



ORIGINAL ARTICLE

Association between time weighted average mechanical power normalized to compliance and prognosis of critically ill patients: A retrospective cohort study based on the MIMIC-IV database

Yukang Dong^{a,b,◇}, Guiyun Li^{c,◇}, Jiangquan Fu^d, Rui Huang^d, Huan Yao^{e,f}, Jingni Wang^a, Ying Wang^a, Feng Shen^{a,*}

^a Department of Intensive Care Unit, Guizhou Medical University Affiliated Hospital, Guiyang, China

^b Department of Emergency, Guizhou Provincial People's Hospital, Guiyang, China

^c Department of Emergency, The Second People's Hospital of Guiyang, Guiyang, China

^d Department of Emergency Intensive Care Unit, Guizhou Medical University Affiliated Hospital, Guiyang, China

^e Xiangya School of Nursing, Central South University, Changsha, Hunan, China

^f Nursing Department, Guizhou Provincial People's Hospital, Guiyang, Guizhou, China

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KEYWORDS

Critically ill;
Mechanical ventilation;
Mechanical power normalized to compliance;
Retrospective cohort study;
MIMIC IV

Abstract

Objective: This study aims to evaluate the association of time-weighted average mechanical power normalized to compliance (TWA-MP_{CRS}) with all-cause mortality to determine its value as a prognostic tool in intensive care patients.

Design: Retrospective observational study.

Setting: Intensive care unit (ICU).

Patients or participants: 4387 first-time ICU-admitted patients in the Medical Information Mart for Intensive Care (MIMIC) IV.

Interventions: None.

Main variables of interest: TWA-MP_{CRS}, ICU mortality and in-hospital mortality.

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Abbreviations: ARDS, acute respiratory distress syndrome; AUC, area under the curve; BMI, Body mass index; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRS, compliance of respiratory system; FiO₂, inspired fraction of oxygen; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial blood pressure; MIMIC, Multi-parameter Intelligent Monitoring in Intensive Care; MP, mechanical power; OR, Odds ratios; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PF, PaO₂/FiO₂; Ppeak, peak inspiratory pressure; ROC, receiver operating characteristic; RRT, renal replacement therapy; SAPS, Simplified acute physiology score; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SpO₂, pulse oxygen saturation; SQL, Structured Query Language; TWA, time-weighted average; VIF, variance inflation factor; VILI, ventilator-induced lung injury; Vt, tidal volume.

* Corresponding author.

E-mail address: doctorshenfeng@163.com (F. Shen).

◇ These authors contributed equally to this work.

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PALABRAS CLAVE

Pacientes críticos;
Ventilación
mecánica;
Potencia mecánica
normalizada por
complianza;
Estudio de cohorte
retrospectivo;
MIMIC IV

Results: Participants' mean age was 61.4 ± 16.9 years and the median [IQR] baseline TWA-MP_{CRS} was 0.3 (0.2, 0.6) J/min/mL/cmH₂O. When TWA-MP_{CRS} was divided into quintiles (with quintile 1 representing the lowest values), after adjusting for covariates, the odds ratios [95% confidence intervals (CIs)] for ICU mortality were 1.49 (95% CI: 1.15–1.94), 1.67 (95% CI: 1.29–2.16), 1.79 (95% CI: 1.37–2.33), and 3.96 (95% CI: 3.01–5.21) for quintiles 2, 3, 4, and 5 respectively, with quintile 1 as reference. Similar results were found for hospital mortality.

Conclusion: Higher TWA-MP_{CRS} is associated with poor clinical outcomes in critically ill patients. Higher TWA-MP_{CRS} can lead to a higher mortality among ICU and in-hospital patients.

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Asociación entre la potencia mecánica promedio ponderada en el tiempo normalizada al cumplimiento y el pronóstico de pacientes críticos: un estudio de cohorte retrospectivo basado en la base de datos MIMIC-IV

Resumen

Objetivo: Este estudio tiene como objetivo evaluar la asociación entre la potencia mecánica promedio en el tiempo y normalizada por la complianza (TWA-MP_{CRS}) y la mortalidad por todas las causas, con el fin de determinar su valor como herramienta pronóstica en pacientes de cuidados intensivos.

Diseño: Estudio observacional retrospectivo.

Entorno: Unidad de Cuidados Intensivos (UCI).

Pacientes o participantes: 4387 pacientes ingresados por primera vez en la UCI, seleccionados de la base de datos Medical Information Mart for Intensive Care (MIMIC) IV.

Intervenciones: Ninguna.

Variables de interés principales: TWA-MP_{CRS}, mortalidad en la UCI y mortalidad hospitalaria.

Resultados: La edad promedio de los participantes fue de 61.4 ± 16.9 años, y la mediana [IQR] de TWA-MP_{CRS} basal fue de 0.3 (0.2, 0.6) J/min/mL/cmH₂O. Cuando el TWA-MP_{CRS} se dividió en quintiles (siendo el quintil 1 el de los valores más bajos), tras ajustar por covariables, las razones de odds [intervalos de confianza (IC) del 95%] para la mortalidad en UCI fueron 1.49 (IC 95%: 1.15–1.94), 1.67 (IC 95%: 1.29–2.16), 1.79 (IC 95%: 1.37–2.33) y 3.96 (IC 95%: 3.01–5.21) para los quintiles 2, 3, 4 y 5, respectivamente, teniendo el quintil 1 como referencia. Se encontraron resultados similares para la mortalidad hospitalaria.

Conclusión: Un TWA-MP_{CRS} más alto se asocia con peores resultados clínicos en pacientes críticos. Un TWA-MP_{CRS} más elevado puede conducir a una mayor mortalidad entre los pacientes en la UCI y en el hospital.

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Introduction

High-intensity mechanical ventilation in critically ill patients under general anesthesia or with respiratory failure increases the risk of ventilator-induced lung injury (VILI). VILI occurs when small airways and alveoli are repeatedly opened and closed, or become over-distended.^{1,2} Lung-protective ventilation is recommended in acute respiratory distress syndrome (ARDS) management to reduce VILI and improve mortality in acute respiratory failure patients.^{3–6} Previous studies have linked parameters such as end expiration pressure (PEEP) and driving pressure to poor outcomes in invasive ventilation,^{7–10} and factors like flow and breathing frequency also contribute to tissue injury. However, tidal volume (Vt) and end-expiratory lung impedance remain primary contributors to VILI-associated stress and strain.¹¹ Mechanical power (MP)—which integrates Vt, driving pres-

sure, airflow, and frequency—quantifies the work rate on the lungs and has been proposed as a predictor of VILI pathogenesis.^{4,12,13}

Mechanical ventilation generates mechanical stress and strain within the respiratory system. The magnitude of this load, known as the intensity of ventilation, can be quantified by MP, which is independently associated with mortality in both Intensive care unit (ICU) and ARDS patients.^{14–16} Importantly, the risk of VILI at a given MP depends on factors such as lung size, recruitability, and homogeneity,^{11,17,18} often referred to as the “baby lung” concept.^{19,20} Therefore, adjusting MP by normalizing it to compliance of respiratory system (MP_{CRS}) accounts for functional lung size and may improve prognostic accuracy in ARDS patients, as recently demonstrated.^{20,21} However, it remains unclear whether MP_{CRS} predicts outcomes across all mechanically ventilated ICU patients, as relatively few studies have explored

this. This study thus aims to evaluate the association of time-weighted average MP_{CRS} ($TWA-MP_{CRS}$) with all-cause mortality to assess its prognostic value in the intensive care setting.

Methods

Data source

The data used in this retrospective cohort study was obtained from the Medical Information Mart for Intensive Care (MIMIC)-IV (2.0). This database contains clinical data for patients hospitalized at the Beth Israel Deaconess Medical Center from 2008 to 2019. To access pertinent data from MIMIC-IV, our team successfully completed the Protecting Human Research Participants test and the National Institutes of Health training course and the accompanying exams (certification number: 44545022/39719844). The guidelines for "Strengthening the Reporting of Observational Studies in Epidemiology" were used to report the findings in this article.²²

Study population

Patients listed in the MIMIC IV database who underwent invasive mechanical ventilation were eligible for inclusion in this study. The inclusion criteria were as follows: (1) receipt of invasive ventilation initiated within 24 h of ICU admission; (2) patients receiving invasive ventilation for at least 48 consecutive hours; (3) patients aged ≥ 18 years; and (4) only the first ICU admission was considered.¹⁴ The exclusion criteria were as follows: Patients for missing ventilation variables associated to MP_{CRS} . The percentage of missing values for all participants is summarized in Supplementary Table 1. To impute the missing values, a multivariate imputation approach using chained equations was employed, assuming that the missingness was random.

Date extraction

The data were extracted using Structured Query Language (SQL) and PostgreSQL (version 9.6). Key demographic data were collected (within 24 h of admission), including age, gender, race (white, black or other), Body mass index (BMI), simplified acute physiology II (SAPS II) score, and sequential organ failure assessment (SOFA) score. Predicted body weight (PBW) was calculated as follows: $50 + 0.91 \times [\text{height (cm)} - 152.4]$ (for male); $45.5 + 0.91 \times [\text{height (cm)} - 152.4]$ (for female). On the first day of ICU admission, the average values of vital signs and laboratory parameters were recorded. Intervention measures within 24 h of ICU admission, including vasoactive drug administration, renal replacement therapy (RRT) and fluid balance. The time and value of ventilation parameters on the second day of mechanical ventilation, including V_t , PEEP, peak inspiratory pressure (Ppeak), total respiratory rate, and fraction of inspired oxygen (FiO2), were extracted for further calculation. Invasive ventilation data at all time points were collected from the database (typically every 4 h, which may vary depending on the individual condition), thus allowing

us to calculate the corresponding dynamic MP and its associated exposure duration (until the next recorded time point).

The reason we analyzed ventilation parameters from the second 24-h period is that, during the initial phase—particularly the first 24 h—patients commonly undergo rapid changes in respiratory parameters,²³ treatment strategies, and organ function. This period often reflects acute stress responses and temporary interventions, requiring time for patients to adapt to ventilator settings.²⁴ In contrast, the 24–48 h window is more likely to provide ventilation parameters that represent a near-steady state, allowing for a more accurate assessment of ventilator-induced lung stress and injury risk. Previous studies have also identified the second day as a key time point at which MP can serve as a valuable predictor of patient outcomes.^{14,25,26}

Study endpoint and calculations

The primary outcome was ICU, while secondary outcome was in-hospital mortality. MP was estimated as follows:

$$MP(J/min) = 0.098 \times \text{respiratoryrate} \times \text{tidal}$$

$$\text{volume} \times (P_{\text{peak}} - 0.5 \times \text{dynamic} \Delta P),^{11,27} \text{ where the}$$

$$\text{dynamic driving pressure} (\Delta P) = P_{\text{peak}} - PEEP^{7,27}$$

$$MP_{CRS} = MP / (\text{dynamic lung compliance})^{18,28,29}$$

Where dynamic lung compliance = $V_t / \text{dynamic } \Delta P$

Since ventilation is a dynamic process, we calculated the time-weighted average MP ($TWA-MP$) and $TWA-MP_{CRS}$ over the second 24 h of ventilation. For each patient, the multiplicative product of the MP_{CRS} and the duration of exposure to that MP_{CRS} were obtained. The products were summed up and divided by the total duration of ventilation observation time to obtain the $TWA-MP_{CRS}$, using the following equation:

$$TWA-MP_{CRS} = \sum (MP_{CRS_i} \times \Delta T_i) \div \sum \Delta T_i$$

The i th MP_{CRS} measurement was recorded as MP_{CRS_i} , the time interval between the i th and the $i + 1$ th MP_{CRS} measurement was recorded as ΔT_i . $TWA-MP$ was calculated using the same method as $TWA-MP_{CRS}$.

Statistical analysis

Before performing statistical analysis, the missing values for other variables were first supplemented. Patient characteristics were analyzed in the groups based on MP_{CRS} quartiles. Categorical variables were described using frequency and percentages, whereas continuous variables were described using median with quartile range (IQR) for skewed distributions and mean with standard deviation (SD) for normally distributed data. Chi-square, one-way analysis of variance, or Kruskal-Wallis tests, as appropriate, was applied to the continuous variables of classification, normal distribution, and non-normal distribution. To study the association between the $TWA-MP_{CRS}$ and ICU or in-hospital mortality,

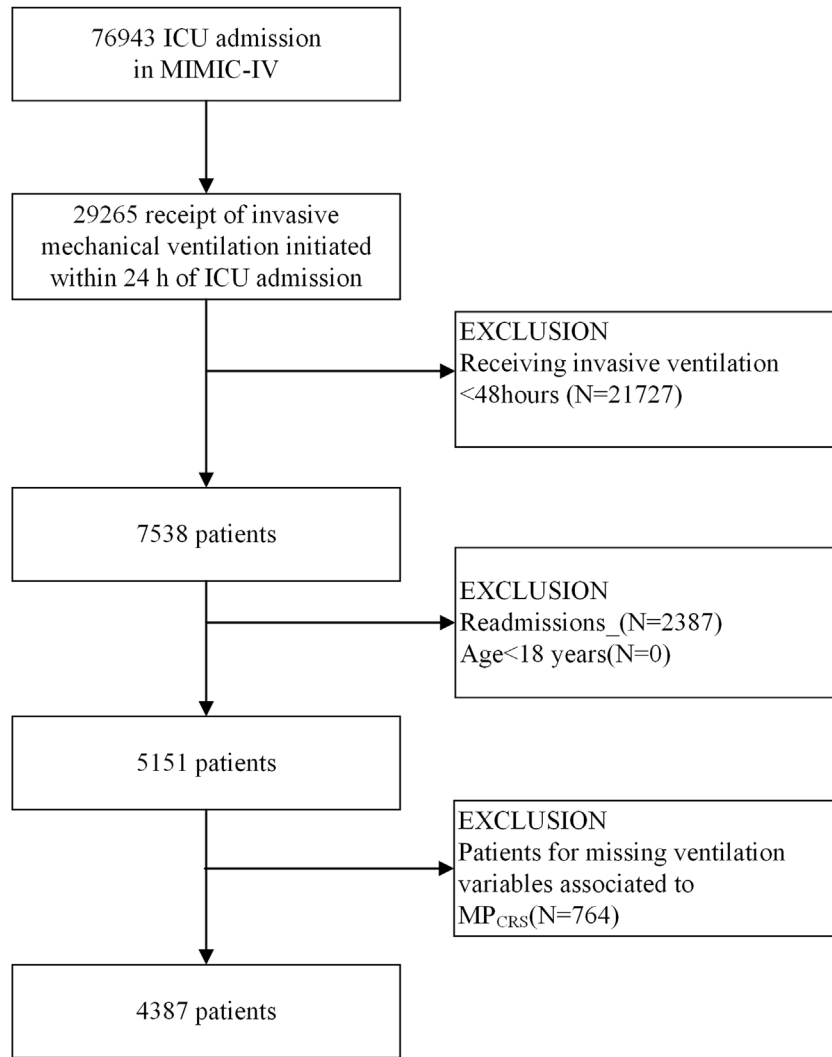


Figure 1 A flow chart of patient inclusion procedure. Abbreviations: ICU, intensive care unit; MP, mechanical power; CRS, compliance of respiratory system.

both univariable linear regression and multivariate logistic regression analyses were conducted. We developed three models: the model 1 (with no covariates adjusted), model 2 (with age, gender and BMI adjusted); and model 3 (model 2 with additional covariates). To assess potential confounders, we entered the covariates one by one into the subsequent binary logistic regression model and eliminated them from the complete model. Covariates that were associated with clinical prognosis or whose initial regression coefficient changed by more than 10% were chosen as confounders. To avoid overfitting the model due to multicollinearity among variables, a variance inflation factor (VIF) was calculated as well. Variables with $VIF \geq 5$ were excluded (Supplementary Table 2).

We flexitively modeled and visualized the association between TWA- MP_{CRS} and ICU and in-hospital mortality using restricted cubic splines. Based on the quintiles, TWA- MP_{CRS} was first converted into a categorical variable. The resulting P value was used to explore a nonlinear pattern of associ-

ation. The TWA- MP_{CRS} , as a continuous variable, was then used to test the linear trend. In addition, receiver operating characteristic (ROC) analysis was performed to compare the predictive power of SOFA score, TWA-MP, and TWA- MP_{CRS} for ICU mortality. The model's performance was evaluated using calibration plots and the Hosmer-Lemeshow goodness-of-fit test (with $P > .05$ indicating satisfactory calibration).

For sensitivity analysis, interaction and stratified analyses were conducted based on age, gender, BMI, ventilation parameter (PEEP, Ppeak, Vt and compliance), disease severity score (SAPSII score and SOFA score), and comorbidities [Congestive heart failure, chronic obstructive pulmonary disease (COPD) and ARDS]. We also conducted sensitivity analyses restricted to survivors for both hospital length of stay and ICU length of stay. In addition, we used complete data to determine whether sensitivity analysis was stable compared with the results of raw data analysis. All data were analyzed using R 4.1.2 (R Foundation) 1 and Free Statistics version 1.9, with $P < .05$ as the significance level.

Results

Baseline characteristics of patients

Fig. 1 shows a flowchart depicting the study process. Based on the inclusion/exclusion criteria, a total of 4387 eligible patients, with a mean age of 61.4 ± 16.9 years, were enrolled, comprising 2531 men (57.7%) and 1856 women. The median [IQR] baseline TWA-MP_{CRS} was 0.3 (0.2, 0.6) J/min/mL/cmH₂O. The population characteristics by TWA-MP_{CRS} quintile are provided in Table 1. Participants, who received a higher level of TWA-MP_{CRS}, presented with a higher level of BMI, SAPS II values, SOFA values, heart rate, arterial partial pressure of carbon dioxide (PaCO₂), lactate and fluid balance but had lower age, mean arterial blood pressure (MAP), pulse oxygen saturation (SpO₂), PH, arterial partial pressure of oxygen (PaO₂), bicarbonate and PaO₂/FiO₂ ratio (PF ratio). It was also found that congestive heart failure, cerebrovascular disease, COPD, and sepsis significantly differed between the stratified groups. Additionally, patients in the high TWA-MP_{CRS} group had higher rates of vasoactive drugs and RRT, as well as higher fluid balance than patients in the low TWA-MP_{CRS} group. With an increase in TWA-MP_{CRS}, there was an increase in PEEP, dynamic driving pressure, Ppeak, total respiratory rate, FiO₂ and TWA-MP (Table 1).

Association between TWA-MP_{CRS} and outcomes

Compared to patients with lower TWA-MP_{CRS}, those with higher TWA-MP_{CRS} experienced fewer ventilator-free days, longer ICU stays, higher ICU mortality, and increased hospital mortality rates (Table 1). The results of univariate analysis of variables and ICU and in hospital mortality are shown in Supplemental Tables 3–4. Further, we used multivariable logistic regression analyses to assess the association of TWA-MP_{CRS} with all-cause ICU and in-hospital mortality in critically ill patients requiring mechanical ventilation (Table 2). After adjusting for age/gender/BMI (model 2), we found that TWA-MP_{CRS} was significantly associated with a higher risk of ICU mortality (OR, 4.27; 95% CI, 3.46–5.26; $P < .001$). Notably, even after adjusting for all potential covariates (model 3), this association remained strong with TWA-MP_{CRS} as a continuous variable (OR, 4.10; 95%CI, 3.19–5.26; $P < .001$; Table 2). A similar trend was observed for in-hospital mortality (Table 2). After adjusting for ICU mortality, ORs, in Q2, Q3, Q4 and Q5 based on TWA-MP_{CRS} quintile, with quintile 1 as reference, were 1.49 (95% CI: 1.15–1.94), 1.697 (95% CI: 1.29–2.16), 1.79 (95% CI: 1.37–2.33), and 3.96 (95% CI: 3.01–5.21), respectively, in model 3. Similarly, after adjusting for in-hospital mortality, using quintile 1 as a reference, the adjusted ORs in Q2, Q3, Q4 and Q5 were 1.28 (95%CI: 1.04–1.63), 1.28 (95%CI: 1.02–1.61), 1.42 (95%CI: 1.12–1.79), and 2.88 (95%CI: 2.25–3.70), respectively, in model 3. Notably, these TWA-MP_{CRS} trends were statistically significant in all models (Table 2, $P < .001$).

The association between TWA-MP_{CRS} and mortality among mechanically ventilated patients was further explored using restricted cubic splines plots of TWA-MP_{CRS} against the ICU and hospital mortality rates (Fig. 2). After adjusting for all

covariates, we found that TWA-MP_{CRS} had a continuous linear association with both ICU mortality (Fig. 2A) and in-hospital mortality (Fig. 2B). This result was in line with the incremental changes in OR obtained in further multivariable logistic regression.

Analysis of receiver operating characteristics

Respective ROC curves were constructed to further analyze the predictive significance of TWA-MP_{CRS}, TWA-MP, and SOFA scores on ICU mortality in critically ill patients (Fig. 3). The results showed that the area under the curve (AUC) (95% CI) of TWA-MP_{CRS}, TWA-MP, and SOFA scores were 0.613 (0.592, 0.633), 0.585 (0.565, 0.605) and 0.612 (0.572, 0.615), respectively. The AUC of TWA-MP_{CRS} was significantly better than that of TWA-MP ($P < .001$) and comparable to SOFA scores ($P = .915$) (Supplemental Table 5). The results of calibration plots and the Hosmer-Lemeshow goodness-of-fit test demonstrated good model fit, ($\chi^2 = 14.16$, $P = .078$) with high consistency between the predicted and observed probabilities of mortality risk (Supplementary Fig. 1).

Subgroup analyses and sensitivity analysis

We further conducted interaction analyses and stratified analyses to determine the relationship between TWA-MP_{CRS} and ICU mortality. As depicted in Fig. 4, in the adjusted Model3, the results demonstrated that an increase in TWA-MP_{CRS} levels related to higher ICU mortality among various patient subgroups. In addition, there were no significant interaction between patient and clinical characteristics, including age, gender, BMI, ventilation parameter (PEEP, Ppeak, Vt and lung compliance), disease severity score (SAP-SII and SOFA), and comorbidities (congestive heart failure, COPD and ARDS) and ICU mortality. A similar outcome was observed for in-hospital mortality, as shown in Fig. 4.

Sensitivity analyses restricted to survivors were performed for both hospital and ICU length of stay (Supplementary Tables 6–7). These analyses showed that the association between TWA-MP_{CRS} and ICU/hospital length of stay remained significant among survivors. In addition, a sensitivity analysis without missing values verified the robustness of the results, showing a strong link between TWA-MP_{CRS} and clinical outcomes (Supplementary Table 8).

Discussion

In this retrospective cohort analysis, we confirmed that TWA-MP_{CRS} is independently associated with ICU and in-hospital mortality in patients under invasive ventilation. The TWA-MP_{CRS} during the second 24 h was associated with a linear positive relationship with mortality risk in patients with ventilation exceeding 48 h. The association was strong and unaffected by key covariables and confounding variables. Furthermore, our results demonstrate that the TWA-MP_{CRS} is a superior predictor of outcomes in comparison to TWA-MP alone. To our knowledge, this is the first study to examine the prognostic value of TWA-MP_{CRS} in critically ill patients with mechanical ventilation.

Table 1 Baseline characteristics and clinical outcomes of the included patients.

Variables	Total (n = 4387)	TWA-MP _{CRS} quintiles (J/min/mL/cmH ₂ O)					P value
		Q1 (0.01–0.14) (n = 878)	Q2 (0.14–0.27) (n = 877)	Q3 (0.27–0.41) (n = 877)	Q4 (0.41–0.67) (n = 877)	Q5 (0.67–1.49) (n = 878)	
Age, (years)	61.4 ± 16.9	63.6 ± 15.7	62.9 ± 17.1	62.0 ± 17.8	60.9 ± 17.2	57.6 ± 16.1	<.001
Gender, (male)	2531 (57.7)	504 (57.4)	502 (57.2)	487 (55.5)	517 (59)	521 (59.3)	.504
BMI, (kg/m ²)	29.7 ± 8.5	27.9 ± 6.8	28.0 ± 7.7	29.1 ± 7.3	30.4 ± 7.9	33.1 ± 10.8	<.001
Ethnicity							.543
White	2321 (52.9)	474 (54)	459 (52.3)	448 (51.1)	477 (54.4)	463 (52.7)	
Black	328 (7.5)	57 (6.5)	77 (8.8)	66 (7.5)	69 (7.9)	59 (6.7)	
Other	1738 (39.6)	347 (39.5)	341 (38.9)	363 (41.4)	331 (37.7)	356 (40.5)	
SAPS II score	45.5 ± 15.6	41.7 ± 14.5	43.5 ± 15.0	45.6 ± 15.3	46.3 ± 15.6	50.4 ± 16.2	<.001
SOFA score	9.3 ± 4.3	7.8 ± 4.0	8.1 ± 4.0	9.0 ± 4.0	9.9 ± 4.0	11.6 ± 4.2	<.001
Congestive heart failure, n (%)	1136 (25.9)	172 (19.6)	226 (25.8)	245 (27.9)	258 (29.4)	235 (26.8)	<.001
Cerebrovascular disease, n (%)	934 (21.3)	138 (15.7)	193 (22)	215 (24.5)	207 (23.6)	181 (20.6)	<.001
Renal disease, n (%)	802 (18.3)	146 (16.6)	162 (18.5)	164 (18.7)	176 (20.1)	154 (17.5)	.416
COPD, n (%)	710 (16.2)	112 (12.8)	111 (12.7)	127 (14.5)	163 (18.6)	197 (22.4)	<.001
ARDS, n (%)	903 (20.6)	93 (10.6)	131 (14.9)	165 (18.8)	211 (24.1)	303 (34.5)	<.001
Sepsis, n (%)	3974 (90.6)	760 (86.6)	762 (86.9)	785 (89.5)	812 (92.6)	855 (97.4)	<.001
Vasopressor use, n (%)	2650 (60.4)	396 (45.1)	467 (53.2)	527 (60.1)	592 (67.5)	668 (76.1)	<.001
RRT use, n (%)	346 (7.9)	37 (4.2)	53 (6)	61 (7)	75 (8.6)	120 (13.7)	<.001
Fluid balance(L)	4.4 ± 5.5	3.2 ± 4.2	3.5 ± 4.7	3.9 ± 5.6	5.0 ± 5.8	6.5 ± 6.3	<.001
Heart rate, (bpm)	88.1 ± 17.5	85.6 ± 16.2	85.8 ± 16.3	86.5 ± 17.8	88.2 ± 17.0	94.2 ± 18.7	<.001
MAP, (mmHg)	77.4 ± 9.7	78.5 ± 9.7	78.4 ± 10.1	77.5 ± 9.4	76.6 ± 9.4	76.0 ± 9.5	<.001
Temperature, °C	37.0 ± 0.8	37.1 ± 0.6	37.0 ± 0.7	36.9 ± 0.8	36.9 ± 0.9	36.9 ± 1.0	<.001
SpO ₂ , %	98.0 (96.4, 99.2)	98.7 (97.5, 99.5)	98.6 (97.0, 99.5)	98.2 (96.8, 99.4)	97.6 (96.3, 98.8)	96.5 (94.8, 98.2)	<.001
PF ratio	257.3 ± 112.6	297.5 ± 117.9	288.1 ± 117.8	268.8 ± 106.7	236.4 ± 99.8	195.6 ± 85.8	<.001
Hemoglobin, (g/L)	10.9 ± 2.5	10.9 ± 2.3	10.9 ± 2.4	10.8 ± 2.4	10.9 ± 2.4	11.1 ± 2.7	.098
pH	7.3 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	<.001
PaCO ₂ , (mmHg)	44.1 ± 14.0	40.1 ± 10.3	42.0 ± 11.9	42.8 ± 12.8	45.4 ± 13.9	50.1 ± 17.7	<.001

Table 1 (Continued)

Variables	Total (n = 4387)	TWA-MP _{CRS} quintiles (J/min/mL/cmH ₂ O)					P value
		Q1 (0.01–0.14) (n = 878)	Q2 (0.14–0.27) (n = 877)	Q3 (0.27–0.41) (n = 877)	Q4 (0.41–0.67) (n = 877)	Q5 (0.67–1.49) (n = 878)	
PaO ₂ , (mmHg)	153.7 ± 117.1	157.7 ± 111.0	163.9 ± 121.6	158.4 ± 123.0	155.0 ± 121.4	133.7 ± 105.4	<.001
Bicarbonate, (mmol/L)	21.7 ± 5.3	21.5 ± 4.4	22.2 ± 5.0	21.8 ± 5.0	21.8 ± 5.9	21.3 ± 5.8	.006
Lactate (mmol/L)	2.0 (1.3, 3.4)	1.7 (1.2, 2.7)	1.9 (1.3, 3.1)	2.0 (1.3, 3.4)	2.1 (1.4, 3.9)	2.3 (1.4, 4.3)	<.001
FiO ₂ , %	35.1 ± 14.8	32.6 ± 11.6	33.4 ± 12.3	33.4 ± 13.5	35.6 ± 14.9	40.7 ± 19.1	<.001
Ppeak (cm H ₂ O)	21.2 ± 7.1	12.5 ± 2.1	17.1 ± 2.5	20.6 ± 2.6	24.6 ± 2.8	31.2 ± 4.6	<.001
Vt (mL/kg PBW)	7.8 ± 3.7	8.9 ± 5.6	7.8 ± 5.1	7.6 ± 2.2	7.4 ± 1.6	7.2 ± 1.4	<.001
Dynamic driving pressure (cm H ₂ O)	13.6 ± 5.4	7.0 ± 1.7	10.8 ± 2.3	13.9 ± 2.7	16.4 ± 3.1	20.0 ± 4.5	<.001
PEEP, (cm H ₂ O)	7.6 ± 3.6	5.5 ± 1.3	6.3 ± 2.3	6.7 ± 2.5	8.3 ± 3.2	11.3 ± 4.6	<.001
Total respiratory rate(breaths/min)	20.4 ± 5.5	16.8 ± 4.7	18.4 ± 4.3	19.6 ± 4.4	21.2 ± 4.3	25.9 ± 5.1	<.001
Lung compliance (mL/H ₂ O)	34.9 (26.8, 54.3)	77.9 (63.6, 97.3)	45.5 (37.3, 57.1)	33.2 (29.1, 40.0)	28.9 (24.7, 33.9)	23.5 (19.7, 28.0)	<.001
TWA-MP (J/min)	11.9 (8.4, 17.2)	7.0 (5.8, 8.7)	9.0 (7.6, 11.4)	11.2 (9.7, 13.3)	15.0 (12.8, 18.0)	22.9 (18.5, 28.7)	<.001
TWA-MP _{CRS} (J/min/mL/cm H ₂ O)	0.3 (0.2, 0.6)	0.1 (0.1, 0.1)	0.2 (0.2, 0.2)	0.3 (0.3, 0.4)	0.5 (0.5, 0.6)	0.9 (0.8, 1.2)	<.001
Length of hospital stay (days)	18.3 ± 15.8	19.2 ± 17.5	18.1 ± 13.9	17.4 ± 15.0	18.3 ± 15.3	18.5 ± 16.9	.209
Length of ICU stay (days)	10.6 ± 8.6	9.5 ± 7.2	9.9 ± 7.8	10.2 ± 8.6	11.0 ± 8.5	12.5 ± 10.4	<.001
Ventilator-free days	2.0 ± 2.9	2.2 ± 3.2	2.1 ± 2.8	2.0 ± 3.1	1.8 ± 2.5	1.7 ± 2.9	.003
ICU mortality, n (%)	1015 (23.1)	124 (14.1)	176 (20.1)	197 (22.5)	198 (22.6)	320 (36.4)	<.001
Hospital mortality, n (%)	1292 (29.5)	199 (22.7)	243 (27.7)	245 (27.9)	248 (28.3)	357 (40.7)	<.001

For skewed variables, the data were presented as mean ± SD or median (IQR), and for categorical variables, as numbers (proportions). SAPSII, Simplified acute physiology score II; SOFA, Sequential Organ Failure Assessment; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; bpm, beats per minute; MAP, mean arterial blood pressure; SpO₂, pulse oxygen saturation; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; Ppeak, peak inspiratory pressure; Vt, tidal volume; PEEP, positive end-expiratory pressure; PF ratio, PaO₂/FiO₂ ratio; MP, mechanical power; CRS, compliance of respiratory system.

Table 2 Multivariable logistic regression analyses of TWA-MP_{CRS} and ICU and in-hospital mortality.

Variable	Model 1 OR (95%CI)	P value	Model 2 OR (95%CI)	P value	Model 3 OR (95%CI)	P value
ICU Mortality						
TWA-MP _{CRS}	3.14 (2.58~3.81)	<.001	4.27 (3.46~5.26)	<.001	4.1 (3.19~5.26)	<.001
Q1	1 (Ref)		1 (Ref)		1 (Ref)	
Q2	1.53 (1.19~1.96)	<.001	1.56 (1.21~1.2.01)	.001	1.49 (1.15~1.94)	.003
Q3	1.76 (1.38~2.26)	<.001	1.87 (1.45~2.4)	<.001	1.67 (1.29~2.16)	.001
Q4	1.77 (1.38~2.27)	<.001	1.98 (1.54~2.55)	<.001	1.79 (1.37~2.33)	<.001
Q5	3.49 (2.76~4.41)	<.001	4.50 (3.52~5.74)	<.001	3.96 (3.01~5.21)	<.001
Trend.test		<.001		<.001		<.001
In-hospital Mortality						
TWA-MP _{CRS}	2.26 (1.88~2.71)	<.001	3.24 (2.65~3.95)	<.001	3.15 (2.48~4.00)	<.001
Q1	1 (Ref)		1 (Ref)		1 (Ref)	
Q2	1.31 (1.05~1.62)	.015	1.34 (1.08~1.68)	.035	1.28 (1.04~1.63)	.023
Q3	1.32 (1.07~1.64)	.011	1.42 (1.14~1.77)	.043	1.28 (1.02~1.61)	.034
Q4	1.35 (1.08~1.67)	.007	1.54 (1.23~1.92)	.013	1.42 (1.12~1.79)	.004
Q5	2.34 (1.9~2.88)	<.001	3.18 (2.56~3.96)	<.001	2.88 (2.25~3.7)	<.001
Trend.test		<.001		<.001		<.001

Model 1: adjusted for nothing.

Model 2: adjusted for age, gender, BMI.

Model 3: adjusted for age, gender, BMI, SAPS II score, SOFA score, MAP, heart rate, lactate fluid balance, bicarbonate, PH, PaCO₂, PF ratio, FiO₂ and SpO₂.

OR, odds ratio; CI, confidence interval; BMI, Body mass index; MAP, mean arterial blood pressure; PaCO₂, arterial partial pressure of carbon dioxide; PF ratio, PaO₂/FiO₂ ratio; SpO₂, pulse oxygen saturation.

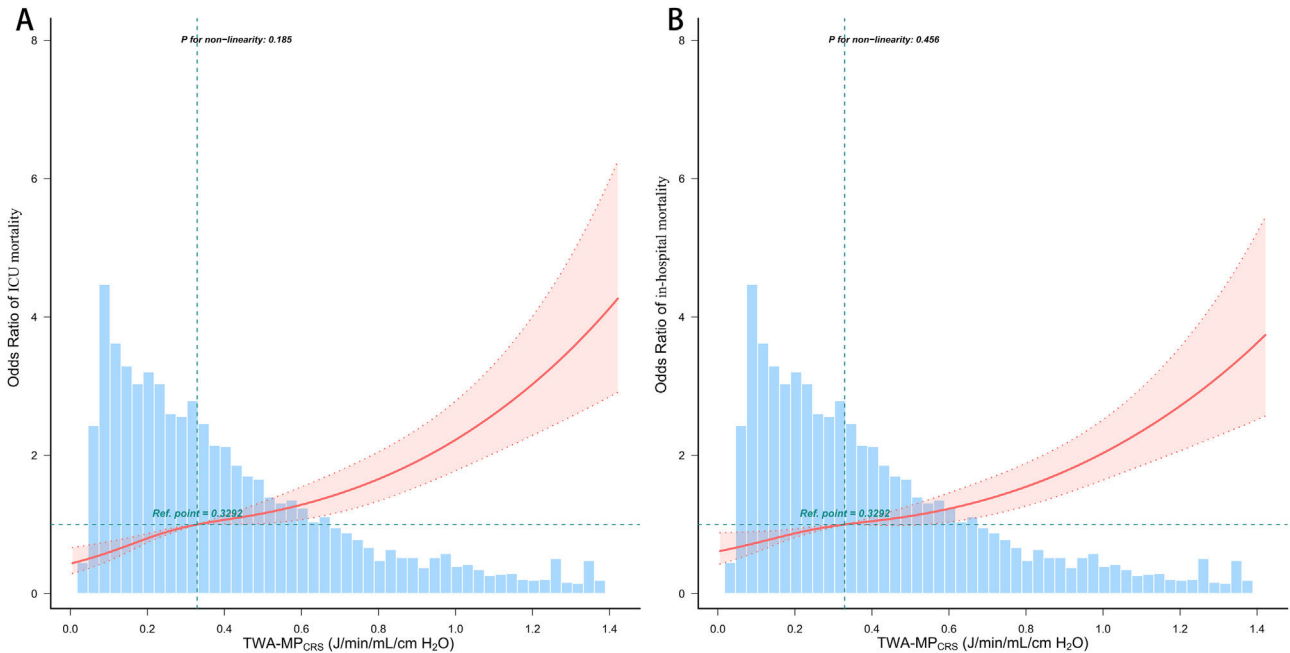


Figure 2 Relationship between TWA-MP_{CRS} and all-cause mortality risk. (A) Relationship between TWA-MP_{CRS} and ICU mortality. (B) Relationship between TWA-MP_{CRS} and in-hospital mortality. Shaded areas around the curves depict 95% confidence intervals.

Previous studies have shown that MP is associated with poorer outcomes in critically ill patients ventilated for more than 48 h.¹⁴ However, MP does not account for the heterogeneous distribution of lung energy load, and the same MP may cause more severe VILI when aerated lung volume is reduced or pulmonary heterogeneity is increased.³⁰ The effects of MP also vary based on lung pathophysiology,

such as function, recruitability, and heterogeneity. Evidence further suggests that lung size and its heterogeneity can influence the impact of MP on VILI in patients with acute respiratory failure. Therefore, to more accurately predict VILI risk, specific power—the energy delivered per unit of ventilated lung tissue^{19,31,32}—should be considered by nor-

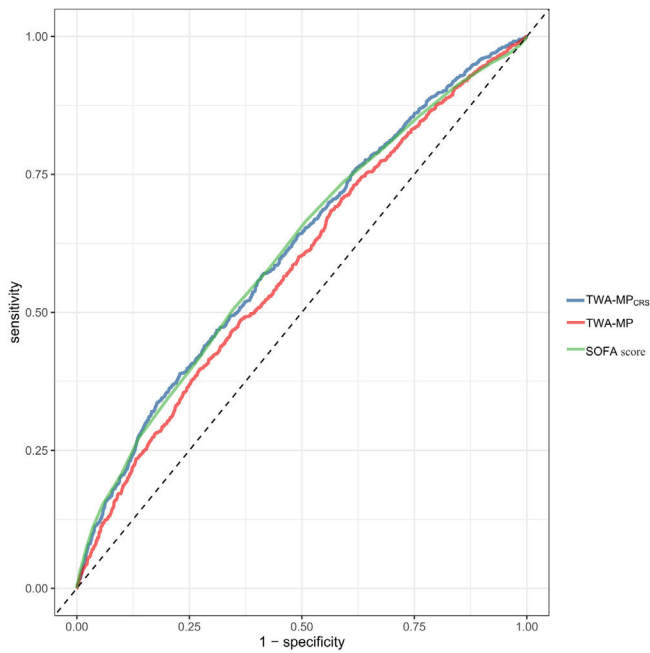


Figure 3 Receiver operating characteristic curves for the prediction of the ICU mortality in critically ill patients.

malizing MP to lung volume, thus better representing the actual energy burden delivered to the lung.^{18,30,33}

ARDS patients often exhibit variability and significantly reduced lung size ("baby lungs"),^{34,35} with respiratory compliance reflecting the amount of functional lung tissue.^{19,31,36} MP_{CRS} is more appropriate than normalization by body weight, as lung size is more influenced by disease severity.^{28,35,37} Zhang et al.³⁸ found that MP_{CRS} had the highest ability to predict mortality in ARDS. Similarly, Coppola et al.²⁰ reported that while MP had no causal association with mortality, MP_{CRS} was independently linked to ICU mortality. Further, in severe ARDS patients receiving extracorporeal membrane oxygenation, MP_{CRS} demonstrated better predictive power for 90-day mortality than either MP alone or MP normalized to predicted body weight.²¹ However, whether these findings apply broadly to all mechanically ventilated patients remains unclear. In our study, we initially examined the association between TWA- MP_{CRS} quintiles and key clinical parameters, including SOFA scores, oxygenation index, lactate levels, as well as ICU and in-hospital mortality, in mechanically ventilated patients. The analysis revealed that a higher TWA- MP_{CRS} was significantly associated with increased disease severity, as demonstrated by elevated SOFA scores and lactate levels, reduced oxygenation index, and higher ICU and in-hospital mortality rates. While TWA- MP_{CRS} , like MP, does not directly cause lung injury or death, it serves as a reflection of the intensity of mechanical ventilation.¹⁵ Elevated TWA- MP_{CRS} values are often linked to more severe underlying disease or greater respiratory dysfunction, indicating a need for higher levels of ventilatory support. Consequently, TWA- MP_{CRS} may hold significant prognostic value in mechanically ventilated patients and can assist in identifying those at greatest risk of adverse outcomes. Importantly, the study identified a continuous linear relationship between TWA- MP_{CRS} and mortality in mechanically

ventilated patients. After adjusting for confounding variables, multivariate regression analysis confirmed TWA- MP_{CRS} as an independent risk factor for both ICU and in-hospital mortality. These findings suggest that TWA- MP_{CRS} may serve as a valuable stratification marker for recognizing high-risk patients, supporting clinical decision-making by prioritizing more intensive monitoring and therapeutic interventions for those with the most severe conditions.

Moreover, we determined that the AUC of TWA- MP_{CRS} was similar to that of SOFA score, but superior to TWA-MP alone, which is in agreement with previous research on ARDS.³⁸ Compared to TWA-MP, TWA- MP_{CRS} more accurately predicts ICU mortality by capturing the true mechanical power delivered to the lungs. Unlike broader scores such as SOFA, TWA- MP_{CRS} offers a focused physiologic measure of ventilatory intensity and VILI risk. Automated calculation by ventilators or workflow integration could enhance bedside use. While SOFA remains valuable for overall organ dysfunction, TWA- MP_{CRS} adds insight into ventilatory mechanics, helping identify high-risk patients needing closer monitoring. However, the AUC value of TWA- MP_{CRS} indicates only a moderate discriminatory ability, which may reflect the inherent limitations of being a unidimensional metric. The heterogeneity of mechanically ventilated populations (e.g., ARDS, neurological injury, COPD) leads to variability in the mortality risk thresholds associated with MP.^{39,40} MP may be more strongly associated with mortality in certain subgroups but less predictive of risk in others, diluting its discriminative power when applied to the overall ICU population. Integrating TWA- MP_{CRS} with other clinical predictors, employing stratified modeling techniques, and leveraging advanced machine learning methods could potentially enhance its discriminatory performance. Additionally, MP has limitations in assessing and quantifying VILI and the severity of lung injury. For instance, the energy required to overcome airway resistance does not necessarily lead to VILI.⁴¹ Future research in mechanically ventilated patients might explore normalizing specific components of MP, such as elastic power,⁴² which could have the potential to improve its prognostic predictive value. Further investigations are needed to address these challenges and enhance the utility of TWA- MP_{CRS} in guiding ICU management decisions.

No single component of MP was found to significantly contribute to overall MP.¹¹ Although our subgroup analyses based on PEEP, Vt, Ppeak, and lung compliance showed consistent associations between TWA- MP_{CRS} and increased ICU and hospital mortality, the complex interactions among these variables make it difficult to clarify the specific roles of individual components in VILI. Further research is needed to address this. In addition, our analysis confirms that patients with the highest BMI have correspondingly higher TWA- MP_{CRS} , similar to the findings of González et al., which associate this with reduced chest wall compliance in obesity and the need for higher PEEP to counterbalance the weight load.⁴³ However, further stratified analysis reveals that BMI does not influence the relationship between TWA- MP_{CRS} and mortality. Moreover, no significant interactions were observed for variables such as age, gender, congestive heart failure, COPD or ARDS when patients were stratified according to potential confounding factors. This suggests that the relationship between TWA- MP_{CRS} and mortality is

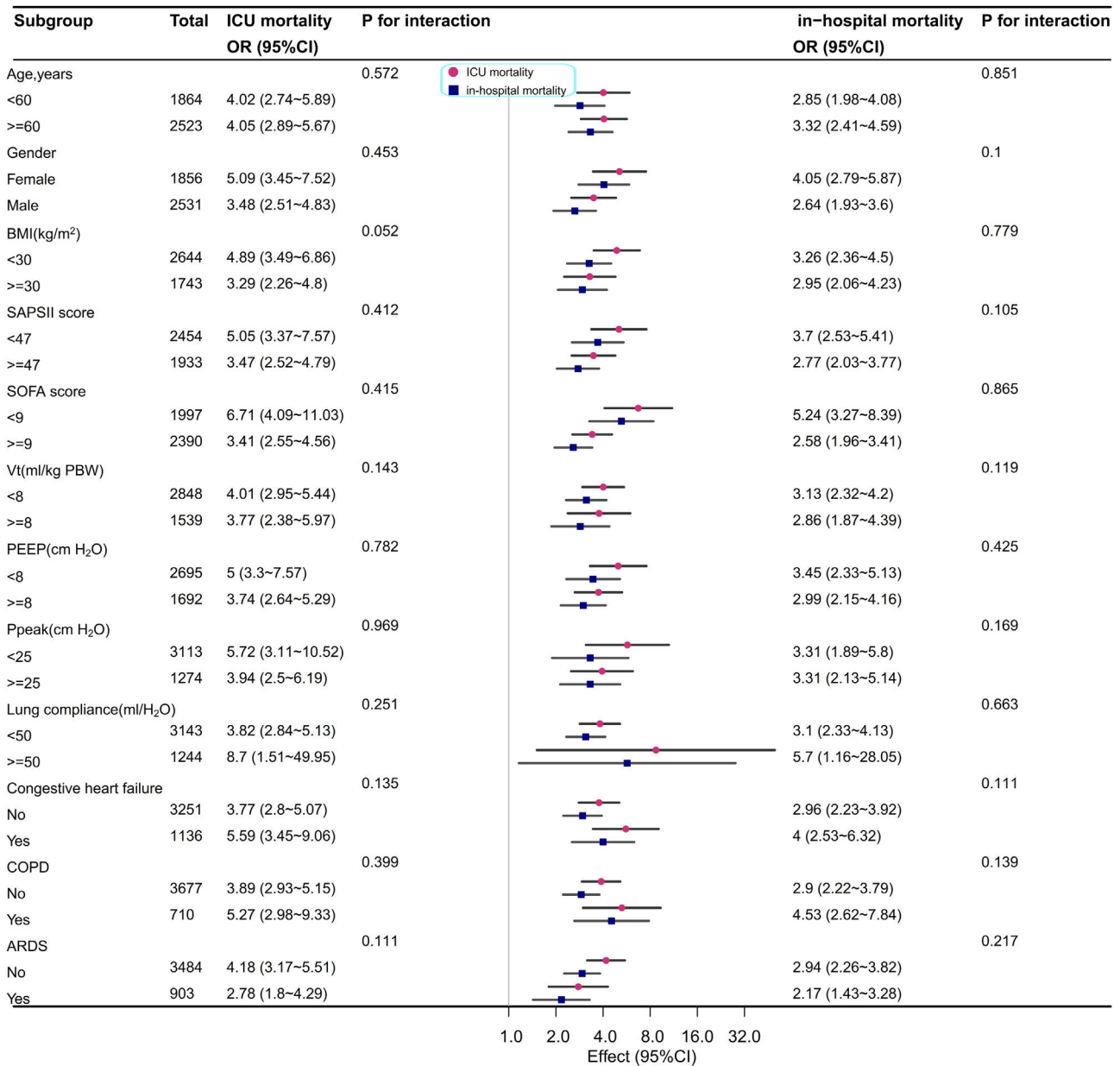


Figure 4 Effect size of TWA-MP_{CRS} on ICU mortality and in-hospital mortality in pre-specified and exploratory subgroups. Multivariable logistic regression analysis in subgroups adjusted the same covariates as for Model 3 in Table 2. BMI, Body mass index; SAPSII, Simplified acute physiology score II; SOFA, Sequential organ failure assessment; Vt, tidal volume; PEEP, positive end-expiratory pressure; Ppeak, peak inspiratory pressure; PBW, predicted body weight; COPD, Chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome.

consistent and independent of these variables, supporting the broader applicability of TWA-MP_{CRS} as a metric for evaluating ventilation dynamics and their association with outcomes in diverse ICU patients. Specifically, in non-ARDS patients, factors such as chest wall compliance, hyperinflation (in COPD), or fluid overload (in congestive heart failure) can alter respiratory mechanics, yet TWA-MP_{CRS} appears to remain a robust indicator of prognosis. Its ability to integrate various components of mechanical ventilation makes it a reliable measure of ventilation-associated stress and strain on the respiratory system, even under differing underlying conditions. Further studies are warranted to explore its

utility in guiding ventilatory strategies tailored to heterogeneous patient groups.

Static parameters based on plateau pressure were not used in this study because plateau pressure is often not routinely measured in clinical practice, especially without adequate sedation or standardized inspiratory pauses. This limits data accuracy in large databases like MIMIC-IV. Additionally, plateau pressure may underestimate the maximal pressure experienced by vulnerable lung units during dynamic inflation.⁴⁴ Therefore, we relied on real-time, automatically recorded Ppeak and PEEP to calculate dynamic driving pressure and dynamic MP.^{27,45} These dynamic param-

eters offer the advantage of being automatically displayed by the ventilator with each breath, facilitating continuous monitoring of physiological changes and remaining independent of ventilation mode.^{27,46,47} Numerous studies have also supported the reliability of these dynamic indices as substitutes for static measurements, and evidence shows that elevated dynamic MP is significantly associated with increased 30-day mortality in patients with acute respiratory failure^{27,46} and a higher risk of postoperative pulmonary complications,⁴⁷ regardless of ventilation mode. The use of dynamic MP overcomes the limitations of static measurements and provides a more universal and clinically valuable method for assessing VILI risk and enabling early intervention.

This study has several limitations. First, the conclusions can only be applied to patients who have been ventilated longer than 48 h. Second, we did not account for patients' sedation status or restrict analysis to a single ventilation modality; patients under various ventilatory modes were included, and sedation was not uniformly documented. As MP may vary across different ventilation modes,⁴⁸ this heterogeneity may affect the accuracy and interpretation of MP values, especially since the MP formula has not been fully validated for all ventilation modes. These methodological limitations may impact the generalizability of our findings. This limitation should be taken into account when interpreting our results, and future prospective studies should aim to rigorously document both sedation depth and ventilation modality to more accurately validate these associations. Third, as the study was retrospective, we measured functional lung size using compliance. Transpulmonary pressures³³ or lung computed tomography (CT) scan may provide more accurate pulmonary⁴⁹ function expansion and pulmonary heterogeneity or the recruitability measurements.^{38,50} However, as these specific data are not available in MIMIC-IV, it is necessary to further investigate the normalization of MP to lung volume using transpulmonary pressures or CT in the future.

Conclusion

According to our study, TWA-MP_{CRS} can predict poor clinical outcomes in critically ill patients. TWA-MP_{CRS} is positively associated with ICU/in-hospital mortality.

CRedit authorship contribution statement

YKD and YGL carried out the design, conducted data analysis and wrote the manuscript. JQF and RH conducted data collection and interpreted the analysis. HY, JNW and YW participated in the manuscript revision. FS designed the study and conducted data analysis and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Institutional Review Board of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. De-identification was performed to ensure patients' confidentiality. Written informed consent for participation

was not required for this study in accordance with the National Legislation and the Institutional requirements.

Consent for publication

Not applicable.

Declaration of Generative AI and AI-assisted technologies in the writing process

No artificial intelligence was used in the study and writing of the manuscript.

Funding

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Data availability

The datasets supporting the conclusions of this article are available in the physionet (<https://physionet.org/content/mimiciv/2.0/>).

Declaration of competing interest

The authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.medicine.2025.502258>.

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