93 – 1.08)	0.9260
Comorbidities		
Chronic lung disease	1.22 (0.81 – 1.85)	0.3366
Chronic liver disease	1.10 (0.68 – 1.77)	0.7129
Congestive heart failure	1.02 (0.59 – 1.75)	0.9454
Diabetes mellitus	0.84 (0.53 – 1.33)	0.4583
Chronic kidney disease	1.24 (0.76 – 2.03)	0.3937
Sequential organ failure assessment score[a]	1.01 (0.94 – 1.09)	0.7563
Red blood cell transfusion[c]	1.16 (0.75 – 1.81)	0.5061
Fresh frozen plasma transfusion[c]	1.20 (0.66 – 2.16)	0.5533
Platelet transfusion[c]	0.98 (0.55 – 1.72)	0.9329
Pressors on the day of intubation	1.02 (0.64 – 1.63)	0.9329
Use of intravenous opioids[d]	3.15 (0.70 – 14.21)	0.1364
Use of intravenous sedatives[e]	1.25 (0.47 – 3.34)	0.6559

Definition of abbreviations: PBW = Predicted Body Weight; VAE = Ventilator-associated event

a. Mean of the highest recorded daily tidal volumes prior to the VAE onset day in cases or the match day in controls
b. Sequential organ failure assessment score calculated on the day of intubation
c. Transfusion of at least one unit prior to VAE onset day in cases or match day in controls
d. Any use of intravenous fentanyl, morphine or hydromorphone prior to VAE onset day in cases or match day in controls
e. Any use of IV midazolam, lorazepam, propofol or dexmedetomidine prior to VAE onset day in cases or match day in controls

Table 5. Multivariable model of the association between mean tidal volume and infection-related ventilator-associated events

Variable	Odds Ratio (95% CI) [e]	P-value
Tidal volume, ml/kg PBW[a]	1.22 (0.99 – 1.50)	0.0565
Age, per 10 years	0.99 (0.80 – 1.23)	0.9723
Male sex	**2.79 (1.34 – 5.82)**	**0.0063**
Race		
White	Reference	-
Black	0.71 (0.32 – 1.56)	0.3925
Other/unknown	**3.64 (1.55 – 8.57)**	**0.0031**
Charlson comorbidity index	0.94 (0.83 – 1.06)	0.2905
Comorbidities		
Chronic lung disease	0.60 (0.28 – 1.28)	0.1862
Chronic liver disease	0.58 (0.23 – 1.42)	0.2309
Congestive heart failure	1.44 (0.58 – 3.55)	0.4322
Diabetes mellitus	0.69 (0.31 – 1.53)	0.3622
Chronic kidney disease	1.16 (0.52 – 2.61)	0.7172
Sequential organ failure assessment score[b]	1.04 (0.91 – 1.19)	0.5870
Red blood cell transfusion[c]	1.10 (0.50 – 2.45)	0.8141
Fresh frozen plasma transfusion[c]	2.32 (0.83 – 6.44)	0.1068
Platelet transfusion[c]	0.57 (0.20 – 1.64)	0.2989
Pressors on the day of intubation	1.05 (0.47 – 2.34)	0.9105
Use of intravenous opioids[d]	3.40 (0.40 – 29.15)	0.2651

Definition of abbreviations: PBW = Predicted body weight; VAE = Ventilator-associated event

a. Mean of the highest recorded daily tidal volumes prior to the VAE onset day in cases or the match day in controls
b. Sequential organ failure assessment score calculated on the day of intubation
c. Transfusion of at least one unit prior to VAE onset day in cases or match day in controls
d. Any use of intravenous fentanyl, morphine or hydromorphone prior to VAE onset day in cases or match day in controls
e. Use of intravenous sedatives was excluded from the analyses

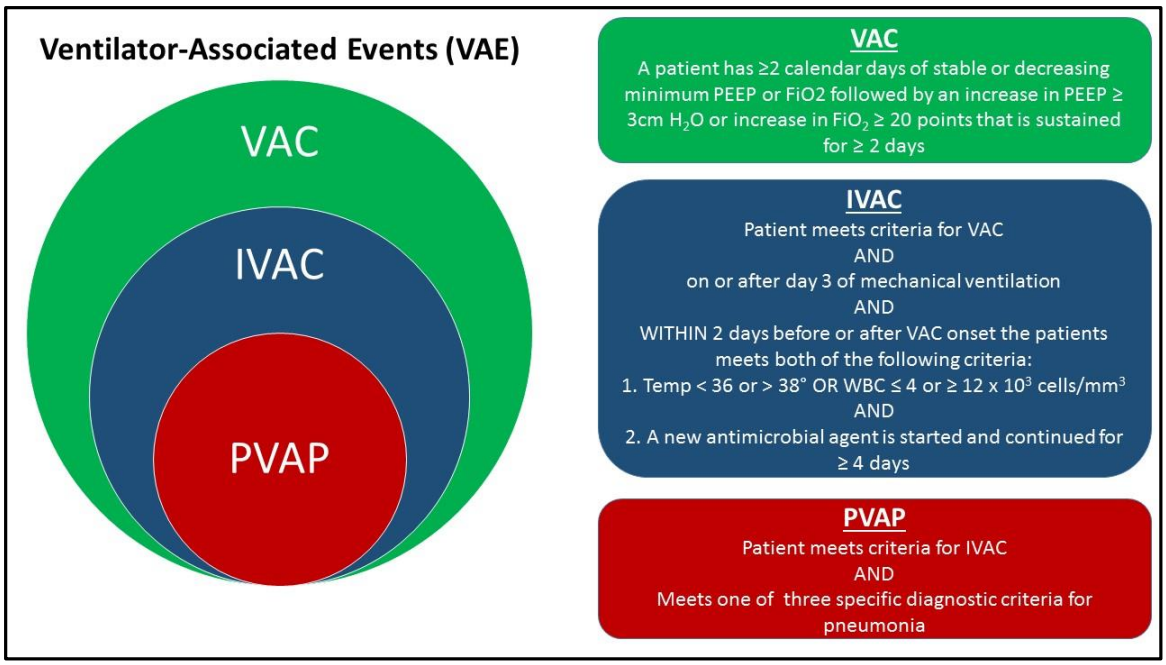

Figure 1. Surveillance definitions of ventilator-associated events

Definition of abbreviations: FiO_2 = Fraction of inspired oxygen; IVAC = Infection-related ventilator-associated complications; PEEP = Positive end-expiratory pressure; PVAP = Possible ventilator-associated pneumonia; VAC = Ventilator-associated conditions; WBC = White blood cell

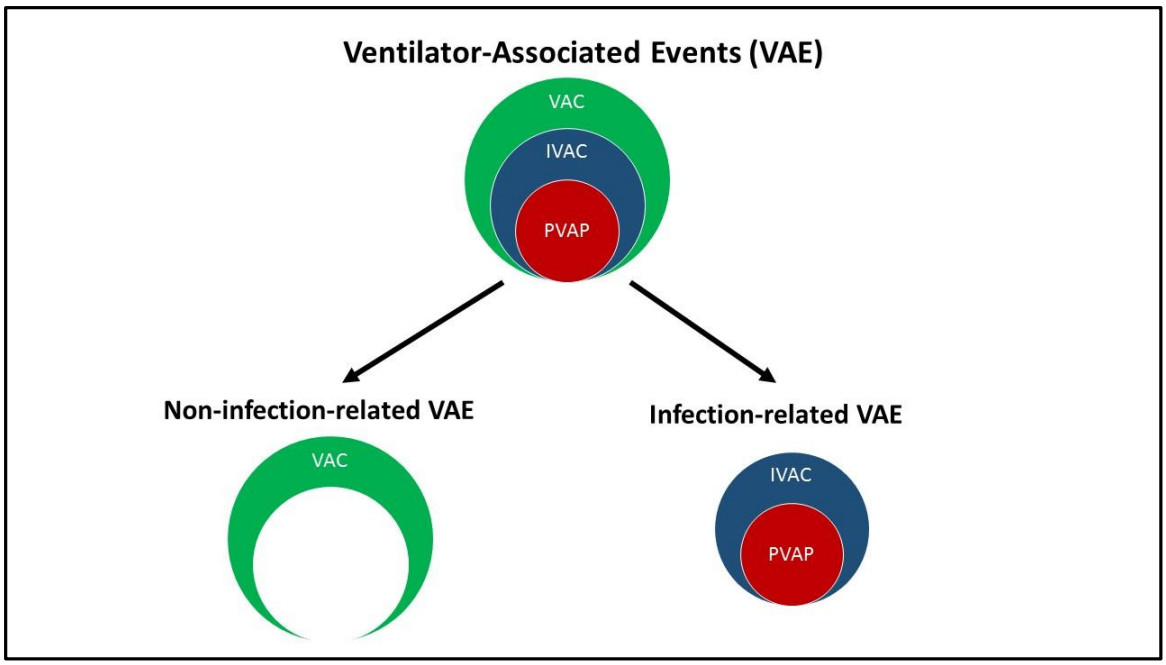

Figure 2. Classification of ventilator-associated events

Definition of abbreviations: FiO2 = Fraction of inspired oxygen; IVAC = Infection-related ventilator-associated complications; PEEP = Positive end-expiratory pressure; PVAP = Possible ventilator-associated pneumonia; VAC = Ventilator-associated conditions; WBC = White blood cell

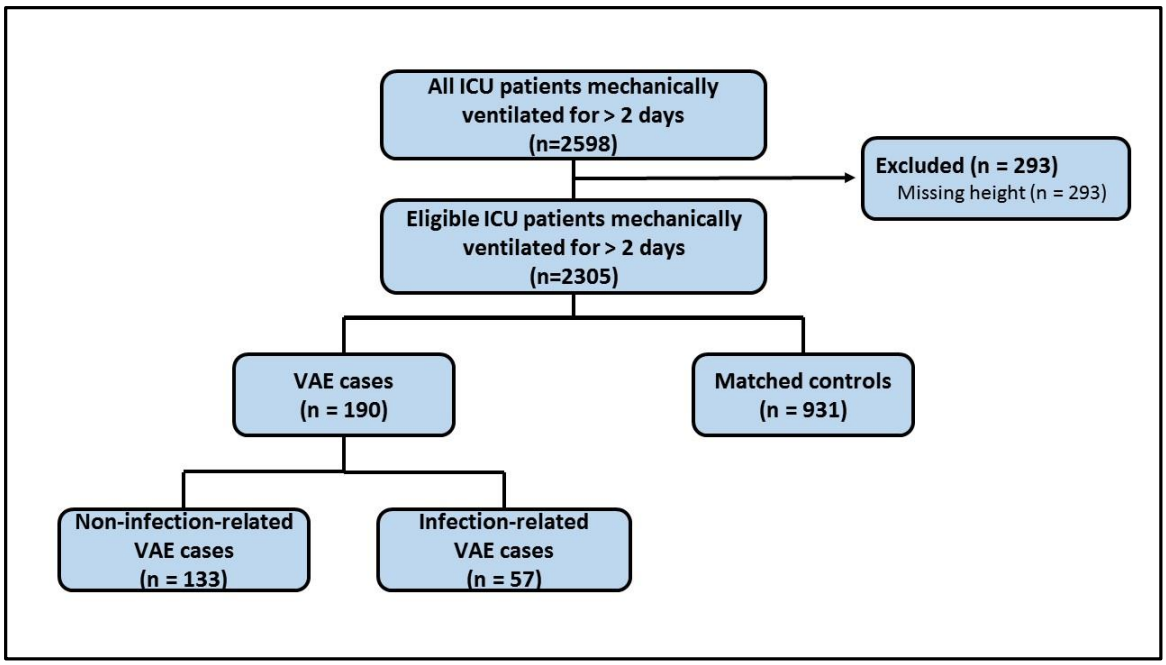

Figure 3. Flow diagram showing the selection of VAE cases and matched controls
Definition of abbreviations: VAE = Ventilator-associated events

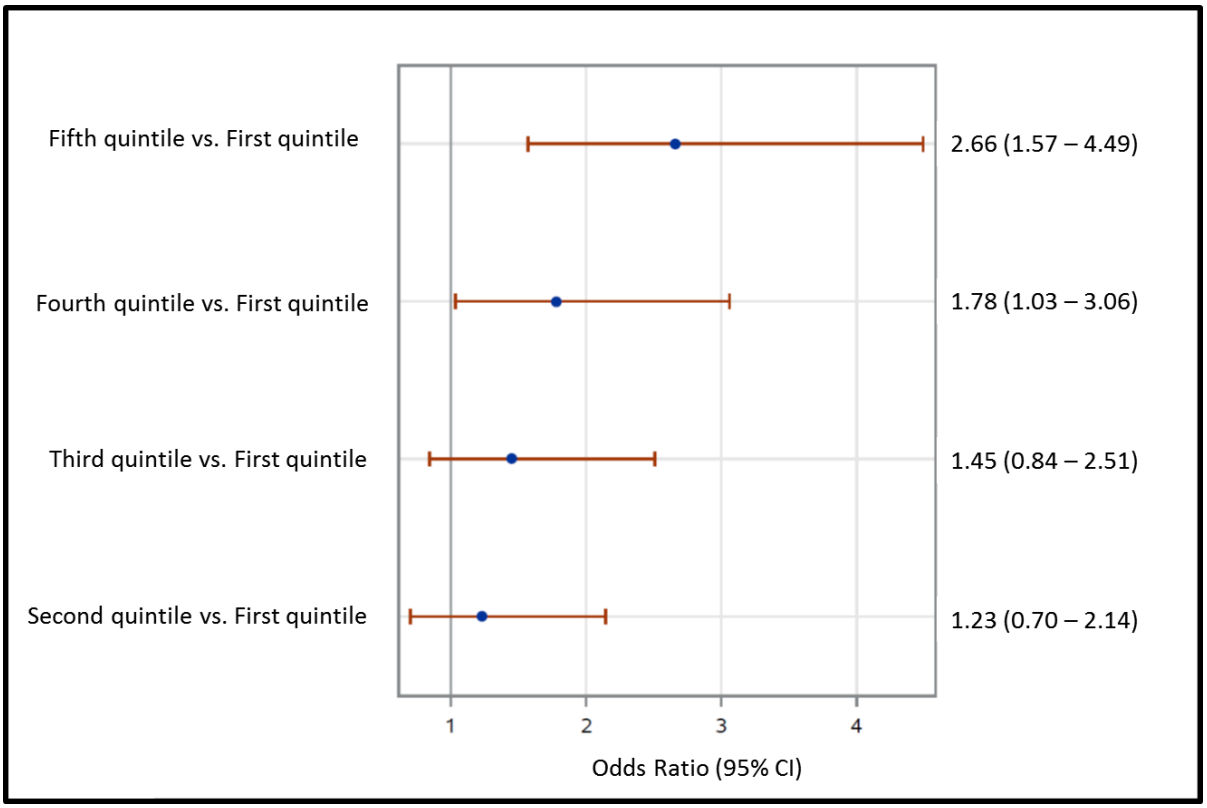

Figure 4. The association between tidal volume (quintiles) and ventilator-associated events adjusted for matching variables

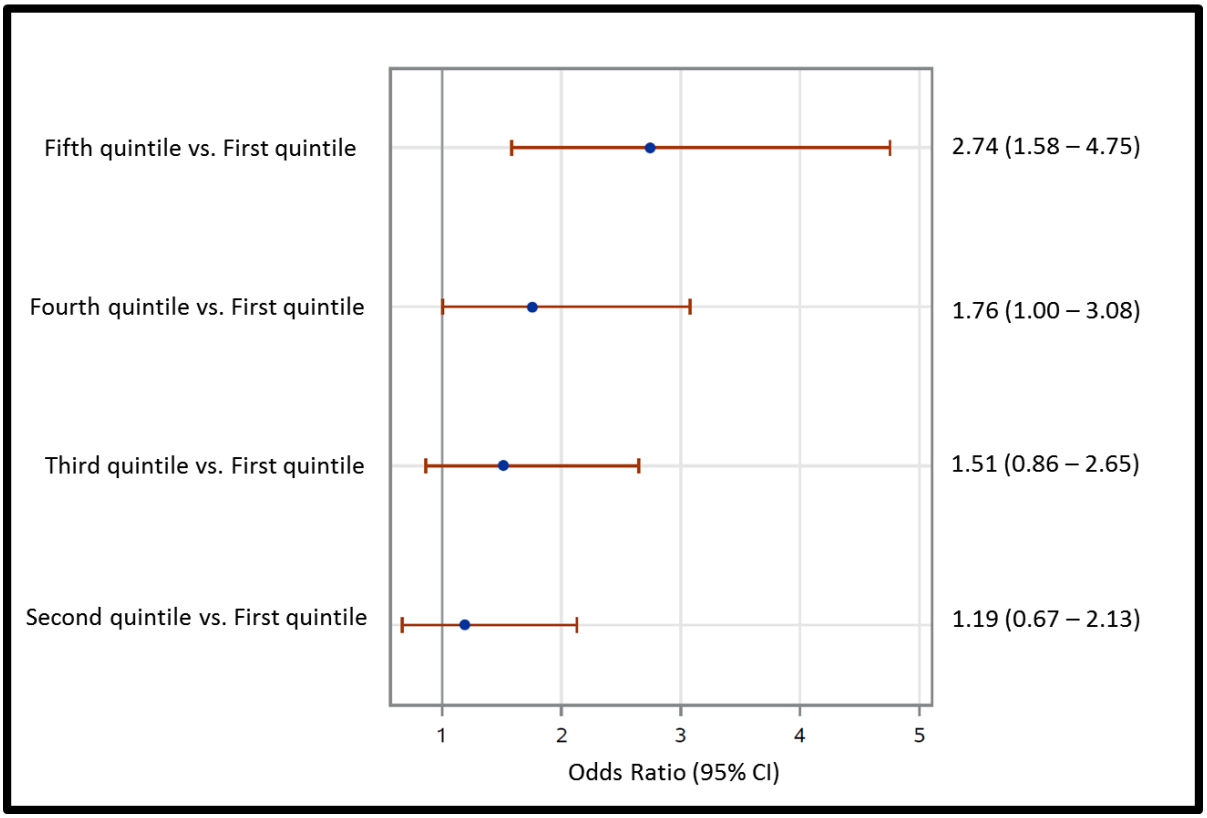

Figure 5. The association between tidal volume (quintiles) and ventilator-associated events adjusted for matching variables and 16 pre-specified patient characteristics.