Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts

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MECHANICAL POWER OF VENTILATION IS ASSOCIATED WITH MORTALITY IN CRITICALLY ILL PATIENTS – an analysis of patients in two observational cohorts

MECHANICAL POWER IN CRITICALLY ILL PATIENTS

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TAKE-HOME MESSAGE

Mechanical power unifies variables known to be related with development of ventilator–induced lung injury. Mechanical power is independently associated with worse outcomes in patients receiving invasive ventilation. Of additional interest, even at low tidal volume and low driving pressure, high mechanical power is associated with worse patient-centered outcomes.

TWEET

High mechanical power is associated with worse outcomes in patients receiving invasive ventilation, even at low tidal volume and driving pressure.

ABSTRACT

PURPOSE: Mechanical power (MP) may unify variables known to be related with development of ventilator–induced lung injury. The aim of this study is to examine the association between MP and mortality in critically ill patients receiving invasive ventilation for at least 48 hours.

METHODS: This is an analysis of data stored in the databases of the MIMIC–III, and eICU. Critically ill patients receiving invasive ventilation for at least 48 hours were included. The exposure of interest was MP. The primary outcome was in–hospital mortality.

RESULTS: In total, 8,207 patients were analyzed. Median MP during the second 24 hours was 21.4 (16.2 to 28.1) J/min in MIMIC–III and 16.0 (11.7 to 22.1) J/min in eICU. MP was independently associated with in–hospital mortality (odds ratio per 5 J/min increase [OR] 1.06 [95% confidence interval [CI] 1.01 to 1.11]; p = 0.021 in MIMIC–III, and 1.10 [1.02 to 1.18]; p = 0.010 in eICU). MP was also associated with ICU–mortality, 30–day mortality, and with ventilator–free days, ICU and hospital length of stay. Even at low tidal volume, high MP was associated with in–hospital mortality (OR 1.70 [1.32 to 2.18]; $p < 0.001$) and other secondary outcomes. Finally, there is a consistent increase in the risk of death with MP higher than 17.0 J/min.

CONCLUSION: High MP of ventilation is independently associated with higher in–hospital mortality and several other outcomes in ICU patients receiving invasive ventilation for at least 48 hours.

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KEYWORDS: Mechanical ventilation; mechanical power; mortality; critically ill; intensive care unit; ventilator–induced lung injury

INTRODUCTION

With each breath delivered by the mechanical ventilator a certain amount of energy is transferred to patient's respiratory system. This energy is mainly spent to overcome resistance of the airways and to expand the thorax wall [1-4]. A fraction of this energy acts directly on the lung skeleton, or extracellular matrix, as such deforming the epithelial and endothelial cells anchored to it [2]. Lungs 'conserve' small amounts of energy with each breath cycle as the elastic recoil of the lung returns less energy during exhalation than that absorbed during inspiration [1-4]. In fact, mechanical ventilation is associated with substantial dissipation of energy, probably resulting in 'heat' or inflammation, potentially leading to injury of lung tissue.

It has been hypothesized before that the extent of so–called ventilator–induced lung injury (VILI) depends on the amount of energy transferred [1-4], and tidal volume size (V_T), plateau pressure (Pplat), respiratory rate (RR) and air flow all relate to the amount of energy generated by the mechanical ventilator [2]. The amount of energy per unit of time, expressed in Joules per minute (J/min), is often referred to as the 'mechanical power' (MP) [2-9]. MP can be calculated accurately through a 'power equation', increasing its applicability in clinical practice [6]. One recent study in healthy piglets with uninjured lungs elegantly showed that increases in MP during ventilation by increasing RR is associated with more VILI [2,7]. There have been no clinical studies, however, that thoroughly examined the association between MP and outcome in ventilated patients.

It would be helpful and practical to have one single variable combining all possible factors associated with mortality that could be easily calculated and evaluated at the bedside, or maybe even projected on the screen of a ventilator in a continuous fashion [6-8]. Therefore, to test the hypothesis that MP is independently

114 associated with patient–centered outcomes in critically ill patients receiving
115 mechanical ventilator for at least 48 hours, we collected ventilation data to calculate
116 MP using the ‘power equation’ [6] in two large cohorts of intensive care unit (ICU)
117 patients whose data were prospectively collected in two databases. Part of this work
118 was presented as a poster in the XIII World Congress of Intensive and Critical Care
119 Medicine in 2017 [10].
120

METHODS

This study used data stored in the high–resolution databases of two patient cohorts, the 'Medical Information Mart for Intensive Care (MIMIC)'–III [11,12], and the 'eICU Collaborative Research Database' (eICU) [13]. An extensive description of methods is reported in the online supplement.

Study design

This investigation concerns a posthoc analysis of data from critically ill patients admitted to the intensive care units (ICUs) of a total of 59 hospitals in the USA (including the Beth Israel Deaconess Medical Center [BIDMC], Boston, MA, in MIMIC, and 58 other hospitals in eICU).

Study population

All patients in the MIMIC–III version v1.4 and eICU version v1.2 databases were eligible for inclusion in the present investigation. The following two inclusion criteria were used for the present study: 1) age ≥ 16 years; and 2) receiving invasive ventilation for at least 48 consecutive hours. Patients receiving ventilation through a tracheostomy cannula at any time during the first 48 hours of ventilation, and patients who were extubated or died during the first 48 hours were excluded. Only data of the first ICU admission of the first hospitalization were used. Patients who had incomplete datasets or datasets that did not sufficiently capture the ventilatory variables needed to calculate MP were excluded. As an additional exclusion criterion for the eICU database, hospitals that did not routinely document ventilation settings within the eICU system were deselected.

Data extraction

All ventilation variables were extracted as the highest and the lowest values per each time–frame of six hours during the first 48 hours of ventilation (eFigure 1). Presence

of the acute respiratory distress syndrome (ARDS) in the first 48 hours of ventilation was scored according to the Berlin definition [14], using original data to reclassify patients before publication of this definition.

Mechanical power

The primary exposure of interest was MP expressed in J/min in the second 24 hours of ventilation. MP was calculated as proposed previously [6,8], using V_T, peak pressure (Ppeak), RR, and driving pressure (ΔP) data:

$$MP\ (J/minutes) = 0.098 \times V_T \times RR \times (Ppeak - \tfrac{1}{2} \times \Delta P)$$

Since the patients had several measurements available, the mean between the highest and the lowest value in the second 24 hours was used. Since ventilation is a dynamic process, and to check the consistency of the findings, the time weighted–average MP over the first 48 hours of ventilation was calculated as the area under the MP–versus–time plot (eFigure 1) [15]. Moments where data necessary to calculate MP were missing were not included in the time weighted–average calculation and the calculation was adjusted by the number of observations available.

Outcomes

The primary outcome was in–hospital mortality. Secondary outcomes included ICU–, 30–day and 1–year mortality; the number of ventilator–free days at day 28 (defined as the number of days from successfully weaning to day 28; patients who died before weaning were deemed to have no ventilator–free days), and ICU– and hospital length of stay.

Statistical analysis

Continuous variables are presented as medians with their interquartile ranges and categorical variables as total number and percentage. Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using the *t* test or Wilcoxon rank sum test, as appropriate. Patients were categorized into groups according to the cohort analyzed, i.e., MIMIC–III or eICU.

MP in the second 24 hours of ventilation was used as a continuous variable for the primary analysis. Multivariable regression was selected as the analysis technique for all outcomes to account for factors that may influence outcomes. Relevant covariates known to predict outcome were entered into the model (description in the online supplement). To evaluate consistency of findings, sensitivity analyses, including the adjustment for the covariate balancing propensity score and considering the inverse–probability–of–treatment weighting, were performed for the primary outcome as described in the online supplement. To account for potential changes in clinical practice through the years, a sensitivity analysis including the year of admission as a random factor in mixed-effect models was carried out.

Since the exclusion of patients in the MIMIC–III database due to missing data could have led to biased analyses, we re–evaluate all analyses and models in the cohort of excluded patients, calculating MP using maximum airway pressure (Pmax) instead of Pplat. To avoid bias introduced by missing data, the analysis of the primary outcome was replicated after multiple imputation as described in the online supplement. Also, in a cohort including data from both databases, we analyzed the MP partitioned into 14 quantiles to identify the best cut-off associated with higher mortality. A receiver-operating characteristic (ROC) curve analysis was used to confirm the best cut-off. Recently, the impact of the driving pressure in obese patients

was questioned [16]. Thus, an additional analysis was conducted only in obese patients, defined as patients with body mass index ≥ 30 kg/m^2 [16]. To check if MP adds additional information, patients were stratified according to different levels of MP, V_T size and ΔP level (as described in the Supplement). Finally, as subgroup analyses, the association between MP and the primary outcome was assessed according to the presence of ARDS and the use of neuromuscular blocking agents (NMBA).

Statistical significance was considered to be at 2–sided $p < 0.05$. All analyses were performed with R v.3.3.2 (http://www.R-project.org).

RESULTS

Patients

The MIMIC–III database contained 53,423 ICU admissions of 38,597 unique patients. After exclusion of patients who received invasive ventilation for less than 48 hours and patients who received ventilation through a tracheostomy cannula, we had 5,003 patients, of whom 3,846 patients admitted from 2001 till 2012 had a complete data (eFigure 2). In eICU, from the total of 99,837 unique patients, and after the exclusion of patients receiving invasive ventilation less than 48 hours and with no data on ventilation variables, 4,361 patients admitted from 2014 till 2015 were included (eFigure 2).

Baseline characteristics of patients are shown in Table 1; characteristics of ICUs involved are presented in eTable 1. The majority of patients in the two cohorts were male and most patients were admitted from the emergency room due to a clinical condition. In MIMIC–III, 11.5% of patients had ARDS in the first 48 hours, and in eICU 9.8%. Vital signs and laboratory variables are presented in eTable 2, and outcomes in eTable 3. Overall in–hospital mortality was 29.9% in MIMIC–III, and 31.0% in eICU. Ventilation characteristics of patients are shown in Table 2.

Mechanical power

There was a decrease in MP from the first to the second 24 hours of ventilation in both cohorts ($p < 0.001$ by the Wilcoxon rank sign test) to 21.4 (16.2 – 28.1) J/min in MIMIC–III, and 16.0 (11.7 – 22.1) J/min in eICU (Table 2).

Primary outcome

Results of the univariable analysis of the primary outcome are shown in eTable 4 and the complete multivariable analysis eTable 5 and Figure 1. There was no missing data for the primary outcome in both datasets. After adjusting for covariates, MP in

the second 24 hours of ventilation was significantly associated with higher in–hospital mortality in both cohorts, and this association remained when using adjustments for the covariate balancing propensity score (eTable 6 and Figure 1), and after considering the inverse–probability–of–treatment weighting (eTable 7 and Figure 1). The amount of missing data in the variables is shown in eTable 8 and eFigure 3 and 4. The results were consistent after multiple imputation for missing values in variables of interest (eTable 9). There is no influence of the year of admission on the effect of mechanical power (eTable 10).

After adjustments, there was an association between time weighted–average MP and higher in–hospital mortality in both cohorts (eTable 11). This association remained significant after adjustment for the covariate balancing propensity score and in the inverse–probability–of–treatment weighting analysis (eTable 12).

Secondary outcomes

MP in the second 24 hours of ventilation was also associated with ICU–mortality, and 30–day mortality (in eICU only) (Figure 2A), and with the number of ventilator–free days, ICU and hospital length of stay (Figure 2B). Time weighted–average MP was associated with higher ICU–mortality, with 30–day mortality (in eICU) but not with 1–year mortality (eTable 12). Time weighted–average MP was associated with less ventilator–free days, and longer ICU length of stay, but no association was found with hospital length of stay (eTable 12).

Subgroup and sensitivity analyses

Baseline characteristics, vital signs, mechanical ventilation variables and clinical outcomes in the cohort of patients excluded from the MIMIC–III database due to missing values are exposed in eTable 13 and 14. Generally, patients excluded due to missing values were less ill than patients included in the main analysis. All the

reproduced analyses confirmed the findings from the main analyses, with exception of the absence of association between MP and ICU and hospital length of stay in the cohort of excluded patients (eTable 15).

Figure 3 shows the increase in the risk of in–hospital mortality as a function of progressive percentiles of MP in the pooled cohort. There is a consistent increase in the risk of death with MP higher than 17.0 J/min. The best cut-off found in the ROC analyses was 19.0 J/min, but this had a poor predictive power (AUC of 0.521 [0.507 – 0.536]; sensitivity of 48% [46% – 50%]; specificity of 56% [55% – 58%]) (eFigure 5). Considering only obese patients, MP remained associated with higher risk of in-hospital mortality, though this was only found in the eICU dataset (eTable 16).

In the analysis according to the V_T size, even at low V_T, high MP was associated with in-hospital mortality and other secondary outcomes (eTable 17). In the analysis according to the ΔP, even at low ΔP, high MP was associated with ICU mortality, ventilator-free days and ICU length of stay (eTable 17).

Mechanical ventilator parameters in patients with and without ARDS in both datasets are shown in eTable 19. There was no significant interaction between the effect of MP on primary outcome and presence of ARDS at the beginning of ventilation (eFigure 6) or use of NMBA in the first two days of ventilation (eFigure 7) in any of the cohorts, meaning that the presence of ARDS and the use of NMBA did not affect the association between mechanical power and mortality.

DISCUSSION

The findings of this investigation can be summarized as follows: 1) MP in the second 24 hours of ventilation is independently associated with higher in–hospital mortality of critically ill patients who receive invasive ventilation for more than 48 hours; 2) higher MP is independently associated with higher ICU mortality, a lower number of ventilator–free days and alive at day 28, and longer stay in ICU and hospital; 3) the impact of MP is consistent, and independent of the presence of ARDS or use of NMBA; and 4) even at low V_T and low ΔP, high MP was associated with worse outcomes, suggesting that MP adds additional information beyond volume and pressure.

This is the first clinical investigation testing the hypothesis that MP generated by the mechanical ventilator is associated with patient–centered outcomes. Strengths of this posthoc analysis are that the MIMIC–III and the eICU databases contain comprehensive and high–quality data capture throughout the hospital course of a large group of well–defined and characterized ICU patients in 59 different hospitals from USA, with different ventilatory practices and from different periods, covering from 2001 till 2015. The incidence of ARDS in the cohorts is comparable to that reported in previous studies of ventilated ICU patients [17,18], suggesting that our cohort is similar to those studied previously. Our analysis leverages the availability of time–stamped vital signs, laboratory results, and ventilatory variables to build models that incorporate the dynamic characteristics of the invasive ventilation. The findings are consistent across several sensitivities analyses, indicating that conclusions were not dependent on the chosen statistical approach. Also, the studied cohorts were homogenous, and the 48–hour time–interval inclusion criterion guaranteed that all patients were exposed to invasive ventilation for a sufficient period of time. The

findings were consistent in patients with and without ARDS, increasing its external validity. Finally, the confirmatory analysis using the time weighted–average helps to avoid surveillance bias.

Originally, MP was calculated according to the classical equation of motion with the addition of PEEP [2,6,19], and has three important components [6,20]. The first is respiratory system elastance, which is the energy associated with the $V_T/\Delta P$. The second component is airway resistance that is related with the energy associated with gas movement. The third component equals energy needed to overcome the fibers tension due to PEEP [6]. Recently, a so–called 'power equation' was suggested, showing a good relationship with the original equation, but being simpler, and without the need of pressure–volume curves [6]. In the original description of MP, 'measured' MP showed a good correlation with MP computed using this power equation, with a mean difference of only 0.196 J/min when computed in patients without ARDS [6]. This simplified 'power equation' was used here.

Understanding how ventilation could harm lungs has improved over recent years [21]. The association between volumes and pressures delivered and generated by the mechanical ventilator and outcomes of critically ill patients who receive invasive ventilation has been subject of many investigations so far [17,22-27]. Volumes and pressures, mostly studied separately, in fact are components of the MP [6]. Other components of MP, such as RR so far received much less attention, but could play important roles in development of lung injury, even when volumes and pressures are chosen so that MP will remain low [20,28]. The results of this analysis provides evidence that ventilation characteristics that are considered predictors of outcomes in ARDS patients may also have prognostic capacity in patients who do not

fulfill the criteria for this complication of critical illness. Indeed, two important elements of the MP are tidal volume and driving pressure and, even though we did not access the impact of the driving pressure directly, it is plausible that driving pressure is an important predictor of outcomes in a more general population.

Different mechanical ventilator variables have been shown to contribute to ventilator–induced lung injury, including V_T [22,23], Pplat [22], ΔP [9,17,26,27], PEEP [24,25], flow and respiratory rate, all of which have been addressed separately in previous experimental or clinical studies. The MP represents the result of a combination of such variables, and therefore, might have a higher predictive value for patient-centered outcomes, including mortality. Since most of the evidence supporting protective ventilation supports the use of low V_T, we addressed the impact of MP in in-hospital in the presence of different V_T sizes. In agreement with the core hypothesis, we found that even at low V_T, high MP was associated with in-hospital mortality.

VILI originates from the interaction between the MP transferred to the lung parenchyma and the anatomic–pathophysiological characteristics of the latter [6]. It is suggestive that if damage to lung parenchyma is a function of MP, it is possible that different combinations of its components, resulting in a MP greater than a certain threshold, may produce similar damage [2,6]. In fact, changes in V_T, ΔP, and inspiratory flow produced an identical exponential increase of MP in a previous investigation [6]. The impact of changes in RR is less pronounced, while an increase of PEEP caused only a linear increase in MP [6].

It could be an attractive concept to use MP to set a ventilator, as it combines the effects of different ventilatory variables. Changing one single variable may not always protect the lungs if it does not result in a change in the amount of energy

actually delivered to lung tissue [8]. For example, a reduction in volume may not translate into benefit when it requires a higher respiratory rate to compensate for loss of minute volume [20,28]. Likewise, PEEP increases may not be beneficial when it does not result in a decline in ΔP, e.g., when it does not lead to recruitment of atelectatic lung tissue – PEEP increases may be even harmful when it results in an increase in the ΔP, e.g., when it results in overdistension [27]. Further, excessive increases in PEEP, even if associated with reduced ∆P, in some cases may promote lung injury due to higher static strain. In fact, according to the 'power equation' used, even if PEEP leads to a decrease in driving pressure, the MP could increase. In the future, ventilators may be able to display the MP applied to the respiratory system, helping the caregiver to titrate ventilation so that the least possible energy is being used. Smart algorithms aiming at the lowest amount of MP, built–in in ventilators, may help further preventing VILI.

The present analysis has some limitations. Its posthoc nature should be taken into account when considering the findings. Residual confounding may also mar our findings, although we attempted to account for this through several adjustments and models. Also, we tried to minimize interaction or effect modification by limiting our analysis to the first ICU stay for patients and excluding patients who had a tracheostomy or who had undergone a tracheostomy procedure during the first 72 hours of their ICU admission. We considered only patients who received invasive ventilation for at least 48 hours, aiming to select more severely ill patients and also those patients who had been exposed to the primary exposure of interest for a sufficient period of time. However, the present findings cannot be translated to patients who were extubated or died in the first 48 hours. Around 25% of the patients receiving invasive ventilation for more than 48 hours in the MIMIC–III database were

375 excluded due to lack of Pplat measured accordingly, and this may lead to important
376 biases if such patients are considerably different from the included cohort. This
377 number, though, is lower than those found in two recent reports in patients with and
378 without ARDS [17,18], and sensitivity analyses in the cohort of excluded patients
379 considering the Pmax instead of the Pplat for calculating MP led to the similar results.
380 We were unable to report potential complications associated with invasive ventilation
381 and MP, including development of ARDS in patients who did not have ARDS at onset
382 of ventilation, ventilator–associated pneumonia, atelectasis or barotrauma, as these
383 were not consistently captured and stored in the studied databases. It is important to
384 emphasize that some kind of normalization, e.g., adjusted for the size of the lung,
385 could be necessary to get an optimal cut-off that could be used to guide therapy. The
386 amount of missing data in the variables assessed in the study is a potential limitation.
387 However, the analyses after multiple imputation yielded similar results. Since the
388 datasets used in this study are for clinical purposes and the present analysis is a
389 secondary analysis of these data, we cannot guarantee that plateau pressure was
390 collected under standard conditions, i.e, in the absence of spontaneous breathing
391 efforts, at an adequate level of sedation, and with a sufficiently long end-inspiratory
392 pause. Also, we present the MP applied to the respiratory system. As transpulmonary
393 pressure data were not captured in the two databases, it is impossible to estimate the
394 MP applied to the lung. In addition, prone positioning was not used in patients in the
395 MIMIC–III and was not available in the eICU, and this could be a confounding factor.
396 No sample size calculation was done, and the sample consisted of a convenience
397 sample of patients who fulfilled the inclusion cohort in both datasets. The V_T used in
398 the patients, especially those with ARDS, is higher than expected and recommended
399 by the guidelines, however, this represent the way that these patients were

ventilated, even today. Although our findings do support an association between high MP and mortality, stronger evidence such as randomized controlled trials are necessary to establish a causal relationship.

CONCLUSIONS

In adult critically ill patients who receive invasive ventilation for at least 48 hours, high mechanical power is independently associated with higher in–hospital mortality and several other important patient–centered outcomes.

LEGEND TO FIGURES

Figure 1 – Mechanical power (MP) in the second 24 hours of ventilation and in-hospital mortality. Sensitivity analyses were performed to determine whether results were dependent on method of covariate adjustment. The odds ratio represents the odds of death per 5 J/min increase in MP.

Abbreviations: MP: mechanical power; CBPS: covariate balancing propensity score; IPTW: inverse probability of treatment weight.

Figure 2 – Mechanical power (MP) in the second day of ventilation and secondary outcomes. A – The odds ratio represents the odds of death per 5 J/min increase in MP. B – Effect estimates and 95% confidence interval from the multivariable linear regression for: ventilator–free days, ICU length of stay, hospital length of stay. Effect estimate refers to the change in the outcome variable per 5 J/min increase in MP. Abbreviations: MP: mechanical power; ICU: Intensive Care Unit.

Figure 3 – Adjusted odds ratio for in–hospital mortality according to percentiles of mechanical power (MP) in the pooled cohort after multivariable adjustment. The pooled cohort was partitioned into 14 quantiles of mechanical power, and the adjusted odds ratio for each quantile was calculated in relation to the median mechanical power of the whole cohort. The odds ratio and 95% confidence intervals (error bars) for each percentile were calculated after multivariable adjustment for age, prognostic score, SOFA, pH, mean arterial pressure, PaO_2/FiO_2, SpO_2, temperature and $PaCO_2$.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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AUTHORS' CONTRIBUTIONS

ASN designed the study, conducted the data collection, data analysis, and data interpretation, and wrote the manuscript.

ROC conducted the data collection, the data interpretation, and reviewed the manuscript.

AEWJ conducted the data collection, the data interpretation, and reviewed the manuscript.

LDB conducted the data collection, the data interpretation, and reviewed the manuscript.

PA designed the study, conducted the data collection, and reviewed the manuscript.

SMP designed the study, conducted the data collection, and reviewed the manuscript.

DCC designed the study, and reviewed the manuscript.

RLC designed the study, and reviewed the manuscript.

TDC designed the study, and reviewed the manuscript.

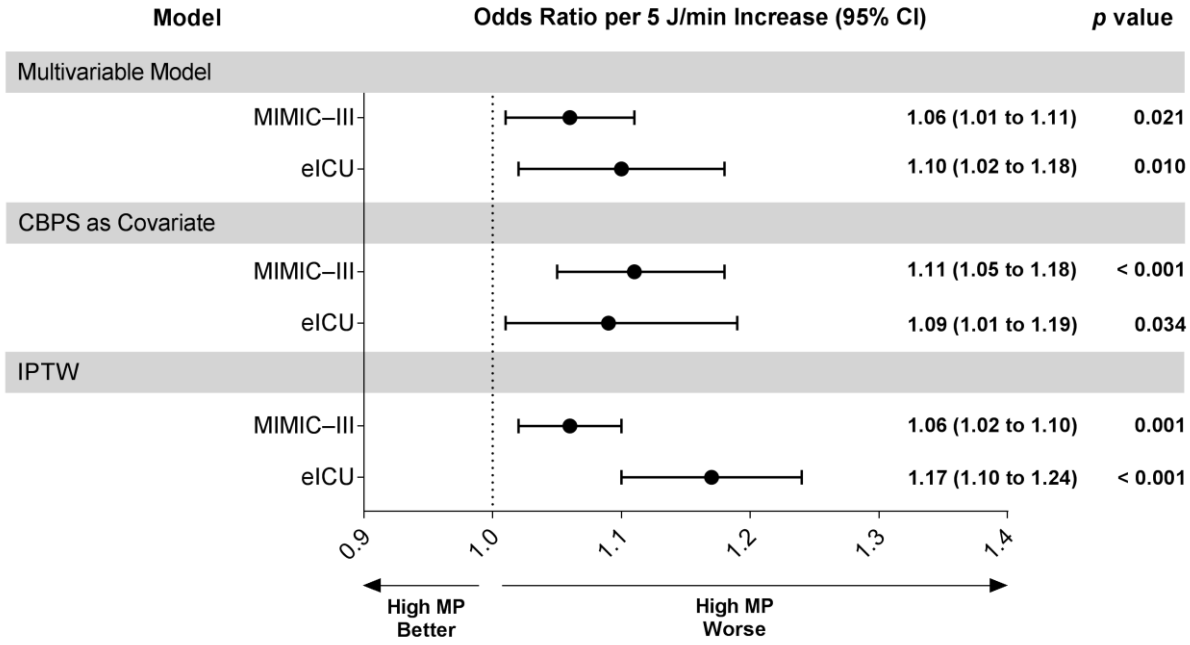
GPPS designed the study, and reviewed the manuscript.

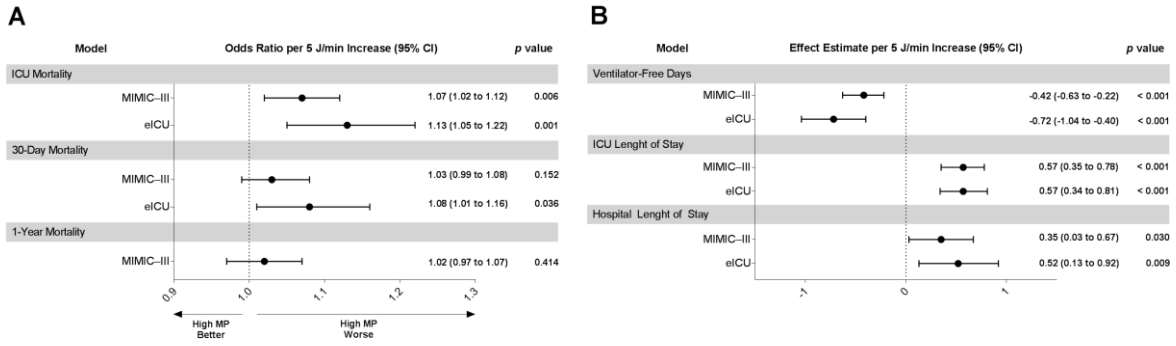
KTT designed the study, and reviewed the manuscript.

PP designed the study, conducted the data interpretation and reviewed the manuscript.

MGA designed the study, conducted the data interpretation, and reviewed the manuscript.

MJS designed the study, conducted the data interpretation, and reviewed the manuscript.





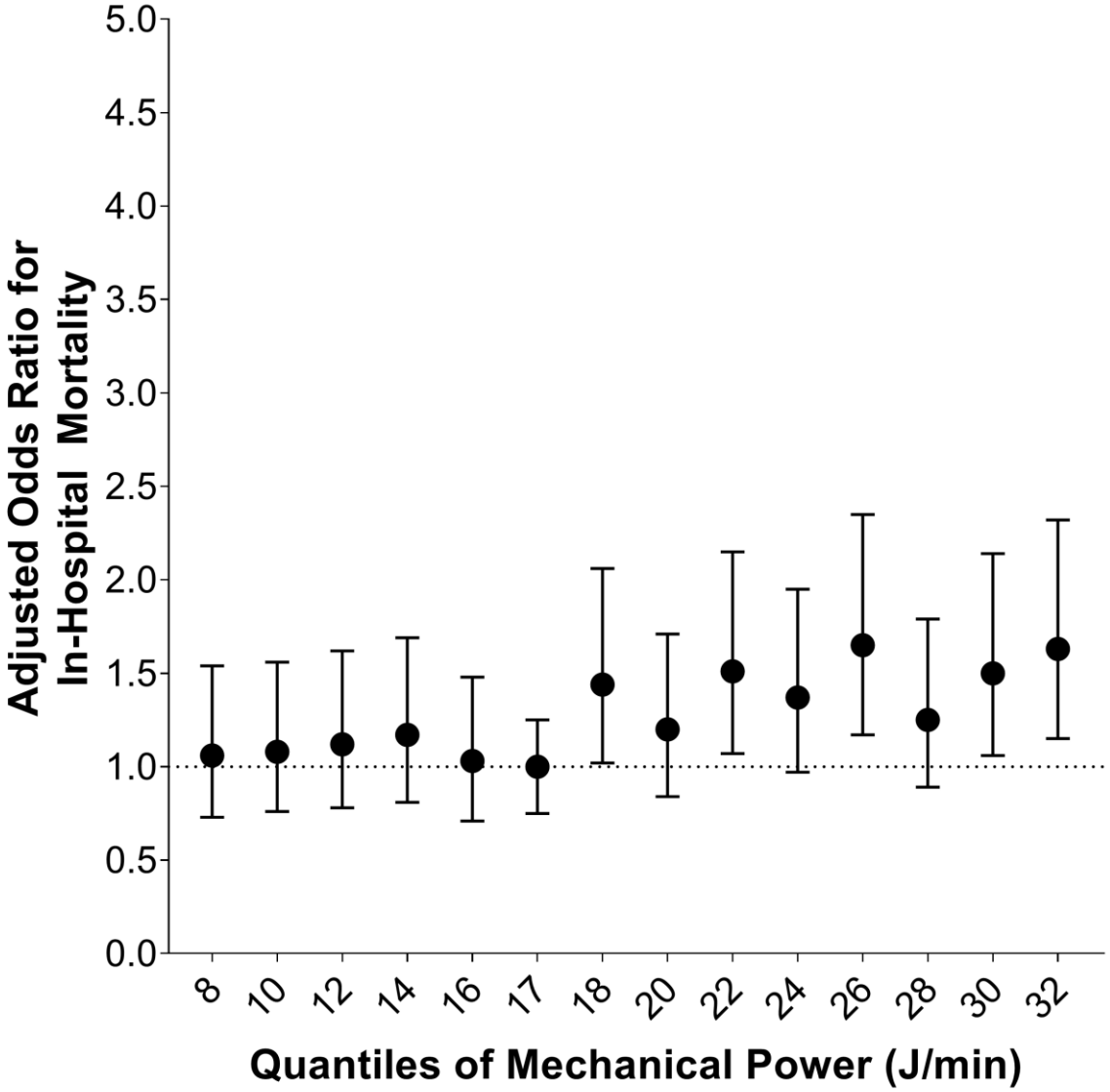


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Table 1 – Baseline characteristics of the included patients

	MIMIC–III (*n* = 3,846)	eICU (*n* = 4,361)
Baseline characteristics		
Age, years	64.6 (50.7 – 76.7)	63.0 (52.0 – 73.0)
Male gender	2,161 / 3,846 (56.2)	2,432 / 4,361 (55.8)
Weight, kg	80.0 (66.6 – 96.0)	82.6 (68.1 – 101.0)
Height, cm	170 (163 – 178)	170 (163 – 178)
BMI, kg/m^2	27.8 (24 – 32.9)	28.3 (23.9 – 34.3)
PBW, kg	64.0 (54.7 – 73.1)	64.0 (54.8 – 73.1)
Admission type		
Surgical elective	290 / 3,846 (7.5)	396 / 4,361 (9.1)
Surgical urgency	154 / 3,846 (4.0)	146 / 4,361 (3.3)
Medical	3,402 / 3,846 (88.5)	3,819 / 4,361 (87.6)
Source of admission		
Ward or Step-Down Unit	564 / 3,846 (14.7)	855 / 4,361 (19.6)
Emergency room	1,888 / 3,846 (49.1)	2,229 / 4,361 (51.1)
Office or operating room	403 / 3,846 (10.5)	1,049 / 4,361 (24,0)

Transferred from other hospital	965 / 3,846 (25.1)	221 / 4,361 (5.1)
Other	26 / 3,846 (0.7)	7 / 4,361 (0.2)
Ethnicity		
Black	256 / 3,846 (6.7)	382 / 4,361 (8.9)
Hispanic	128 / 3,846 (3.3)	82 / 4,361 (1.9)
White	2,582 / 3,846 (67.1)	3,570 / 4,361 (83.1)
Other	880 / 3,846 (22.9)	259 / 4,361 (6.0)
Initial diagnosis		
Sepsis (including pneumonia)	805 / 3,846 (21.0)	1,226 / 4,361 (32.0)
Cardiovascular disease	892 / 3,846 (23.2)	464 / 4,361 (12.1)
Other respiratory condition	569 / 3,846 (14.8)	621 / 4,361 (16.2)
Neurological condition	701 / 3,846 (18.2)	886 / 4,361 (23.1)
Renal condition	42 / 3,846 (1.0)	46 / 4,361 (1.2)
Others	837 / 3,846 (21.8)	590 / 4,361 (15.4)
Co-morbidities		
COPD	208 / 3,846 (5.4)	940 / 4,361 (21.5)
Smoking	1,808 / 3,846 (47.8)	---
Elixhauser comorbidity score	6 (1 – 12)	---
ARDS at baseline	443 / 3,846 (11.5)	427 / 4,361 (9.8)
Mild	43 / 443 (9.7)	98 / 427 (22.9)
Moderate	230 / 443 (51.9)	215 / 427 (50.3)
Severe	170 / 443 (38.4)	114 / 427 (26.7)
Need of support in the first 24 hours		
Vasopressor	1,959 / 3,846 (50.9)	2,378 / 4,361 (55.5)
Renal replacement therapy	204 / 3,846 (5.3)	---
Limitation of support	902 / 3,846 (25.0)	134 / 4,361 (3.2)
Severity of illness		
SAPS II	43 (33 – 54)	---
OASIS	38 (33 – 44)	36 (30 – 42)
APACHE IV	---	80 (61 – 103)
SOFA	6 (4 – 9)	7 (4 – 9)
Vital signs in the beginning of ventilation		
Heart rate, bpm	92 (80 – 104)	92 (81 – 105)
MAP, mmHg	80 (73 – 89)	82 (74 – 92)
SpO_2, %	96 (94 – 98)	95 (93 – 97)
Temperature, ºC	37.1 (36.6 – 37.6)	36.9 (36.5 – 37.4)
Laboratory in the beginning of ventilation		
pH	7.36 (7.31 – 7.41)	7.35 (7.29 – 7.41)
PaO_2 / FiO_2, mmHg	255 (183 – 357)	211 (144 – 308)
$PaCO_2$, mmHg	39 (35 – 44)	41 (35 – 48)

Data are median (interquartile range) or No / Total (%)

BMI: body mass index; PBW: predicted body weight; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; bpm: beats per minute; SpO_2: pulse oximetry; MAP: mean arterial blood pressure

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Table 2 – Characteristics of mechanical ventilation in included patients

	MIMIC–III (*n* = 3,846)	**eICU (*n* = 4,361)**
First day of ventilation		
Mechanical power, J/min	24.0 (18.1 – 31.2)	17.0 (12.4 – 23.1)
Tidal volume, ml/kg PBW	8.8 (7.8 – 10.0)	7.8 (6.9 – 8.7)
PEEP, cmH_2O	6 (5 – 8)	5 (5 – 7)
Plateau pressure, cmH_2O	21 (17 – 25)	20 (16 – 24)
Driving pressure, cmH_2O	14 (11 – 17)	15 (11 – 18)

Total respiratory rate, bpm	20 (17 – 23)	20 (17 – 23)
Minute ventilation, L/min	11.7 (9.9 – 13.8)	9.7 (8.0 – 11.9)
FiO_2, %	0.55 (0.50 – 0.70)	0.67 (0.45 – 0.72)
Patients receiving NMBA*	346 / 3,846 (8.9)	612 / 2,246 (27.2)
Second day of ventilation		
Mechanical power, J/min	21.4 (16.2 – 28.1)	16.0 (11.7 – 22.1)
Tidal volume, ml/kg PBW	8.6 (7.6 – 9.7)	7.6 (6.8 – 8.5)
PEEP, cmH_2O	6 (5 – 10)	5 (5 – 8)
Plateau pressure, cmH_2O	21 (17 – 25)	20 (16 – 24)
Driving pressure, cmH_2O	13 (11 – 16)	14 (11 – 18)
Total respiratory rate, bpm	20 (16 – 23)	20 (17 – 24)
Minute ventilation, L/min	10.8 (9.1 – 13.0)	9.6 (8.0 – 11.7)
FiO_2, %	0.45 (0.40 – 0.55)	0.40 (0.37 – 0.55)
Patients receiving NMBA*	324 / 3,846 (8.4%)	116 / 2,246 (5.1)

Data are median (interquartile range) or No / Total (%)
The values are the mean between the highest and the lowest values measured during the day.
* Defined as any infusion of neuromuscular blocking agents continuously and for more than 3 hours in the day.
NMBA: neuromuscular blocking agents; PBW: predicted body weight; PEEP: positive end-expiratory pressure; bpm: breaths per minute; FiO_2: inspired fraction of oxygen; SIMV: synchronized mandatory ventilation; CPAP: continuous positive airway pressure; FiO_2: inspired fraction of oxygen

MECHANICAL POWER OF VENTILATION IS ASSOCIATED WITH MORTALITY CRITICALLY ILL PATIENTS – an analysis of patients in two observational cohorts

Online Supplement

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Additional Methods

Additional References

ADDITIONAL METHODS

Study design

The data were prospectively collected and stored in three different databases. The Medical Information Mart for Intensive Care III database (MIMIC–III v1.4), is a freely accessible and conveniently–sized database that contains high resolution information from hospital monitoring systems (including laboratory data, medication, and hospital administrative data) and bedside monitoring systems (vital signs, caregivers notes, radiology reports). This database is hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (MIT) and contains data for over 50,000 de–identified patient admissions to ICUs at the BIDMC from 2001 to 2012.[1] We used the MIMIC Code Repository to define many concepts in MIMIC-III.[2]

The Philips eICU program is a transformational critical care telehealth program that delivers need-to-know information to caregivers, empowering them to care for the patients, and the data utilized by the remote caregivers is archived for research purposes. Through this work, a large database was generated which has potential for facilitating additional research initiatives on patient outcomes, trends, and other best practice protocols in use today at most healthcare facilities. The Philips eICU Research Institute (eRI) and the Laboratory for Computational Physiology at the MIT, which maintains the data, has generously contributed the eICU Collaborative Research Database described here. The eICU Collaborative Research Database v1.2 is populated with data from a combination of many critical care units throughout the continental United States. The data in the collaborative database covers 200,678 adult patients who were admitted to 208 critical care units in 2014 and

2015.[3] For this database, we've used an additional exclusion criteria, where we selected hospitals who had at least 10% of patients with documented peak pressures in the first 24 hours of their ICU stay. We removed hospitals who had fewer than 10 patients admitted in total.

Ethical approval

The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001–P–001699/14) and the Massachusetts Institute of Technology (No. 0403000206) approved use of the MIMIC database. The eICU was exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2).

Other data extracted

Data was extracted from the database using structured query language (SQL), and included V_T, positive end–expiratory pressure (PEEP), peak pressure (Ppeak) and Pplat, RR, and the inspired fraction of oxygen (FiO_2). For patients who received ventilation in a volume–controlled assist mode, driving pressure (ΔP) was calculated as Pplat *minus* PEEP. The following demographic data (using first 24 hours of admission data) were collected: age, gender, ethnicity (white, black, Hispanic or Latino, or other), height, weight, comorbidities (using the Elixhauser comorbidity score for the MIMIC–III database),[4,5] active smoking status (by Natural Language Processing searches in provider notes, categorized as 'yes', 'no', or 'unknown'), primary diagnoses category on hospital discharge using the primary International Classification of Diseases (ICD)–9

diagnosis, and disease severity scores (Simplified Acute Physiology Score [SAPS] II,[6] Sequential Organ Failure Assessment [SOFA],[7] the Oxford Acute Severity of Illness Score [OASIS],[8] and the Acute Physiology And Chronic Health Evaluation [APACHE] IV).[9]

Vital signs and laboratory measurements were captured as lowest and the highest values in the first and in the second day of ventilation. Use of vasopressors and need of renal replacement therapy during the first 24 hours of admission was collected, as was the latest code status of each patient. Presence of ARDS was scored according to the Berlin definition in the first 48 hours of ventilation.[10]

Data preparation and definitions

The data was assessed for completeness and consistency; outliers, defined as an observation that lies outside 1.5 x Interquartile Range (IQR), were checked and substituted by the 5^{th} or 95^{th} percentile. V_T size was collected as an absolute volume (ml) and then normalized for predicted body weight (ml/kg PBW). The PBW was calculated as equal to 50 + 0.91 (centimeters of height – 152.4) in males, and 45.5 + 0.91 (centimeters of height – 152.4) in females.[11] Patients with any order different from full code at the end of their ICU stay were considered as patients with limitation of support. In the eICU, the calculation of 30-day mortality and ventilator-free days was done considering only hospital mortality and hospital length of stay, since there is no fixed follow-up at day 28 or day 30 in this database. The absence of breathing effort was assessed comparing the set with the total respiratory rate in the ventilator.

Statistical analyses

The MP in the second day of ventilation was chosen because during the first 24 hours usually mechanical ventilation is subjected to several changes and may result in more noise. However, the measurements during the first day of ventilation were took into account in the time weighted-average calculation.

Multivariable regression was selected as the analysis technique for all outcomes to account for factors that may influence outcomes. Relevant covariates known to predict outcome were entered into the model including age, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) IV, Oxford acute severity illness score (OASIS), Elixhauser comorbidity score, Sequential Organ Failure Assessment (SOFA) score on day 1, arterial pH, PaO_2/FiO_2, mean arterial pressure, SpO_2, temperature and arterial $PaCO_2$. These variables were selected due to their clinical relevance. The same model was validated in the eICU. Variables not available in the eICU were excluded (i.e., Elixhauser comorbidity score), and APACHE IV score was used instead of SAPS II.

Alternate methods employed for adjustments included a covariate balancing propensity score (CBPS)[12] and inverse–probability–of–treatment weighting. CBPS is a robust method which concurrently maximizes the covariate balance and the treatment assignment prediction.[12] The inverse probability of treatment weight was calculated as: iptw = 1 / ((*z* * cbps) + ((1 - *z*) * (1 - cbps))) where *z* is receipt of high mechanical power (according to the median in each cohort) and cbps is the covariate balancing propensity score. The iptw was included as weights in the generalized linear model. In the eICU database and in the pooled analyses (described below), all models described

were assessed considering mixed-effect models taking into account the center as random effect.

Since mechanical ventilation is a dynamic process, and to check the consistency of the findings, the time weighted–average mechanical power during the first 48 hours of ventilation was calculated as the area under the mechanical power–versus–time plot[13] and included in a multivariable model including the same covariates as described in the main manuscript. Moments where the data on mechanical power was missing were not included in the time weighted-average calculation. The time weighted–average was calculated for the highest and for the lowest values over the first 48 hours of ventilation, and the mean of these values was considered in the analysis.

To avoid bias introduced by missing data, and assuming that data were missing at random, the analysis of the primary outcome was replicated after multiple imputation. For this imputation the following variables were considered: age, gender, BMI, prognostic score (APACHE IV in eICU, OASIS in MIMIC–III and eICU, and SAPS II in MIMI–III), Elixhauser comorbidity score (only in MIMIC–III), SOFA, PaO_2 / FiO_2 ratio, pH, mean arterial pressure, SpO_2, temperature, $PaCO_2$, need of renal replacement therapy in the first 24 hours, need of vasoactive drugs in the first 24 hours, ICU and hospital length of stay, and hospital mortality. Multiple imputation was conducted using the method of predictive mean matching for continuous variable, logistic regression for categorical variables, and ten databases were created. The multivariable model was reproduced in the ten databases after multiple imputation and the results were pooled.

To check if mechanical power adds additional information, patients in the pooled cohort were stratified according to different levels of mechanical power (MP), tidal volume (V_T) size, and driving pressure (ΔP) level. First, the patients were categorized in four groups according to the mechanical power and the tidal volume: 1) group low mechanical power and low tidal volume (MP ≤ 17 J/min and V_T ≤ 7.5 ml/kg PBW); 2) group low mechanical power and high tidal volume (MP ≤ 17 J/min and V_T > 7.5 ml/kg PBW); 3) group high mechanical power and low tidal volume (MP > 17 J/min and V_T ≤ 7.5 ml/kg PBW); and 4) group high mechanical power and high tidal volume (MP > 17 J/min and V_T > 7.5 ml/kg PBW). Then, the patients were categorized in four groups according to the mechanical power and the driving pressure: 1) group low mechanical power and low driving pressure (MP ≤ 17 J/min and ΔP ≤ 13 cmH_2O); 2) group low mechanical power and high driving pressure (MP ≤ 17 J/min and ΔP > 13 cmH_2O); 3) group high mechanical power and low driving pressure (MP > 17 J/min and ΔP ≤ 13 cmH_2O); and 4) group high mechanical power and high driving pressure (MP > 17 J/min and ΔP > 13 cmH_2O). The individual effect of mechanical power was assessed in each subgroup against the reference group (group low mechanical power and low tidal volume or groups low mechanical power and low driving pressure) and adjusted by the same set of covariates used in the primary analyses. The cut-offs were defined according to the median in the overall cohort and to well established values in the literature.

In addition to the analysis using the quantiles, the best cut-off of mechanical power was assessed using a receiver-operating characteristics (ROC) curve. The best cut-off was determined using the Youden index. In all the analysis, we did not consider V_T, PEEP, Pplateau or ΔP as continuous

variables together with mechanical power. Further, mechanical power was analyzed together with the other covariates but not with any of these ventilatory variables.

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eTable 1 – Characteristics of the hospitals included in the two databases

	MIMIC	eICU	
	Number of Hospitals (*n* = 1)	**Number of Hospitals (*n* = 58)**	**Number of Patients (*n* = 4,361)**
Hospital size			
< 100 beds	0 / 1 (0.0)	5 / 51 (9.8)	33 / 4,107 (0.8)
100 – 249 beds	0 / 1 (0.0)	21 / 51 (41.2)	666 / 4,107 (16.2)
250 – 499 beds	0 / 1 (0.0)	13 / 51 (25.4)	908 / 4,107 (22.1)
≥ 500 bed	1 / 1 (100.0)	12 / 51 (23.5)	2,500 / 4,107 (60.9)
Teaching hospital	1 / 1 (100.0)	8 / 58 (13.8)	1,801 / 4,361 (41.3)
Hospital region			
Midwest	0 / 1 (0.0)	19 / 54 (35.2)	2,142 / 4,361 (50.6)
Northeast	0 / 1 (0.0)	6 / 54 (11.1)	397 / 4,361 (9.4)
South	1 / 1 (100.0)	16 / 54 (29.6)	1,051 / 4,361 (24.8)
West	0 / 1 (0.0)	13 / 54 (24.1)	639 / 4,361 (15.1)
North	0 / 1 (0.0)	0 / 54 (0.0)	0 / 4,361 (0.0)

eTable 2 – Vital signs and laboratory variables in included patients

	MIMIC–III (*n* = 3,846)	eICU (*n* = 4,361)
First day of ventilation		
Heart rate, bpm	92 (80 – 104)	92 (81 – 105)
MAP, mmHg	80 (73 – 89)	82 (74 – 92)
SpO_2, %	96 (94 – 98)	95 (93 – 97)
Temperature, ºC	37.1 (36.6 – 37.6)	36.9 (36.5 – 37.4)
pH	7.36 (7.31 – 7.41)	7.35 (7.29 – 7.41)
PaO_2 / FiO_2, mmHg	255 (183 – 357)	211 (144 – 308)
$PaCO_2$, mmHg	39 (35 – 44)	41 (35 – 48)
SAS	3 (1 – 3)	---
Second day of ventilation		
Heart rate, bpm	90 (78 – 101)	89 (78 – 101)
MAP, mmHg	80 (73 – 90)	81 (74 – 91)
SpO_2, %	97 (95 – 98)	96 (94 – 98)
Temperature, ºC	37.3 (36.8 – 37.7)	37.0 (36.6 – 37.5)
pH	7.40 (7.35 – 7.43)	7.40 (7.34 – 7.44)
PaO_2 / FiO_2, mmHg	244 (185 – 321)	212 (152 – 295)
$PaCO_2$, mmHg	38 (34 – 43)	38 (33 – 44)
SAS	3 (2 – 3)	---

The values are the mean between the highest and the lowest values measured during the day.
MAP: mean arterial pressure; SpO_2: pulse oximetry; SAS: Sedation Agitation Scale

eTable 3 – Clinical outcomes of the overall cohort

	MIMIC–III (*n* = 3,846)	eICU (*n* = 4,361)
Primary outcome		
In-hospital mortality	1,150 / 3,846 (29.9)	1,351 / 4,361 (31.0)
Secondary outcomes		
ICU mortality	985 / 3,846 (25.6)	1,122 / 4,361 (25.7)
30-day mortality	1,121 / 3,846 (29.1)	1,319 / 4,361 (30.2)
1-year mortality	1,681 / 3,846 (43.7)	---
Ventilator-free days at day 28	19.4 (0.0 – 24.0)	20.7 (0.0 – 24.5)
ICU length of stay	9.7 (5.9 – 16.2)	7.1 (4.5 – 11.8)
Survivors	10.5 (6.5 – 17.5)	7.8 (5.0 – 12.5)
Hospital length of stay	15.6 (9.5 – 24.8)	11.4 (6.8 – 17.8)
Survivors	18.0 (12.0 – 26.8)	13.6 (8.8 – 19.9)

Data are median (interquartile range) or No / Total (%)
ICU: intensive care unit

eTable 4 – Univariable models assessing impact of mechanical power and other important factors on in-hospital mortality

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio[a] (95% CI)**	***p* value**
Mechanical power*	1.07 (1.02 to 1.12)	0.005	1.16 (1.10 to 1.22)	< 0.001
Age	1.03 (1.02 to 1.03)	< 0.001	1.02 (1.01 to 1.02)	< 0.001
Prognostic Score**	1.04 (1.03 to 1.05)	< 0.001	1.02 (1.01 to 1.02)	< 0.001
OASIS	1.06 (1.05 to 1.07)	< 0.001	1.04 (1.03 to 1.05)	< 0.001
Elixhauser comorbidity score	1.04 (1.03 to 1.05)	< 0.001	---	---
SOFA	1.09 (1.07 to 1.11)	< 0.001	1.14 (1.12 to 1.16)	< 0.001
Mean Arterial Pressure	0.97 (0.96 to 0.98)	< 0.001	0.98 (0.97 to 0.99)	< 0.001
PaO_2 / FiO_2	0.99 (0.99 to 1.00)	0.039	0.99 (0.99 to 0.99)	< 0.001
pH	0.03 (0.01 to 0.08)	< 0.001	0.04 (0.02 to 0.11)	< 0.001
SpO_2	0.97 (0.96 to 0.98)	< 0.001	0.95 (0.93 to 0.97)	< 0.001
Temperature	0.71 (0.64 to 0.79)	< 0.001	0.67 (0.62 to 0.73)	< 0.001
$PaCO_2$	0.98 (0.98 to 0.99)	0.003	0.99 (0.98 to 0.99)	0.034

[a] Calculated in a mixed-effect model with centers as random effects

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III and APACHE-IV for the eICU databases

SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 5 – Full multivariable model assessing impact of mechanical power on in-hospital mortality

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio[a] (95% CI)**	***p* value**
Mechanical power*	1.06 (1.01 to 1.11)	0.021	1.10 (1.02 to 1.18)	0.010
Age	1.01 (1.01 to 1.02)	< 0.001	1.01 (1.00 to 1.02)	< 0.001
Prognostic Score**	1.02 (1.01 to 1.03)	< 0.001	1.02 (1.01 to 1.02)	< 0.001
OASIS	1.02 (1.01 to 1.03)	0.003	0.98 (0.97 to 1.01)	0.060
Elixhauser comorbidity score	1.02 (1.01 to 1.03)	0.001	---	---
SOFA	0.98 (0.95 to 1.01)	0.170	1.01 (0.97 to 1.05)	0.547
Mean Arterial Pressure	0.99 (0.98 to 1.00)	0.224	0.99 (0.98 to 1.00)	0.124
PaO_2 / FiO_2	1.00 (0.99 to 1.00)	0.876	0.99 (0.99 to 1.00)	0.055
pH	0.16 (0.05 to 0.55)	0.003	0.08 (0.02 to 0.33)	0.022
SpO_2	0.98 (0.97 to 0.99)	0.044	0.97 (0.93 to 0.99)	< 0.001
Temperature	0.83 (0.74 to 0.93)	0.001	0.78 (0.70 to 0.88)	< 0.001
$PaCO_2$	0.99 (0.98 to 0.99)	0.011	0.98 (0.97 to 0.99)	0.015

[a] Calculated in a mixed-effect model with centers as random effects

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III and APACHE-IV for the eICU databases

SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 6 – Full multivariable model assessing impact of mechanical power on in-hospital mortality considering the covariate balancing propensity score as covariate[a]

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Mechanical power*	1.11 (1.05 to 1.18)	< 0.001	1.09 (1.01 to 1.19)	0.034

[a] Propensity score calculated according to the median of mechanical power in the second day of ventilation included:
MIMIC: age, SAPS-II, OASIS, Elixhauser comorbidity score, RRT in the first day, SOFA, pH, PaO_2/FiO_2, mean arterial pressure, SpO_2, temperature, $PACO_2$, height, weight, gender, and presence of Acute Respiratory Distress Syndrome (at the beginning of ventilation)
eICU: age, SAPS-II, OASIS, SOFA, pH, PaO_2/FiO_2, mean arterial pressure, SpO_2, temperature, $PACO_2$, height, weight, gender, and presence of Acute Respiratory Distress Syndrome (at the beginning of ventilation)
* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

eTable 7 – Full multivariable model assessing impact of mechanical power on in-hospital mortality considering the inverse probability weighting[a]

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Mechanical power*	1.06 (1.02 to 1.10)	0.001	1.17 (1.10 to 1.24)	< 0.001

[a] Inverse probability weighting calculated as 1 / ((mechanical power category * CBPS) + ((1 - mechanical power category) * (1 - CBPS))) and included in the generalized linear model as weight

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

CBPS: covariate balancing propensity score

eTable 8 – Percentage of missing data in the variables of interest

	MIMIC–III (*n* = 3,846)	eICU (*n* = 4,361)
Baseline characteristics		
Age, years	0%	0%
Male gender	0%	0%
Weight, kg	0.49%	0.48%
Height, cm	32.3%	0.66%
BMI, kg/m^2	32.4%	0.96%
PBW, kg	32.3%	0.66%
Admission type	0%	0%
Source of admission	0%	0%
Ethnicity	0%	1.55%
Initial diagnosis	0%	0%
Co-morbidities		
COPD	0%	0%
Smoking	1.76%	---
Elixhauser comorbidity score	0%	---
ARDS at baseline	0%	0%
Need of support in the first 24 hours		
Vasopressor	0%	1.71%
Renal replacement therapy	0%	---
Limitation of support	6.21%	3.62%
Severity of illness		
SAPS II	0%	---
OASIS	0%	0%
APACHE IV	---	0%
SOFA	0%	0%
First day of ventilation		
Mechanical power, J/min	0.20%	17.33%
Tidal volume, ml/kg PBW	32.3%	3.18%
PEEP, cmH_2O	0%	3.62%
Plateau pressure, cmH_2O	0.20%	15.23%
Driving pressure, cmH_2O	0.20%	17.33%
Total respiratory rate, bpm	0%	3.48%
Minute ventilation, L/min	0%	4.28%
FiO_2, %	2.02%	3.09%
Heart rate, bpm	0.02%	0.09%
MAP, mmHg	0%	0.11%
SpO_2, %	0.02%	4.15%
Temperature, ºC	2.83%	0.41%
pH	2.60%	15.54%
PaO_2 / FiO_2, mmHg	4.60%	14.46%
$PaCO_2$, mmHg	2.60%	11.32%
Use of NMBA	0%	48.4%
Second day of ventilation		
Mechanical power, J/min	0.10%	17.17%
Tidal volume, ml/kg PBW	32.3%	3.85%
PEEP, cmH_2O	0%	3.78%
Plateau pressure, cmH_2O	0%	16.94%
Driving pressure, cmH_2O	0%	16.23%
Total respiratory rate, bpm	0%	3.37%
Minute ventilation, L/min	0%	4.42%
FiO_2, %	1.40%	3.11
Heart rate, bpm	0%	0.09%
MAP, mmHg	0%	0.36%
SpO_2, %	0.05%	2.20%
Temperature, ºC	3.04%	0.71%
pH	6.34%	33.36%

PaO_2 / FiO_2, mmHg	7.69%	33.70%
$PaCO_2$, mmHg	6.34%	31.13%
Use of NMBA	0%	48.4%
Primary outcome		
In-hospital mortality	0%	0%
Secondary outcomes		
ICU mortality	0%	0%
30-day Mortality	0%	0%
1-year mortality	0%	---
Ventilator-free days	0%	0%
ICU length of stay	0%	0%
Hospital length of stay	0%	0%

Data are median (interquartile range) or No / Total (%)

BMI: body mass index; PBW: predicted body weight; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; bpm: beats per minute; SpO_2: pulse oximetry; MAP: mean arterial blood pressure; PEEP: positive end-expiratory pressure; FiO_2: inspired fraction of oxygen; NMBA: neuromuscular blocking agents

eTable 9 – Full multivariable model assessing impact of mechanical power on in-hospital mortality after multiple imputation[a]

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Mechanical power[*]	1.06 (1.01 to 1.11)	0.010	1.10 (1.01 to 1.20)	0.022
Age	1.01 (1.00 to 1.02)	< 0.001	1.02 (1.01 to 1.02)	< 0.001
Prognostic Score[**]	1.03 (1.02 to 1.03)	< 0.001	1.01 (1.01 to 1.02)	< 0.001
OASIS	1.02 (1.01 to 1.03)	< 0.001	0.99 (0.98 to 1.00)	0.095
Elixhauser comorbidity score	1.02 (1.01 to 1.03)	0.001	---	---
SOFA	0.96 (0.93 to 0.99)	0.012	1.03 (0.99 to 1.05)	0.069
Mean Arterial Pressure	0.99 (0.99 to 1.00)	0.275	0.99 (0.99 to 1.00)	0.169
PaO_2 / FiO_2	1.00 (0.99 to 1.00)	0.586	0.99 (0.99 to 1.00)	0.098
pH	0.11 (0.03 to 0.38)	< 0.001	0.07 (0.02 to 0.23)	< 0.001
SpO_2	0.98 (0.97 to 1.00)	0.050	0.98 (0.96 to 1.00)	0.094
Temperature	0.83 (0.75 to 0.94)	0.001	0.82 (0.75 to 0.89)	< 0.001
$PaCO_2$	0.98 (0.98 to 0.99)	0.009	0.98 (0.97 to 0.99)	0.003

[a] Multiple imputation considering: age, gender, BMI, prognostic score (APACHE IV in eICU, SAPS II in MIMIC–III, and OASIS in MIMIC–III and eICU), Elixhauser comorbidity score (only in MIMIC–III), SOFA, PaO_2 / FiO_2 ratio, pH, mean arterial pressure, SpO_2, temperature, $PaCO_2$, need of renal replacement therapy in the first 24 hours, need of vasoactive drugs in the first 24 hours, ICU and hospital length of stay, and hospital mortality

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III database and APACHE-IV for the eICU.

SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 10 – Full multivariable model assessing impact of mechanical power on in-hospital mortality with year of inclusion as random effect

	MIMIC–III		eICU	
	Odds Ratio[a] (95% CI)	***p* value**	**Odds Ratio[a,b] (95% CI)**	***p* value**
Mechanical power[*]	1.65 (1.08 to 2.54)	0.021	1.95 (1.13 to 3.36)	0.015
Age	1.30 (1.17 to 1.44)	< 0.001	1.19 (1.07 to 1.32)	< 0.001
Prognostic Score[**]	1.38 (1.19 to 1.61)	< 0.001	1.65 (1.39 to 1.97)	< 0.001
OASIS	1.17 (1.05 to 1.31)	0.003	0.86 (0.75 to 0.99)	0.045
Elixhauser comorbidity score	1.13 (1.04 to 1.23)	0.001	---	---
SOFA	0.91 (0.81 to 1.04)	0.170	1.05 (0.92 to 1.19)	0.452
Mean Arterial Pressure	0.94 (0.87 to 1.03)	0.224	0.92 (0.83 to 1.01)	0.114
PaO_2 / FiO_2	1.01 (0.91 to 1.10)	0.876	0.89 (0.80 to 1.00)	0.057
pH	0.86 (0.78 to 0.95)	0.003	0.81 (0.73 to 0.91)	< 0.001
SpO_2	0.91 (0.84 to 0.99)	0.044	0.90 (0.81 to 0.99)	0.047
Temperature	0.87 (0.80 to 0.95)	0.001	0.81 (0.73 to 0.89)	< 0.001
$PaCO_2$	0.88 (0.81 to 0.97)	0.011	0.87 (0.77 to 0.97)	0.017

[a] Calculated in a mixed-effect model with year of admission as random effects. All variables were re-scaled to the best fit of the model

[b] Calculated in a mixed-effect model with centers as random effects

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III and APACHE-IV for the eICU databases

SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 11 – Full multivariable model assessing impact of time weighted–average mechanical power on in-hospital mortality

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio[a] (95% CI)**	***p* value**
Mechanical power*	1.04 (1.00 to 1.08)	0.049	1.11 (1.02 to 1.20)	0.009
Age	1.01 (1.00 to 1.02)	< 0.001	1.01 (1.00 to 1.02)	< 0.001
Prognostic score**	1.02 (1.01 to 1.03)	< 0.001	1.02 (1.01 to 1.02)	< 0.001
OASIS	1.02 (1.01 to 1.03)	0.002	0.98 (0.96 to 0.99)	0.019
Elixhauser comorbidity score	1.02 (1.01 to 1.03)	0.001	---	---
SOFA	0.98 (0.95 to 1.01)	0.132	1.01 (0.97 to 1.05)	0.536
Mean arterial pressure	0.99 (0.98 to 1.00)	0.155	0.99 (0.98 to 1.00)	0.120
PaO_2 / FiO_2	1.00 (0.99 to 1.00)	0.906	0.99 (0.99 to 1.00)	0.071
pH	0.13 (0.04 to 0.43)	< 0.001	0.09 (0.02 to 0.37)	< 0.001
SpO_2	0.98 (0.97 to 0.99)	0.011	0.97 (0.94 to 0.99)	0.049
Temperature	0.84 (0.75 to 0.94)	0.003	0.80 (0.71 to 0.89)	< 0.001
$PaCO_2$	0.99 (0.98 to 0.99)	0.005	0.99 (0.97 to 0.99)	0.042

[a] Calculated in a mixed-effect model with centers as random effects

* Time weighted–average over the first 48 hours. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III database and APACHE-IV for the eICU database

SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 12 – Impact of time weighted–average mechanical power on sensitivity analyses and secondary outcomes

	MIMIC–III		eICU	
	Odds Ratio[a] (95% CI)	***p* value**	**Odds Ratio[a,b] (95% CI)**	***p* value**
Primary outcome				
In-hospital mortality				
CBPS as covariate	1.08 (1.03 to 1.13)	0.001	1.09 (1.01 to 1.17)	0.032
IPTW	1.05 (1.01 to 1.08)	0.004	1.16 (1.09 to 1.22)	< 0.001
Secondary outcomes				
ICU mortality	1.06 (1.01 to 1.10)	0.006	1.15 (1.06 to 1.25)	< 0.001
30-day mortality	1.03 (0.99 to 1.07)	0.104	1.09 (1.01 to 1.18)	0.028
1-year mortality	1.03 (0.99 to 1.07)	0.181	---	---
Ventilator-free days	-0.33 (-0.50 to -0.15)[*]	< 0.001	-0.77 (-1.11 to -0.42)[*]	< 0.001
ICU length of stay	0.35 (0.17 to 0.54)[*]	< 0.001	0.58 (0.33 to 0.83)[*]	< 0.001
Hospital length of stay	0.14 (-0.12 to 0.42)[*]	0.279	0.26 (-0.17 to 0.70)[*]	0.233

[a] Time weighted–average over the first 48 hours. Odds ratio per 5 J/min increase
[b] Calculated in a mixed-effect model with centers as random effects
[*] Effect estimates and 95% confidence interval from the multivariable linear regression

eTable 13 – Differences between the included MIMIC–III cohort and the excluded cohort due to missing

	MIMIC–III Included (*n* = 3,846)	MIMIC–III Missing (*n* = 1,157)	*p* value
Baseline characteristics			
Age, years	64.6 (50.7 – 76.7)	66.9 (53.2 – 78.1)	< 0.001
Male gender	2,161 / 3,846 (56.2)	659 / 1,157 (56.9)	0.668
Weight, kg	80.0 (66.6 – 96.0)	79.8 (67.0 – 93.2)	0.123
Height, cm	170 (163 – 178)	170 (163 – 178)	0.314
BMI, kg/m^2	27.8 (24 – 32.9)	27.1 (23.9 – 31.7)	0.086
PBW, kg	64.0 (54.7 – 73.1)	63.9 (54.7 – 73.1)	0.354
Admission type			
Surgical elective	290 / 3,846 (7.5)	107 / 1,157 (9.2)	0.001
Surgical urgency	154 / 3,846 (4.0)	23 / 1,157 (2.0)	
Clinical	3,402 / 3,846 (88.5)	1,027 / 1,157 (88.8)	
Source of admission			
Ward	564 / 3,846 (14.7)	208 / 1,157 (18.0)	
Emergency room	1,888 / 3,846 (49.1)	557 / 1,157 (48.1)	0.012
Office or operating room	403 / 3,846 (10.5)	134 / 1,157 (11.6)	
Transferred from other hospital	965 / 3,846 (25.1)	253 / 1,157 (21.9)	
Transferred from skilled nurse	26 / 3,846 (0.7)	4 / 1,157 (0.3)	
Ethnicity			
Black	256 / 3,846 (6.7)	72 / 1,157 (6.2)	
Hispanic	128 / 3,846 (3.3)	31 / 1,157 (2.7)	0.022
White	2,582 / 3,846 (67.1)	831 / 1,157 (71.8)	
Other	880 / 3,846 (22.9)	223 / 1,157 (19.3)	
Initial diagnosis			
Sepsis (including pneumonia)	805 / 3,846 (21.0)	183 / 1,157 (15.9)	
Cardiovascular disease	892 / 3,846 (23.2)	180 / 1,157 (15.5)	
Other respiratory condition	569 / 3,846 (14.8)	141 / 1,157 (12.2)	< 0.001
Neurological condition	701 / 3,846 (18.2)	379 / 1,157 (32.7)	
Renal condition	42 / 3,846 (1.0)	17 / 1,157 (1.5)	
Others	837 / 3,846 (21.8)	257 / 1,157 (22.2)	
Co-morbidities			
COPD	208 / 3,846 (5.4)	48 / 1,157 (4.1)	0.103
Smoking	1,808 / 3,846 (47.8)	486 / 1,157 (42.7)	0.009
Elixhauser comorbidity score	6 (1 – 12)	6 (1 – 12)	0.422
ARDS at baseline	443 / 3,846 (11.5)	88 / 1,157 (7.6)	< 0.001
Mild	43 / 443 (9.7)	13 / 88 (14.8)	
Moderate	230 / 443 (51.9)	34 / 88 (38.6)	0.001
Severe	170 / 443 (38.4)	41 / 88 (46.6)	
Need of support in the first 24 hours			
Vasopressor	1,959 / 3,846 (50.9)	412 / 1,157 (35.6)	< 0.001
Renal replacement therapy	204 / 3,846 (5.3)	45 / 1,157 (3.9)	0.062
Limitation of support	902 / 3,846 (25.0)	258 / 1,157 (24.8)	0.953
Severity of illness			
SAPS II	43 (33 – 54)	40 (31 – 50)	< 0.001
OASIS	38 (33 – 44)	37 (32 – 43)	< 0.001
SOFA	6 (4 – 9)	5 (2 – 7)	< 0.001
Vital signs in the beginning of ventilation			
Heart rate, bpm	92 (80 – 104)	89 (78 – 100)	< 0.001
MAP, mmHg	80 (73 – 89)	82 (74 – 91)	< 0.001
SpO_2, %	96 (94 – 98)	97 (95 – 98)	< 0.001
Temperature, ºC	37.1 (36.6 – 37.6)	37.2 (36.7 – 37.6)	< 0.001
Laboratory in the beginning of ventilation			
pH	7.36 (7.31 – 7.41)	7.39 (7.35 – 7.43)	< 0.001
PaO_2 / FiO_2, mmHg	255 (183 – 357)	272 (197 – 380)	< 0.001
$PaCO_2$, mmHg	39 (35 – 44)	38 (34 – 43)	< 0.001
Clinical outcomes			
In-hospital mortality	1,150 / 3,846 (29.9)	310 / 1,157 (26.8)	0.045

ICU mortality	985 / 3,846 (25.6)	226 / 1,157 (19.5)	< 0.001
30-day mortality	1,121 / 3,846 (29.1)	333 / 1,157 (28.8)	0.838
1-year mortality	1,681 / 3,846 (43.7)	512 / 1,157 (44.2)	0.769
Ventilator-free days at day 28	19.4 (0.0 – 24.0)	21.2 (0.0 – 24.9)	< 0.001
ICU length of stay	9.7 (5.9 – 16.2)	8.2 (5.5 – 12.9)	< 0.001
Survivors	10.5 (6.5 – 17.5)	8.7 (5.8 – 13.2)	< 0.001
Hospital length of stay	15.6 (9.5 – 24.8)	14.0 (9.0 – 21.9)	< 0.001
Survivors	18.0 (12.0 – 26.8)	15.9 (10.7 – 23.7)	< 0.001

Data are median (interquartile range) or No / Total (%)

BMI: body mass index; PBW: predicted body weight; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; bpm: beats per minute; SpO_2: pulse oximetry; MAP: mean arterial blood pressure

eTable 14 – Vital signs and laboratory variables in the included MIMIC–III cohort and the excluded cohort due to missing

	MIMIC–III Included (*n* = 3,846)	MIMIC–III Missing (*n* = 1,157)	*p* value
First day of ventilation			
Mechanical power, J/min*	24.0 (18.1 – 31.2)	17.1 (13.3 – 22.7)	< 0.001
Tidal volume, ml/kg PBW	8.8 (7.8 – 10.0)	8.6 (7.6 – 9.8)	0.003
PEEP, cmH_2O	6 (5 – 8)	5 (5 – 7)	< 0.001
Peak pressure, cmH_2O	26 (22 – 31)	21 (17 – 25)	< 0.001
Driving pressure, cmH_2O	14 (11 – 17)	15 (12 – 19)	< 0.001
Total respiratory rate, bpm	20 (17 – 23)	20 (17 – 23)	0.478
Minute ventilation, L/min	11.7 (9.9 – 13.8)	11.6 (9.8 – 14.0)	0.708
FiO_2, %	0.55 (0.50 – 0.70)	0.50 (0.45 – 70)	< 0.001
Heart rate, bpm	92 (80 – 104)	89 (78 – 100)	< 0.001
MAP, mmHg	80 (73 – 89)	82 (74 – 91)	< 0.001
SpO_2, %	96 (94 – 98)	97 (95 – 98)	< 0.001
Temperature, ºC	37.1 (36.6 – 37.6)	37.2 (36.7 – 37.6)	< 0.001
pH	7.36 (7.31 – 7.41)	7.39 (7.35 – 7.43)	< 0.001
PaO_2 / FiO_2, mmHg	255 (183 – 357)	272 (197 – 380)	< 0.001
$PaCO_2$, mmHg	39 (35 – 44)	38 (34 – 43)	< 0.001
Second day of ventilation			
Mechanical power, J/min*	21.4 (16.2 – 28.1)	12.2 (9.6 – 17.3)	< 0.001
Tidal volume, ml/kg PBW	8.6 (7.6 – 9.7)	8.4 (7.4 – 9.6)	0.004
PEEP, cmH_2O	6 (5 – 10)	5 (5 – 6)	< 0.001
Peak pressure, cmH_2O	26 (21 – 31)	15 (12 – 20)	< 0.001
Driving pressure, cmH_2O	13 (11 – 16)	10 (7 – 13)	< 0.001
Total respiratory rate, bpm	20 (16 – 23)	20 (17 – 23)	< 0.001
Minute ventilation, L/min	10.8 (9.1 – 13.0)	11.2 (9.3 – 13.2)	0.006
FiO_2, %	0.45 (0.40 – 0.55)	0.40 (0.40 – 0.50)	< 0.001
Heart rate, bpm	90 (78 – 101)	89 (78 – 100)	0.280
MAP, mmHg	80 (73 – 90)	83 (75 – 92)	< 0.001
SpO_2, %	97 (95 – 98)	97 (96 – 98)	< 0.001
Temperature, ºC	37.3 (36.8 – 37.7)	37.4 (36.9 – 37.8)	< 0.001
pH	7.40 (7.35 – 7.43)	7.41 (7.37 – 7.44)	< 0.001
PaO_2 / FiO_2, mmHg	244 (185 – 321)	267 (201 – 341)	< 0.001
$PaCO_2$, mmHg	38 (34 – 43)	38.5 (34.5 – 43.6)	0.589

Data are median (interquartile range) or No / Total (%)
The values are the mean between the highest and the lowest values measured during the day
* In MIMIC missing the mechanical power was calculated using maximum airway pressure instead of plateau pressure
MAP: mean arterial pressure; SpO_2: pulse oximetry; PBW: predicted body weight; PEEP: positive end-expiratory pressure; bpm: breaths per minute; FiO_2: inspired fraction of oxygen; SIMV: synchronized mandatory ventilation; CPAP: continuous positive airway pressure; FiO_2: inspired fraction of oxygen

eTable 15 – Effect of mechanical power* on outcomes of the patients excluded from the MIMIC–III database due to missing values

	Odds Ratio** (95% Confidence Interval)	*p* value
Primary outcome		
In-hospital mortality		
Multivariable model	1.28 (1.10 to 1.50)	0.001
CBPS as covariate	1.17 (0.99 to 1.39)	0.060
IPTW	1.18 (1.05 to 1.31)	0.004
Secondary outcomes		
ICU mortality	1.40 (1.19 to 1.65)	< 0.001
30-day mortality	1.29 (1.10 to 1.52)	0.001
1-year mortality	1.26 (1.08 to 1.48)	0.003
Ventilator-free days	-1.13 (-1.84 to -0.42)[a]	0.001
ICU length of stay	0.19 (-0.39 to 0.79)[a]	0.512
Hospital length of stay	-0.22 (-1.13 to 0.68)[a]	0.631

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. The mechanical power was calculated using maximum airway pressure instead of plateau pressure

** Odds ratio per 5 J/min increase

[a] Effect estimate from a linear model

CBPS: covariate balancing propensity score; IPTW: inverse probability treatment weighting

eTable 16 – Multivariable models assessing impact of mechanical power and other important factors on in-hospital mortality of obese patients only (BMI ≥ 30 kg/m^2)

	MIMIC–III		eICU	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio[a] (95% CI)**	***p* value**
Mechanical power*	1.05 (0.95 to 1.15)	0.349	1.21 (1.08 to 1.36)	< 0.001
Age	1.02 (1.01 to 1.03)	0.044	1.01 (0.99 to 1.02)	0.115
Prognostic Score**	1.01 (0.98 to 1.03)	0.378	1.01 (1.00 to 1.02)	0.002
OASIS	1.03 (0.99 to 1.06)	0.072	0.99 (0.97 to 1.02)	0.906
Elixhauser comorbidity score	1.01 (0.99 to 1.04)	0.223	---	---
SOFA	1.04 (0.97 to 1.11)	0.248	1.04 (0.97 to 1.09)	0.213
Mean Arterial Pressure	0.99 (0.97 to 1.01)	0.427	0.99 (0.98 to 1.01)	0.551
PaO_2 / FiO_2	1.00 (0.99 to 1.00)	0.979	0.99 (0.99 to 1.00)	0.080
pH	0.14 (0.01 to 1.85)	0.135	0.82 (0.08 to 7.60)	0.861
SpO_2	0.98 (0.94 to 1.01)	0.140	0.96 (0.91 to 1.01)	0.132
Temperature	0.82 (0.64 to 1.05)	0.113	0.64 (0.54 to 0.77)	< 0.001
$PaCO_2$	0.98 (0.96 to 1.00)	0.085	0.98 (0.96 to 1.00)	0.174

[a] Calculated in a mixed-effect model with centers as random effects

* The value in the second day of ventilation. This value is the mean between the highest and the lowest mechanical power measured during the day. Odds ratio per 5 J/min increase

** SAPS-II for the MIMIC–III and APACHE-IV for the eICU databases

BMI: body mass index; SAPS-II: Simplified Acute Physiology Score II; OASIS: Oxford Acute Severity of Illness Score; SOFA: Sequential Organ Failure Assessment; SpO_2: pulse oximetry

eTable 17 – Effect of mechanical power according to different tidal volume sizes

	Low Mechanical Power				High Mechanical Power			
	Low Tidal Volume (*n* = 955)		High Tidal Volume (*n* = 1,736)		Low Tidal Volume (*n* = 851)		High Tidal Volume (*n* = 2,634)	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Primary outcome								
In-hospital mortality	1 (Reference)	---	1.10 (0.88 to 1.37)	0.413	1.70 (1.32 to 2.18)	< 0.001	1.27 (1.03 to 1.58)	0.025
Secondary outcomes								
ICU mortality	1 (Reference)	---	1.05 (0.83 to 1.33)	0.677	1.68 (1.29 to 2.18)	< 0.001	1.34 (1.08 to 1.68)	0.008
30-day mortality	1 (Reference)	---	1.09 (0.87 to 1.36)	0.469	1.58 (1.22 to 2.03)	< 0.001	1.19 (0.97 to 1.48)	0.104
Ventilator-free days	1 (Reference)	---	-0.58 (-1.55 to 4.06)*	0.249	-3.10 (-4.23 to -1.96)*	< 0.001	-1.78 (-2.72 to -8.48)*	< 0.001
ICU length of stay	1 (Reference)	---	0.08 (-0.86 to 1.02)*	0.865	1.54 (0.45 to 2.63)*	0.005	2.11 (1.21 to 3.01)*	< 0.001
Hospital length of stay	1 (Reference)	---	0.52 (-0.89 to 1.94)*	0.471	0.90 (-0.73 to 2.54)*	0.279	1.99 (0.64 to 3.35)*	0.003

OR: odds ratio; CI: confidence interval; ICU: intensive care unit

* Effect estimate from a linear model

Adjusted by: age, prognostic score, SOFA, pH, mean arterial pressure, PaO_2 / FiO_2, SpO_2, temperature, $PaCO_2$

eTable 18 – Effect of mechanical power according to different driving pressures

	Low Mechanical Power				High Mechanical Power			
	Low Driving Pressure (*n* = 3,156)		High Driving Pressure (*n* = 1,526)		Low Driving Pressure (*n* = 1,713)		High Driving Pressure (*n* = 2,896)	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Primary outcome								
In-hospital mortality	1 (Reference)	---	0.89 (0.76 to 1.06)	0.203	1.09 (0.93 to 1.29)	0.283	1.41 (1.23 to 1.63)	< 0.001
Secondary outcomes								
ICU mortality	1 (Reference)	---	1.07 (0.89 to 1.27)	0.464	1.27 (1.07 to 1.51)	0.006	1.73 (1.48 to 2.01)	< 0.001
30-day mortality	1 (Reference)	---	0.91 (0.77 to 1.08)	0.289	1.07 (0.91 to 1.26)	0.428	1.30 (1.13 to 1.50)	< 0.001
Ventilator-free days	1 (Reference)	---	-0·98 (-1.71 to -0.24)*	0.009	-1.09 (-1.81 to -0.37)*	0.002	-2.78 (-3.42 to -2.14)*	< 0.001
ICU length of stay	1 (Reference)	---	2.68 (1.93 to 3.44)*	< 0.001	2.07 (1.32 to 2.82)*	< 0.001	3.37 (2.70 to 4.04)*	< 0.001
Hospital length of stay	1 (Reference)	---	2.02 (0.57 to 3.47)*	0.006	-0.93 (-2.35 to 0.47)*	0.193	0.42 (-0.83 to 1.69)*	0.505

OR: odds ratio; CI: confidence interval; ICU: intensive care unit

* Effect estimate from a linear model

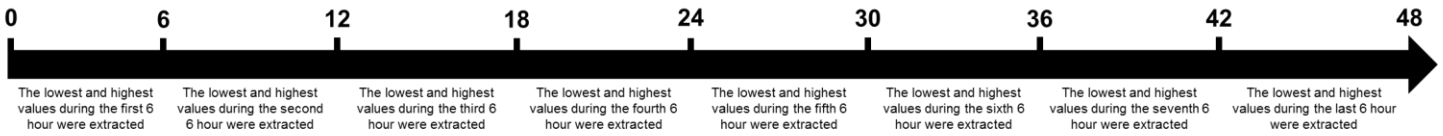
Adjusted by: age, prognostic score, SOFA, pH, mean arterial pressure, PaO_2 / FiO_2, SpO_2, temperature, $PaCO_2$

eTable 19 – Characteristics of mechanical ventilation in included patients according to the diagnosis of ARDS

	MIMIC–III (*n* = 3,846)			eICU (*n* = 4,361)		
	ARDS (*n* = 443)	**Non-ARDS (*n* = 3,403)**	***p* value**	**ARDS (*n* = 427)**	**Non-ARDS (*n* = 3,934)**	***p* value**
First day of ventilation						
Mechanical power, J/min	28.3 (22.3 – 35.8)	23.4 (17.8 – 30.6)	< 0.001	20.1 (14.5 – 26.9)	16.7 (12.2 – 22.8)	< 0.001
Tidal volume, ml/kg PBW	8.6 (7.6 – 9.9)	8.9 (7.9 – 10.1)	0.003	7.7 (6.8 – 8.6)	7.8 (6.9 – 8.7)	0.344
PEEP, cmH_2O	8 (6 – 11)	5 (5 – 7)	< 0.001	6 (5 – 9)	5 (5 – 7)	< 0.001
Plateau pressure, cmH_2O	24 (21 – 28)	21 (17 – 24)	< 0.001	22 (19 – 27)	20 916 – 24)	< 0.001
Driving pressure, cmH_2O	15 (12 – 17)	14 (11 – 17)	< 0.001	15 (12 – 19)	14 (11 – 17)	< 0.001
Total respiratory rate, bpm	22 (19 – 25)	19 (17 – 22)	< 0.001	21 (15 – 25)	19 (16 – 23)	< 0.001
Minute ventilation, L/min	12.5 (10.6 – 15.0)	11.6 (9.8 – 13.6)	< 0.001	10.1 (8.2 – 12.5)	9.7 (8.0 – 11.8)	0.003
FiO_2, %	0.65 (0.54 – 0.70)	0.55 (0.45 – 0.70)	< 0.001	0.70 (0.55 – 0.77)	0.65 (0.45 – 0.70)	< 0.001
Second day of ventilation						
Mechanical power, J/min	24.6 (18.8 – 31.4)	21.0 (15.9 – 27.6)	< 0.001	18.3 (13.1 – 24.3)	15.8 (11.6 – 21.9)	< 0.001
Tidal volume, ml/kg PBW	8.2 (7.2 – 9.5)	8.7 (7.6 – 9.8)	0.001	7.5 (6.6 – 8.5)	7.6 (6.8 – 8.5)	0.207
PEEP, cmH_2O	9 (6 – 12)	5 (5 – 9)	< 0.001	6 (5 – 10)	5 (5 – 7)	< 0.001
Plateau pressure, cmH_2O	23 (20 – 27)	20 (17 – 24)	< 0.001	22 (19 – 27)	20 (16 – 24)	< 0.001
Driving pressure, cmH_2O	14 (11 – 17)	13 (11 – 16)	0.192	14 (11 – 18)	13 (11 – 17)	0.026
Total respiratory rate, bpm	21 (18 – 24)	19 (16 – 22)	< 0.001	21 (17 – 26)	19 (16 – 23)	< 0.001
Minute ventilation, L/min	11.5 (9.6 – 13.7)	10.8 (9.0 – 12.9)	< 0.001	10.4 (8.2 – 12.1)	9.6 (7.9 – 11.6)	0.030
FiO_2, %	0.50 (0.45 – 0.60)	0.45 (0.40 – 0.50)	< 0.001	0.50 (0.40 – 0.65)	0.40 (0.37 – 0.55)	< 0.001

Data are median (interquartile range) or No / Total (%)
The values are the mean between the highest and the lowest values measured during the day.
ARDS: Acute Respiratory Distress Syndrome; PBW: predicted body weight; PEEP: positive end-expiratory pressure; bpm: breaths per minute; FiO_2: inspired fraction of oxygen; SIMV: synchronized mandatory ventilation; CPAP: continuous positive airway pressure; FiO_2: inspired fraction of oxygen

eFigure 1 – Extraction of ventilatory variables and calculation of time-weighted average mechanical power using these values in MIMIC–III and eICU databases

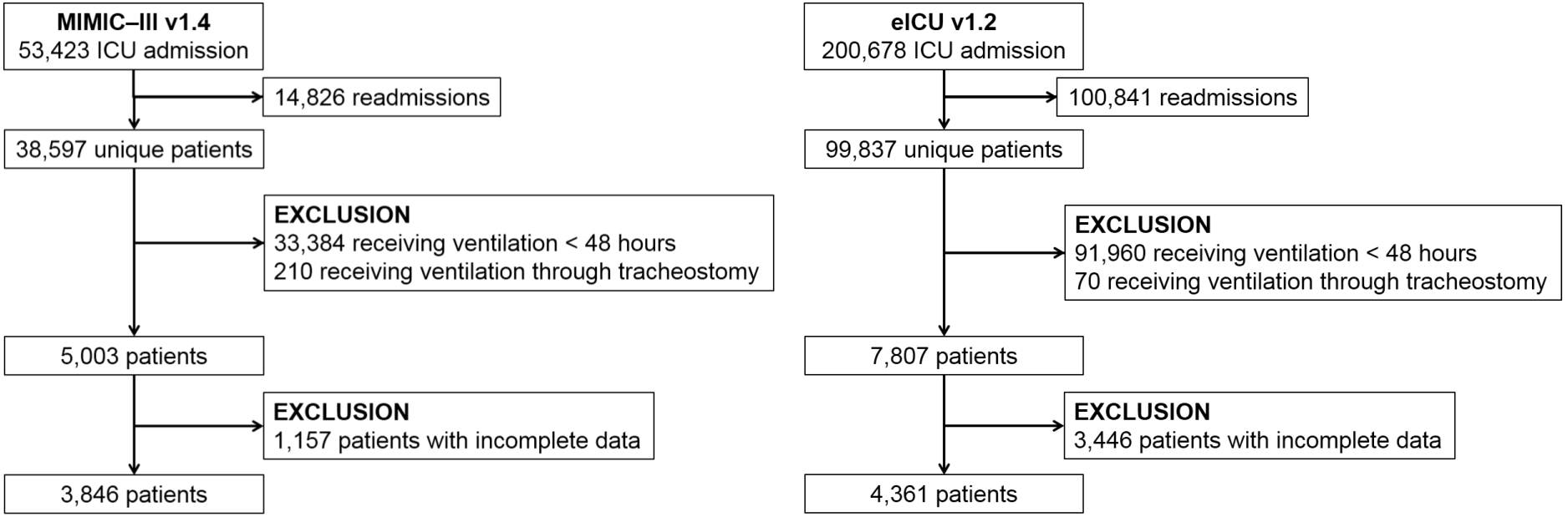


$$\text{Time-Weighted Average (AUC)} = \frac{1}{2} \sum_{i=0}^{n-1} (t_{i+1} - t_i)(y_i + y_{i+1})$$

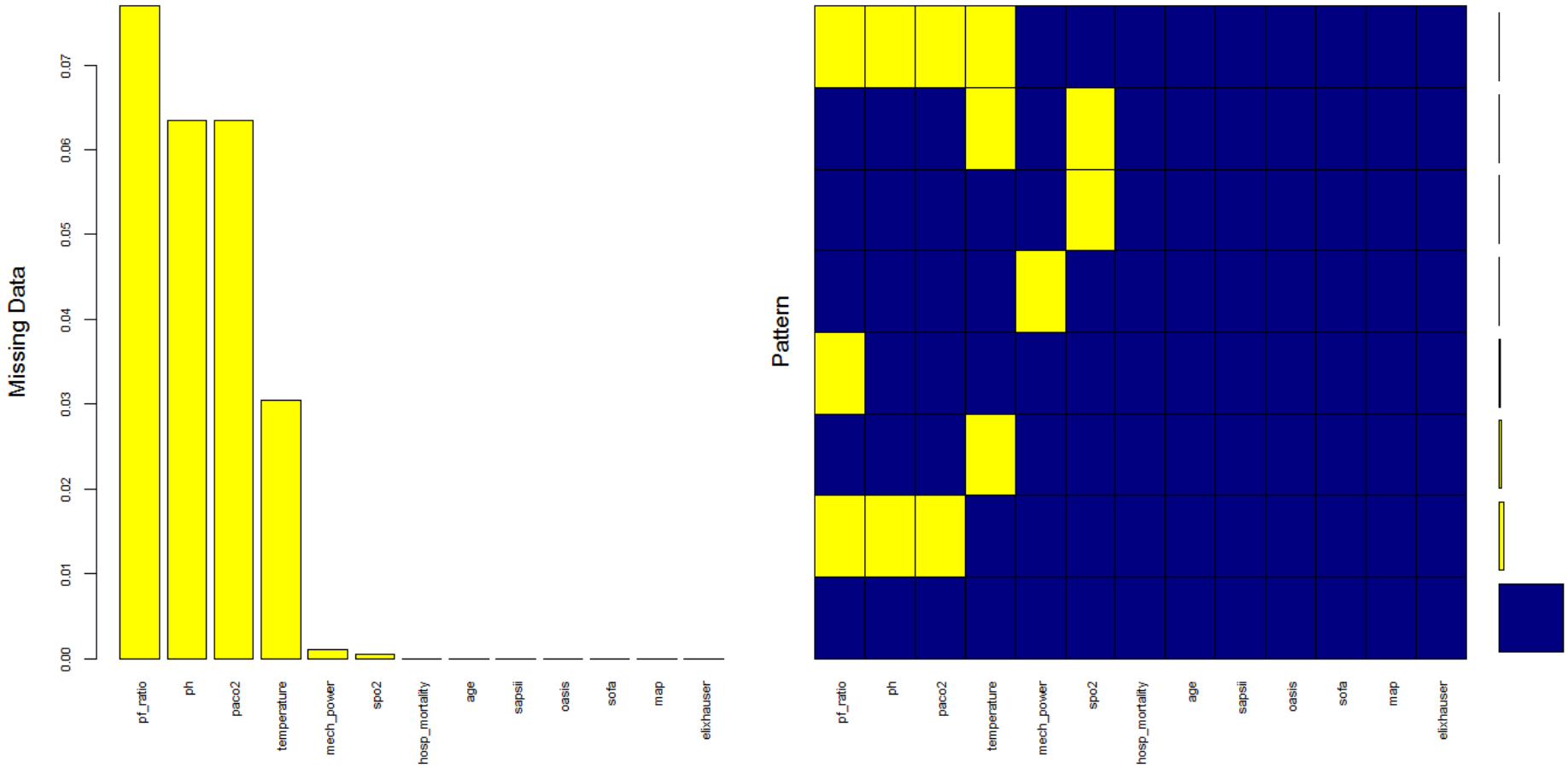
$$\text{Time-Weighted Average (AUC)} = 6 \times \frac{MP_0 + MP_6}{2} + (12–6) \times \frac{MP_6 + MP_{12}}{2} + (18–12) \times \frac{MP_{12} + MP_{18}}{2} + \ldots + (48–42) \times \frac{MP_{42} + MP_{48}}{2} = \text{Time-Weighted Average MP}$$

$$\text{Standardized by the length of observation} = \frac{\text{Time-Weighted Average MP}}{48}$$

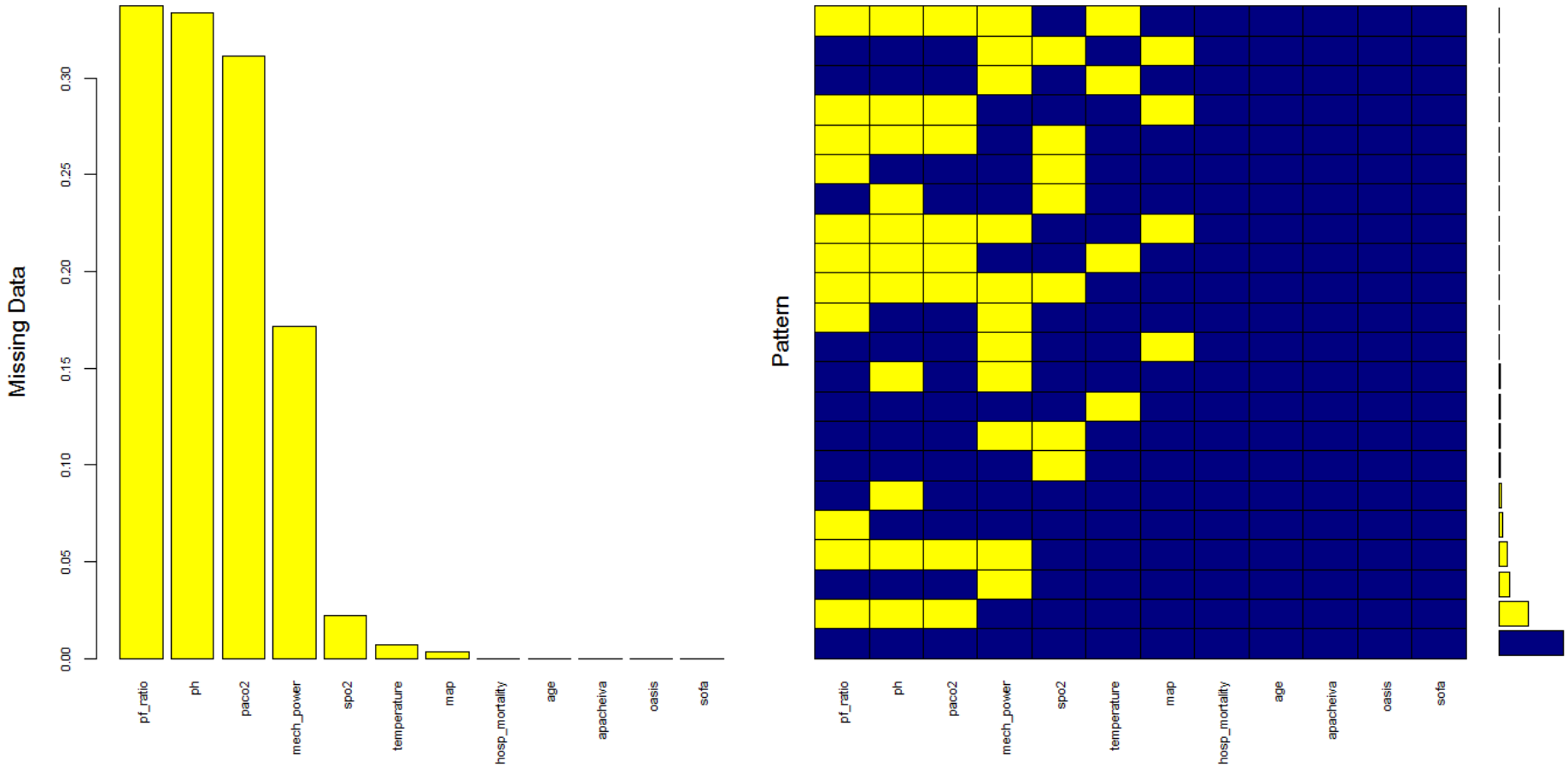
eFigure 2 – Study flowchart



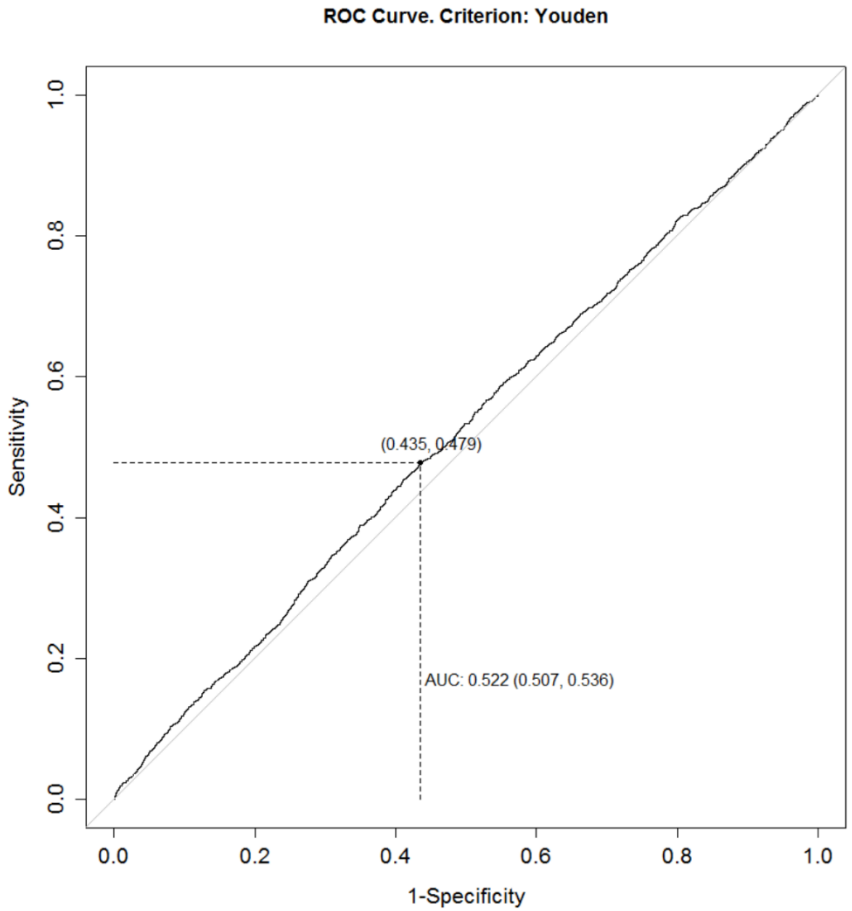
eFigure 3 – Pattern of missing data in variables of interest in MIMIC–III database

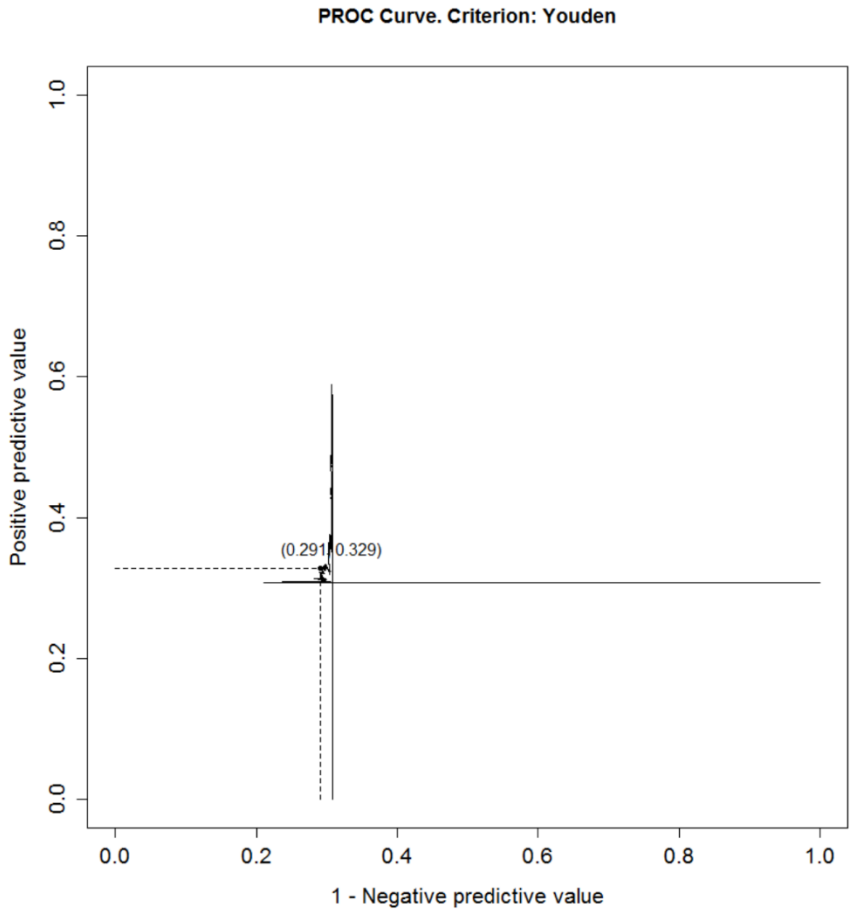


eFigure 4 – Pattern of missing data in variables of interest in eICU database

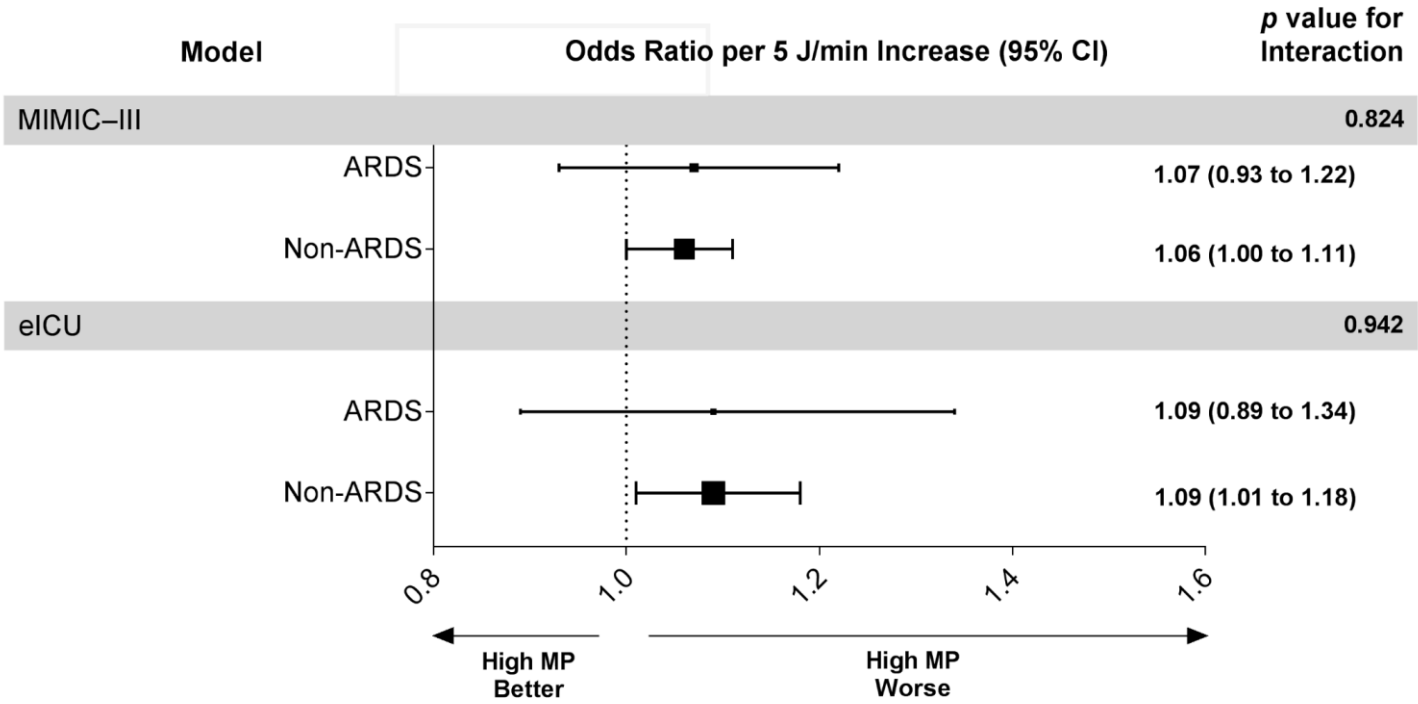


eFigure 5 – Receiver-operating characteristics (ROC) curve analysis of the best cut-off of mechanical power



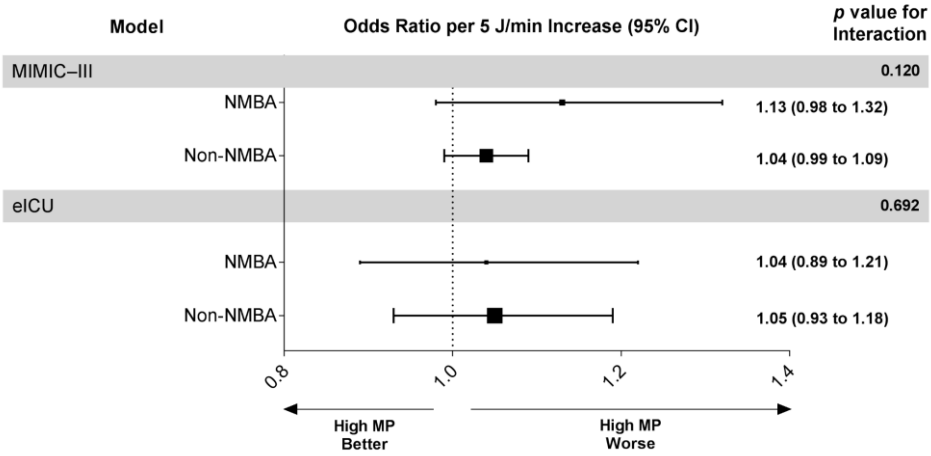


eFigure 6 – Association between mechanical power and in-hospital mortality according to the presence of ARDS in the first days



ARDS: Acute Respiratory Distress Syndrome

eFigure 7 – Association between mechanical power and in-hospital mortality according to the use of neuromuscular blocking agents (NMBA) in the first two days of ventilation



NMBA: neuromuscular blocking agents