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# Different ventilation intensities among various categories of patients ventilated for reasons other than ARDS—A pooled analysis of 4 observational studies

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ABSTRACT

*Purpose:* We investigated driving pressure (ΔP) and mechanical power (MP) and associations with clinical outcomes in critically ill patients ventilated for reasons other than ARDS.

*Materials and methods:* Individual patient data analysis of a pooled database that included patients from four observational studies of ventilation. ΔP and MP were compared among invasively ventilated non–ARDS patients with sepsis, with pneumonia, and not having sepsis or pneumonia. The primary endpoint was ΔP; secondary endpoints included MP, ICU mortality and length of stay, and duration of ventilation.

*Results:* This analysis included 372 (11%) sepsis patients, 944 (28%) pneumonia patients, and 2040 (61%) patients ventilated for any other reason. On day 1, median ΔP was higher in sepsis (14 [11-18] cm$H_2O$) and pneumonia patients (14 [11-18]cm$H_2O$), as compared to patients not having sepsis or pneumonia (13 [10-16]

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[1] Epidemiology of Respiratory Insufficiency in Critical Care;
[2] Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure;
[3] PRactice of VENTilation in critically ill patients without ARDS; and
[4] PRactice of VENTilation in critically ill patients in Middle–income Countries

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$cmH_2O$) ($P < 0.001$). Median MP was also higher in sepsis and pneumonia patients. ΔP, as opposed to MP, was associated with ICU mortality in sepsis and pneumonia patients.

*Conclusions:* The intensity of ventilation differed between patients with sepsis or pneumonia and patients receiving ventilation for any other reason; ΔP was associated with higher mortality in sepsis and pneumonia patients.

*Registration:* This post hoc analysis was not registered; the individual studies that were merged into the used database were registered at clinicaltrials.gov: NCT01268410 (ERICC), NCT02010073 (LUNG SAFE), NCT01868321 (PRoVENT), and NCT03188770 (PRoVENT–iMiC).

## 1. Introduction

Interest in the intensity of ventilation, reflected by driving pressure (ΔP) [1] and mechanical power of ventilation (MP) [2,3], is growing as intensity of ventilation has been shown to have independent associations with outcome. As such, ΔP and MP could be attractive targets in ventilation management [4,5]. ΔP and MP have mainly been investigated in patients with acute respiratory distress syndrome (ARDS) [1,3,6]. The majority of invasively ventilated critically ill patients, however, do not have ARDS [7,8], and these patients likely receive ventilation with lower ΔP and less MP. It is also uncertain whether measures of intensity of ventilation have independent associations with outcome in non–ARDS patients.

Ventilation management may differ between sepsis and pneumonia patients and patients receiving ventilation for other reasons, potentially leading to differences in ΔP and MP. Sepsis patients often have or develop metabolic acidosis [9], triggering the use of a higher respiratory rate (RR), and maybe even the use of higher tidal volumes ($V_T$). Sepsis patients may also need larger volumes of intravenous fluids to correct hypotension and hypoperfusion [10], which could potentially result in pulmonary edema and subsequent reduction in pulmonary compliance, even if a recent study showed that the occurrence of pulmonary edema due to aggressive intravenous fluid treatment in sepsis patients may be less extensive than previously believed [11]. Pneumonia patients can have a lower respiratory system compliance, which may trigger the use of lower $V_T$ and a higher RR.

We calculated and compared ΔP and MP in no–ARDS patients with sepsis or pneumonia, and patients not having sepsis or pneumonia. For this, we used a pooled dataset of four observational studies of ventilation. We hypothesized that ΔP and MP would be different between sepsis and pneumonia patients and patients not having sepsis or pneumonia. Furthermore, we studied associations of ΔP and MP with mortality in the three patient groups.

## 2. Methods

### 2.1. Study design and ethics

This is an individual patient data analysis of a pooled dataset of 4 prospective, observational studies of ventilation in critically ill patients conducted between 2011 and 2018, named 'Epidemiology of Respiratory Insufficiency in Critical Care' (ERICC) [12], 'Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure' (LUNG SAFE) [6], 'PRactice of VENTilation in critically ill patients without ARDS' (PRoVENT) [13], and 'PRactice of VENTilation in critically ill patients in Middle–income Countries' (PROVENT–iMiC) [14]. These studies were chosen because they employed a consistent data collection approach.

The study protocols of each study underwent initial approval by a central Institutional Review Board, followed by subsequent approval by a national or local ethics committee where necessary. Informed consent was obtained when it was deemed necessary according to national legislation. The four studies were registered at clinicaltrials.gov (NCT01268410, NCT02010073, NCT01868321, and NCT03188770. The databases of the 4 studies were standardized, using the case report forms and data dictionaries, and thereafter merged into the pooled database. The creation of the pooled database, including our specific modifications for patient's categorization, did not need additional ethical approval. This post hoc analysis was not registered. Further information regarding the used database, named 'PRoVENT, PRoVENT–iMiC, ERICC and LUNG SAFE' (PRoPERLy) has been published elsewhere [15].

### 2.2. Patients

The studies shared a common set of inclusion criteria, specifically, admission to an ICU for individuals aged 18 years or older (or 16 for LUNG SAFE), along with receiving ventilation within defined time frames. Exclusion criteria varied slightly among the studies, detailed in **Supplementary file eTable 1**.

For the current analyses we excluded patients with ARDS on admission, and patients that could not be labelled as having either sepsis or pneumonia, or neither of these two conditions. We also excluded patients who did not receive invasive ventilation, and patients with an incomplete follow–up.

*Patient labeling*

1. Patients admitted for sepsis, not caused by pneumonia: those patients who exhibited a positive risk factor for sepsis exclusively were placed within the 'sepsis' group.
2. Patients admitted for pneumonia, including patients with pneumo-sepsis: patients who displayed risk factors for both sepsis and pneumonia, or just for pneumonia, were thoughtfully classified into the 'pneumonia' group. This was undertaken to prevent any inadvertent misclassification and to safeguard against the inclusion of patients who could potentially have sepsis-related pulmonary complications or lung damage that might affect ventilation.
3. Patients not having sepsis or pneumonia or pneumo-sepsis: those patients whose admission factors did not align with sepsis or pneumonia risk were grouped as patients admitted for another reason. This category included patients admitted for reasons that were neither related to sepsis nor pneumonia.

### 2.3. Endpoints

The primary endpoint was ΔP. Secondary endpoints included MP, ICU mortality and length of stay (LOS), and duration of ventilation.

*Definitions and calculations.*

We defined 'day 1' as the first full calendar day of ventilation; the following days were named 'day 2' and 'day 3'.

The MP was calculated using eq. 1, wherein ΔP was calculated using eqs. 2 and 3 for patients under volume–controlled ventilation, and for patients under pressure–controlled ventilation [16], respectively:

$$MP\ [J/min] = 0.098^{*}\ V_T\ [mL]^{*}\ RR^{*}\ (Pmax\ [cmH_2O] – 0.5^{*}\ \Delta P\ [cmH_2O]\ ) \quad (1)$$

$$\Delta P\ [cmH_2O] = Pplat\ [cmH_2O] – PEEP\ [cmH_2O] \quad (2)$$

$$\Delta P\ [cmH_2O] = Pmax\ [cmH_2O] – PEEP\ [cmH_2O] \quad (3)$$

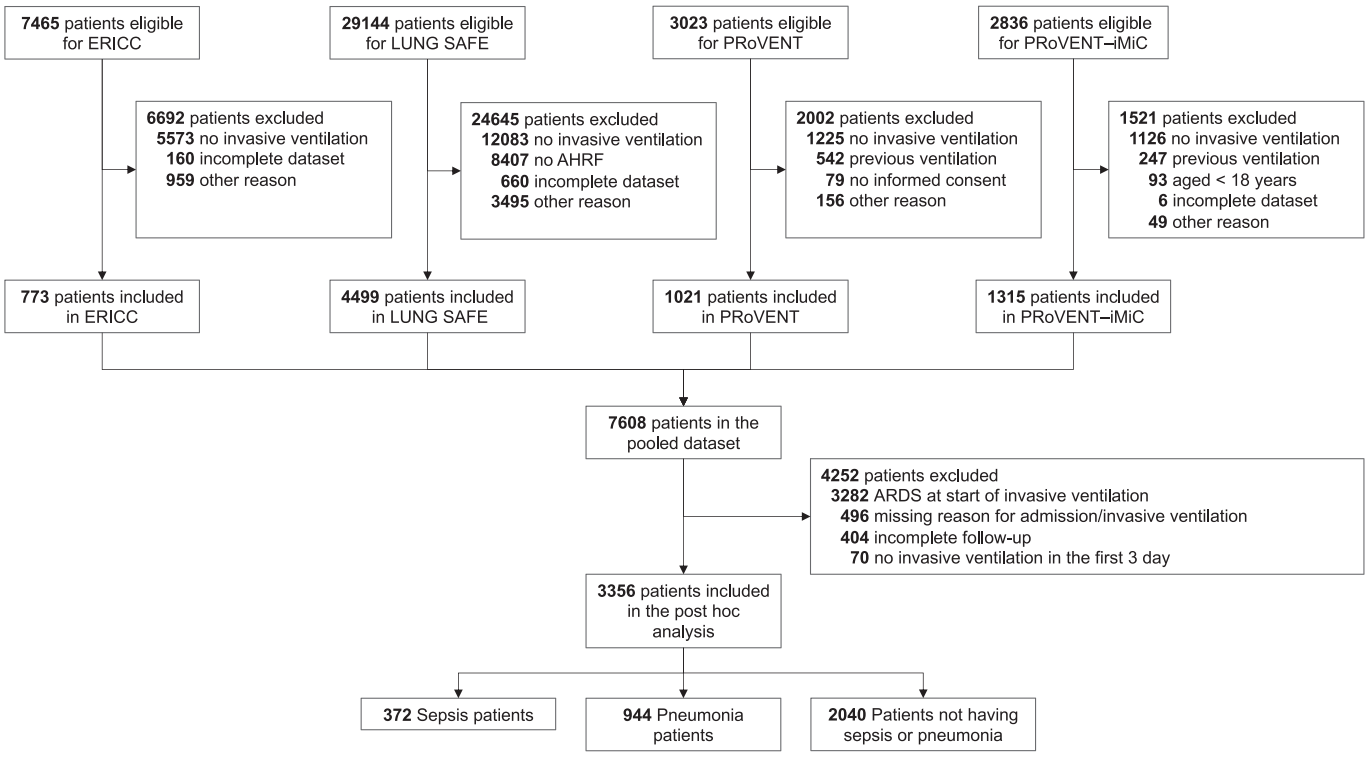


**Fig. 1.** Flow of patients.
Abbreviations: AHRF, Acute Hypoxemic Respiratory Failure; ARDS, Acute Respiratory Distress Syndrome; ERICC, Epidemiology of Respiratory Insufficiency in Critical Care; LUNG SAFE, Large observational study to Understand the Global impact of Severe Acute respiratory Failure; PRoVENT Practice of VENTilation in critically ill patients without ARDS study; PRoVENT–iMiC, Practice of VENTilation in critically ill patients in middle income countries study.

Respiratory system compliance ($C_{RS}$) was calculated using eq. 4:

$$C_{RS}\ [mL/cmH_2O] = V_T\ [mL]/\Delta P\ [cmH_2O] \quad (4)$$

Predicted Body Weight (PBW) was calculated using eqs. 5 and 6, for males and females, respectively:

$$PBW\ [kg] = 50 + 0.91^{*}\ (height\ [cm] – 152.4\ [cm]\ ) \quad (5)$$

$$PBW\ [kg] = 45.5 + 0.91^{*}\ (height\ [cm] – 152.4\ [cm]\ ) \quad (6)$$

Ventilatory Ratio (VR) is calculated using eq. 7, wherein 'ideal $PaCO_2$' is set at 5 kPa for all patients [17].

$$VR = (measured\ minute\ ventilation\ [mL/min]^{*}\ measured\ PaCO_2\ [kPa]\ ) / (predicted\ minute\ ventilation\ [mL/min]\ )^{*}\ ideal\ PaCO_2\ [kPa]) \quad (7)$$

ICU mortality was defined as any death that happened in the ICU. Duration of ventilation was measured as the time a patient received mechanical ventilation support during their ICU stay. ICU–LOS referred to how long a patient stayed in the ICU, starting from admission until they left the ICU or passed away there.

### 2.4. Sample size

We did not perform a formal sample size calculation; the number of available patients in the merged database served as the sample size.

### 2.5. Statistical analysis

Categorical variables were presented as counts and percentages, while continuous data as medians with interquartile range. Numbers of missing data are reported in Supplementary file eTable 2, and we did not use imputation.

Differences in ΔP and MP, and key ventilatory settings and parameters between the three groups were compared using a Kruskal Wallis test for continuous variables and a chi-square test for categorical variables. If a significant difference was found a Wilcoxon rank sum test was used to specify between which of the groups differed with respect to the median ΔP and MP. We applied Bonferroni correction, to correct for multiple testing, setting the significance level to 0.016.

We used cumulative distribution plots to visualize ΔP, MP, and other key ventilatory settings and parameters, on day 1, 2 and 3. Herein, vertical dotted lines indicate the median of the overall population for each day.

The association of ΔP and MP with ICU mortality on day 1 was examined by calculating odds ratios (ORs) using a univariate logistic regression model. To adjust for baseline disease severity, we used a multivariate logistic regression model. Covariates with a known or suspected effect on outcome were entered in the model: arterial pH, baseline SOFA score, presence of active cancer, type of admission, and age. Additionally, duration of ventilation and ICU–LOS were assessed through linear regression models. Effect estimates for duration of ventilation and ICU–LOS were expressed as exponential beta coefficients with 95% confidence interval to enhance interpretability. These models were adjusted for the same baseline characteristics.

We performed a sensitivity analysis excluded patients with evidence of spontaneous breathing activity, defined as total RR exceeding set RR by >2 breaths per minute were excluded [18].

We performed two posthoc analyses. In one additional analysis, we investigated the association of ΔP and MP with two additional endpoints, hospital mortality and hospital lengths of stay. In a second posthoc analysis, we adjusted for the comorbidities COPD, diabetes, chronic renal failure, chronic heart failure, immunosuppression, chronic liver failure in a multivariate logistic regression model.

All statistical analyses were performed using R version 4.0.3 (www.r-project.org). A P–value $< 0.05$ was considered statistically significant.

**Table 1**
Demographic and Clinical Characteristics.

| | Sepsis patients (*N* = 372) | Pneumonia patients (*N* = 944) | Patients not having sepsis or pneumonia (*N* = 2040) | P |
|---|---|---|---|---|
| Age, year | 62 [49–71] | 65 [51–77] | 60 [45–71] | < 0.001 |
| Sex, male | 222/372 (60) | 606/944 (64) | 1265/2038 (62) | 0.277 |
| Height, cm | 165 [159–172] | 168 [160–175] | 167 [160–175] | 0.025 |
| Weight, kg | 80 [69–89] | 70 [60–80] | 75 [65–88] | < 0.001 |
| PBW, kg | 61.5 [52.4–67.8] | 61.6 [53.3–69.7] | 61.5 [52.4–70.6] | 0.038 |
| BMI, kg/m$^2$ | 26.7 [24.3–30.0] | 24.8 [22.1–28.1] | 25.7 [23.1–29.4] | < 0.001 |
| **Admission type** | | | | < 0.001 |
| Medical | 242/371 (65.2) | 785/944 (83.2) | 947/2037 (46.5) | |
| Surgical elective | 17/371 (4.6) | 50/944 (5.3) | 586/2037 (28.8) | |
| Surgical urgency | 108/371 (29.1) | 86/944 (9.1) | 344/2037 (16.9) | |
| Trauma | 4/371 (1.1) | 23/944 (2.4) | 160/2037 (7.9) | |
| **Disease severity** | | | | |
| SOFA score | 9 [6–12] | 8 [5–10] | 7 [4–9] | < 0.001 |
| **Comorbidities** | | | | |
| Diabetes | 109/372 (29.3) | 238/944 (25.2) | 468/2036 (23.0) | 0.025 |
| Chronic renal failure | 59/372 (15.9) | 122/944 (12.9) | 202/2037 (9.9) | 0.001 |
| CHF | 28/372 (7.5) | 96/944 (10.2) | 250/2034 (12.3) | 0.014 |
| COPD | 27/372 (7.3) | 226/944 (23.9) | 205/2028 (10.1) | < 0.001 |
| Immunosuppression | 12/172 (7.0) | 69/751 (9.2) | 79/1202 (6.6) | 0.099 |
| Chronic liver failure | 24/372 (6.5) | 35/944 (3.7) | 79/2036 (3.9) | 0.054 |
| Hematologic neoplasia | 9/338 (2.7) | 31/842 (3.7) | 9/1278 (0.7) | < 0.001 |
| **Specific risk factor** | | | | |
| Non-cardiogenic shock | 107/372 (28.8) | 88/944 (9.3) | 224/2040 (11.0) | < 0.001 |
| Pancreatitis | 6/138 (4.3) | 3/487 (0.6) | 10/444 (2.3) | 0.008 |
| Gastric aspiration | 14/372 (3.8) | 91/944 (9.6) | 198/2040 (9.7) | 0.001 |
| Transfusion related acute lung injury | 4/138 (2.9) | 6/487 (1.2) | 24/444 (5.4) | 0.001 |
| Inhalation | 3/372 (0.8) | 10/781 (1.3) | 44/2040 (2.2) | 0.092 |
| Pulmonary contusion | 1/372 (0.3) | 8/781 (1.0) | 72/2040 (3.5) | < 0.001 |
| Burn | 0/138 (0.0) | 0/487 (0.0) | 6/444 (1.4) | 0.014 |
| Pulmonary vasculitis | 1/138 (0.7) | 4/487 (0.8) | 3/444 (0.7) | 0.967 |
| Near-drowning | 0/372 (0.0) | 0/781 (0.0) | 4/2040 (0.2) | 0.322 |
| Drug overdose | 1/138 (0.7) | 9/487 (1.8) | 17/444 (3.8) | 0.055 |

Data, inherent to day 1, are expressed as median with [IQR] or numbers n/N (proportions) where appropriate. 'N' in n/N may not always represent the total number of individuals within the group due to the existence of missing values, reported in the supplement: Appendix II.
Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; IQR, interquartile range; PBW, predicted body weight; SOFA, Sequential Organ Failure Assessment; CHF, Chronic Heart Failure; COPD, Chronic Obstructive Pulmonary Disease.

Where appropriate, statistical uncertainty was expressed by 95% confidence intervals (CI).

## 3. Results

### 3.1. Patients

Out of 7608 patients in the pooled dataset, 4252 were excluded (Fig. 1). Main reasons for exclusion were the presence of ARDS at start of invasive ventilation or missing data for patient labeling.

Out of the remaining 3356 patients, 372 (11%) had sepsis and 944 (28%) had pneumonia. Patients groups were different with respect to median age, median body weight and the body mass index, and the medical history (Table 1). Sepsis patients and pneumonia patients had higher median SOFA scores than patients not having sepsis or pneumonia. Ventilation characteristics are shown in Table 2 and Supplementary file eFigure 1.

### 3.2. Ventilation intensity

On day 1, median ΔP was higher in sepsis patients and pneumonia patients (14 [11-18] and 14 [11-18] cm $H_2O$) compared to patients not having sepsis or pneumonia (13 [10-16] cm $H_2O$) ($P < 0.001$) (Fig. 2 and Table 2). Differences in ΔP became smaller on the following two days, but remained statistically significant.

On day 1, median MP was higher in sepsis patients and pneumonia patients (13.3 [9.7–18.6], 13.6 [10.1–19.5] J/min) compared to patients not having sepsis or pneumonia (11.2 [8.3–15.4] J/min) (P < 0.001). The differences in MP became smaller on the following two days as well, but differences remained statistically significant.

### 3.3. Associations with outcomes

Findings of the univariate analysis are presented in Supplementary eTable 3. In the multivariable analysis, we observed that both ΔP and MP exhibited odds ratios >1 for ICU mortality, duration of ventilation, and ICU–LOS (Table 3). A higher ΔP was linked to higher ICU mortality in sepsis and pneumonia patients.

### 3.4. Sensitivity analysis

An analysis excluding patients with evidence of spontaneously breathing did not change the findings (Supplementary file eFigure 2 and **eTable 4**).

### 3.5. Posthoc analyses

The posthoc analysis of associations of ΔP and MP with hospital mortality and hospital LOS (Supplementary eTable 5), and the model adjusted for the comorbidities (Supplementary eTable 6) mirrored the findings of the original analyses.

## 4. Discussion

The main findings of this individual patient data analysis of a pooled dataset of 4 studies of ventilation in critically ill patients can be summarized as follows: (1) ΔP and MP are higher in sepsis and pneumonia patients as compared to patients not having sepsis or pneumonia; (2) ΔP

**Table 2**
Ventilatory variables and gas exchanges of the patients according to the type of illness.

| | Sepsis patients ($N = 372$) | Pneumonia patients ($N = 944$) | Patients not having sepsis or pneumonia ($N = 2040$) | P |
|---|---|---|---|---|
| **Mode of Ventilation** | | | | < 0.001 |
| VAC | 125/371 (33.7) | 274/935 (29.3) | 596/2000 (29.8) | |
| PC/BIPAP/APRV | 101/371 (27.2) | 325/935 (34.8) | 562/2000 (28.1) | |
| SIMV | 87/371 (23.5) | 139/935 (14.9) | 549/2000 (27.5) | |
| PSV | 27/371 (7.3) | 102/935 (10.9) | 165/2000 (8.2) | |
| PRVC | 22/371 (5.9) | 56/935 (6.0) | 80/2000 (4.0) | |
| CPAP | 3/371 (0.8) | 15/935 (1.6) | 12/2000 (0.6) | |
| NAVA | 1/371 (0.3) | 0/935 (0.0) | 2/2000 (0.1) | |
| other modes | 5/371 (1.3) | 24/935 (2.6) | 34/2000 (1.7) | |
| $V_T$, mL PBW | 7.92 [6.97–9.14] | 7.48 [6.43–8.76] | 7.90 [6.82–9.09] | < 0.001 |
| PEEP, $cmH_2O$ | 5 [5–8] | 7 [5–8] | 5 [5–8] | < 0.001 |
| Pmax, $cmH_2O$ | 22 [19–27] | 24 [20–29] | 21 [17–25] | < 0.001 |
| Pplat*, $cmH_2O$ | 18 [16–23] | 20 [16–24] | 17 [14–20] | < 0.001 |
| RR tot, bpm | 18 [16–22] | 18 [15–23] | 16 [14–20] | < 0.001 |
| VR | 1.49 [1.07–1.78] | 1.64 [1.23–2.11] | 1.31 [1.05–1.70] | < 0.001 |
| $C_{RS}$ (mL/$cmH_2O$) | 33 [26–45] | 33 [25–45] | 38 [28–51] | < 0.001 |
| $PaO_2/FiO_2$ | 231 [170–300] | 185 [127–246] | 253 [172–351] | < 0.001 |
| $FiO_2$ | 0.50 [0.40–0.60] | 0.50 [0.40–0.70] | 0.50 [0.40–0.60] | < 0.001 |
| pH | 7.35 [7.26–7.41] | 7.36 [7.27–7.43] | 7.36 [7.30–7.42] | 0.006 |
| $PaCO_2$, mmHg | 36.0 [30.0–43.3] | 41.0 [34.0–50.6] | 38.0 [33.0–45.0] | < 0.001 |

Data, inherent to day 1, are expressed as median with [IQR] or numbers n/N (proportions) where appropriate. 'N' in n/N may not always represent the total number of individuals within the group due to the existence of missing values, reported in Appendix II.
Abbreviations: ABW, Actual Body Weight; ARDS, Acute Respiratory Distress Syndrome; APRV, Airway Pressure Release Ventilation; Bi-PAP, Bi–level Positive Airway Pressure; C-PAP, Continuous-Positive Airway Pressure; CRS. Compliance respiratory system; $FiO^2$, Fraction of inspired Oxygen; IQR, interquartile range; NAVA, Neurally Adjusted Ventilatory Assist; $PaCO^2$, Partial pressure of carbon dioxide; PaO2, Partial pressure of Oxygen; PEEP, Positive End Expiratory Pressure; PBW, Predicted Body Weight; PC, Pressure Control; Pmax, peak inspiratory pressure; Pplat, plateau pressure; PRVC, Pressure Regulated Volume Controlled; PSV, Pressure Support Ventilation; RR, Respiratory Rate; SIMV Synchronized Intermittent Mandatory Ventilation; VT, Tidal volume; Vent, Ventilation; VAC, Ventilation Assist Control; VR, Ventilatory Ratio. *values are given only for patients under volumetric controlled mode ventilation.

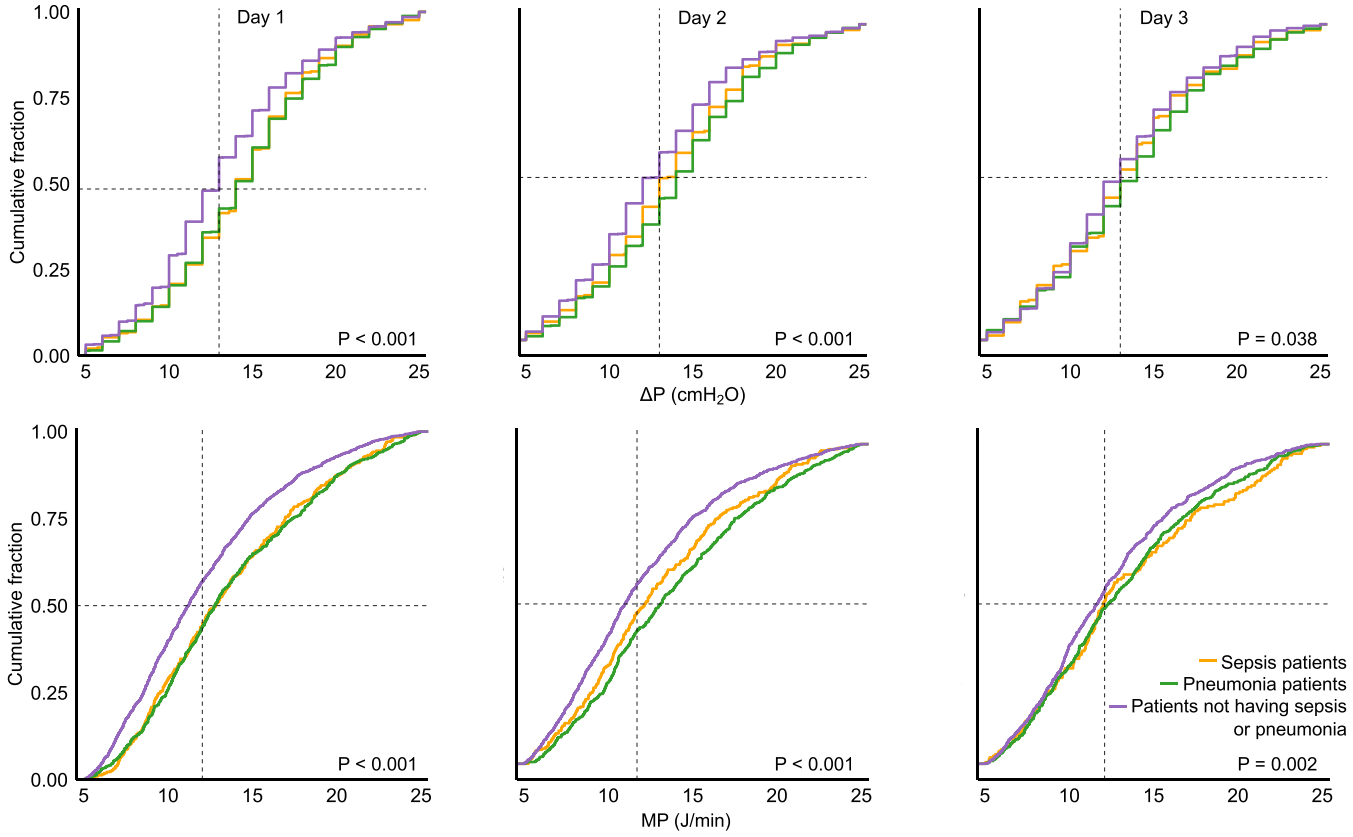


**Fig. 2.** Driving pressure and mechanical power of ventilation on day 1, 2, and 3 in sepsis patients, pneumonia patients, and patients receiving ventilation for any other reason.
Vertical dotted lines indicate the median of the overall population for each day; horizontal dotted lines always represent the proportion of 0.5.
Abbreviations: ΔP, driving pressure; MP, mechanical power of ventilation.

**Table 3**
Association of ΔP and MP with clinical outcomes.

| | Sepsis patients (N = 372) | P | Pneumonia patients (N = 944) | P | Patients not having sepsis or pneumonia (N = 2040) | P |
|---|---|---|---|---|---|---|
| **ICU mortality, odds ratio (95% CI)** | | | | | | |
| ΔP | 1.06 (1.02–1.11) | 0.005 | 1.03 (1.01–1.06) | 0.014 | 1.02 (0.99–1.04) | 0.149 |
| MP | 1.03 (1.00–1.07) | 0.075 | 1.00 (0.98–1.02) | 0.886 | 1.02 (1.00–1.04) | 0.121 |
| **Duration of ventilation, exponential beta coefficient (95% CI)** | | | | | | |
| ΔP | 1.13 (0.95–1.35) | 0.155 | 1.11 (0.97–1.28) | 0.132 | 1.19 (1.09–1.29) | < 0.001 |
| MP | 1.11 (0.93–1.31) | 0.247 | 1.03 (0.92–1.14) | 0.644 | 1.10 (1.02–1.20) | 0.015 |
| **Length of stay in ICU, exponential beta coefficient (95% CI)** | | | | | | |
| ΔP | 1.08 (0.86–1.37) | 0.504 | 1.02 (0.87–1.19) | 0.829 | 1.10 (1.00–1.21) | 0.048 |
| MP | 1.24 (1.00–1.56) | 0.056 | 1.03 (0.92–1.16) | 0.572 | 1.13 (1.03–1.24) | 0.009 |

Data, inherent to day 1, are expressed using logistic or multiple linear regression models as appropriate (95% Confidence Interval). Results were summarized as Odd Ratio (OR) for ICU mortality and exponential beta coefficient for duration of ventilation and length of stay in ICU. Covariates entered in the model are: arterial pH, baseline SOFA score, presence of active cancer, type of admission, and age.
Abbreviations: ΔP, driving pressure; MP, mechanical power of ventilation; ICU, intensive care unit.

and MP remain different during the first 3 days of invasive ventilation; and (3) ΔP, but not MP, has association with ICU mortality in sepsis and pneumonia patients, and not in patients not having sepsis or pneumonia.

Our analysis has strengths. We used the individual patient data of multicenter studies of ventilation, meaning that we could use prospectively collected ventilation data to calculate ΔP and MP. The sample size was large with patients originating from over 500 ICUs in both university–affiliated and non–university hospitals, improving the generalizability of the findings. We had a predefined analysis plan, wherein we excluded patients with ARDS on admission to create homogeneous groups of patients. The analysis plan, including a sensitivity analysis with only patients in whom we could reliably calculate ΔP and MP, was strictly followed.

Our findings contribute significantly to our comprehension of ΔP levels within a highly constrained cohort of invasive ventilated patient not having ARDS. Interestingly, median ΔP levels in our cohort, especially among sepsis and pneumonia patients, closely resemble the levels documented in studies involving patients with ARDS [19-22]. Furthermore, we observed a slight elevation in median ΔP levels from patients not having sepsis or pneumonia to sepsis patients and pneumonia patients, almost aligning with the ΔP levels in patients with mild, moderate and severe ARDS as reported previously [23]. It is worth noting that also range of ΔP values is nearly identical to that of ARDS patients [6,24], and even patients with ARDS related to COVID–19 [18,23,25,26], suggesting that the lungs of sepsis and pneumonia patients not having ARDS are equally stiff as the lungs of patients with ARDS. Diminished lung compliance is a significant factor in increasing ΔP, yet other elements may also contribute to ΔP. In non–ARDS patients higher $V_T$ could be more accepted, thereby elevating ΔP. Similarly, the less frequent use of high PEEP in non–ARDS patients, coupled with higher $V_T$, can also raise ΔP. Additionally, factors such as airway resistance in COPD, prevalent in the pneumonia patient group, may further contribute to a higher ΔP [27].

Opposite to what we found in respect to ΔP, median MP levels in our cohort are remarkably lower compared to those reported in previous studies involving ARDS patients originating from before the COVID–19 pandemic [5,22], as well as those in the numerous reports on studies in patients with ARDS related to COVID–19 [18,25,26,28-30]. The reason for the discrepancy in median MP levels between our patients and those with ARDS in other reports, despite similarities in ΔP, remains speculative. One plausible explanation could be the higher deadspace fraction in ARDS patients, which would require higher RR. The RR is a critical component in calculating MP [31,32], and is essential in this context.

The results of our analysis align with those of previous studies regarding the associations of ΔP with various outcomes. A seminal individual patient data meta–analysis, encompassing nine randomized clinical trials of invasive ventilation in ARDS patients [1], demonstrated that ΔP emerged as the most significant variable for stratifying mortality risk, regardless of $V_T$, PEEP and plateau pressures. Subsequent studies in ARDS patients [5,33,34], in patients not having ARDS [35], and in mixed ICU cohorts [2,29] have consistently reaffirmed this finding. Our study not only confirms the relationship between ΔP and ICU mortality in sepsis and pneumonia patients, but also establishes associations of ΔP with ICU length of stay and duration of ventilation. It is worth noting that in some of our subgroups, the sample size might have been insufficient to confidently confirm associations with outcomes.

Using ΔP and MP as ventilation targets is an appealing approach. ΔP and MP, however, may be differently affected by various factors. Important to notice, is that both ΔP and MP may be inherently elevated due to underlying lung pathology. Yet, other elements may also contribute to ΔP [27]. In non–ARDS patients, higher $V_T$ could be more accepted, thereby elevating ΔP. While is uncertain whether a high PEEP strategy always should be preferred over a low PEEP strategy in patients with ARDS [21,36,37] and those without ARDS [8], ΔP is also tied to the effects of PEEP on lung recruitment and overdistension. Additionally, factors such as airway resistance in COPD, prevalent in the pneumonia patient group, may further contribute to a higher ΔP. Next, MP is influenced by the RR, and it remains uncertain if a lower $V_T$ strategy should be pursued at the cost of a higher RR [24]. The crucial and probably deleterious role of RR is not understood properly yet. Further research is imperative to elucidate the ideal strategies for targeting these parameters and their potential effects on clinical outcomes.

This analysis has limitations. The studies we used for this analysis did not specifically focus on ΔP and MP, and some studies were performed well before interest in these parameters emerged. In none of the studies, inspiratory and expiratory holds were used, which could affect the reliability of the reported ΔP and MP. However, we were able to calculate ΔP and MP at all time points for all patients as all their elements were collected simultaneously. In the presence of spontaneous breathing, calculating ΔP and MP could result in too low levels. Nevertheless, the sensitivity analysis that excluded patients with spontaneous breathing activity revealed comparable findings. We used a simplified equation for calculating MP, which might lack accuracy. While this equation has been validated before [32] and was used in previous studies [3,16,24], MP is ideally calculated from continuous recordings of airway pressure and volume to achieve maximal granularity and accuracy [38]. As with other analyses that pool data from large observational studies, residual confounding cannot be excluded. There was also a large number of missings with regard to the endpoints used in one of the posthoc analyses, related to study design of the original investigations. We made a deliberate decision to categorize patients, and findings might have been slightly different if we had categorized patients differently. The pooled studies included patients who required ventilation for a period exceeding 24 h. This restricts the generalizability. While we excluded patients with ARDS on admission to create homogeneous groups of patients, we had to rely on the accuracy of the original studies with regard to this diagnosis. Last, it is important to note that the associations found do not confirm causal relationships.

## 5. Conclusion

In this cohort of non–ARDS patients, the intensity of ventilation was

higher in sepsis and pneumonia patients as compared to patients not having sepsis or pneumonia. ΔP was associated with higher mortality in sepsis and pneumonia patients, but not in patients not having sepsis or pneumonia.

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## Appendix A. Supplementary data

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