

Early Critical Care Transthoracic Echocardiography Improves the Mortality of Patients Undergoing Mechanical Ventilation: Observational Data From Two Large Databases.

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Research article

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Abstract

Background: Critical care transthoracic echocardiography (TTE) can quickly and accurately assess haemodynamic changes in ICU patients. However, it is not clear whether transthoracic echocardiography improves the prognosis of mechanically ventilated patients. In this study, we hypothesized that early critical care transthoracic echocardiography independently contributes to improvements in mortality in mechanically ventilated patients in the ICU.

Methods: This was a retrospective study based on the Medical Information Mart for Intensive Care III (MIMIC-III) database and the eICU Collaborative Research Database (eICU-CRD). Patients undergoing mechanical ventilation for more than 48 hours were selected. The exposure of interest was early TTE. The primary outcome was in-hospital mortality. We used propensity score matching to analyse the association between early TTE and in-hospital mortality and sensitivity analysis, including the inverse probability weighting model and covariate balancing propensity score model, to ensure the robustness of our findings.

Results: A total of 8862 patients undergoing mechanical ventilation were enrolled. The adjusted OR showed a favourable effect between the early TTE group and in-hospital mortality [MIMIC: OR 0.77, 95% CI (0.63–0.94), (P=0.01); eICU-CRD: OR 0.78, 95% CI (0.68–0.89), (P<0.01)]. Furthermore, TTE was also associated with 30-day mortality in the MIMIC database [OR 0.74, 95% CI (0.6-0.92), P=0.01].

Conclusions: Early application of critical care transthoracic echocardiography during mechanical ventilation is beneficial for improving in-hospital mortality. Further investigation with prospectively collected data is required to validate this relationship.

Background

Mechanical ventilation (MV) is the cornerstone of supportive treatment for patients with acute respiratory failure and is a common and important procedure for patients in intensive care units (ICUs). There are 13 million to 20 million people undergoing mechanical ventilation per year worldwide[1]. However, the mortality of mechanically ventilated patients is still very high (28%-31%) [2, 3]. As research continues, people have realized that the lung is not only a respiratory organ but also a haemodynamic organ[4]. During mechanical ventilation, positive pressure affects the patient's respiration as well as their haemodynamics. Although respiratory failure is the greatest problem to be solved in patients undergoing mechanical ventilation, haemodynamics also play a role that cannot be ignored[5], and a recent study also showed that haemodynamic changes caused by the influence of airway pressure affect the prognosis of patients[6]. Thus, mechanically ventilated patients need to be monitored not only for respiratory function but also for haemodynamic stability[7, 8].

Echocardiography, which can be conveniently performed in the ICU, provide more information on cardiac abnormalities, including anatomical abnormalities and functional abnormalities[9], and quickly and accurately assess haemodynamic changes in the ICU[10]. Understanding the clinical value of early

transthoracic echocardiography (TTE) in mechanically ventilated patients is enormously important. Several studies have suggested that cardiac assessment should be included in management strategies in patients undergoing mechanical ventilation. Transthoracic echocardiography is a safe, non-invasive method that can be used to assess the patient's fluid response under mechanical ventilation[11] and is ideally suited to diagnose weaning failure of cardiac origin[12]. However, there is no strong evidence to support that transthoracic echocardiography should be early performed during mechanical ventilation[13]. The possible reason is that the research on transthoracic echocardiography mainly focuses on the management changes caused by transthoracic echocardiography, but the outcome impact of these changes is unclear[14]. Based on this question, our study was implemented to investigate the impact of earlier transthoracic echocardiography performance on the outcomes of critically ill adult patients undergoing mechanical ventilation. We hypothesized that thoracic echocardiography in the early stages of mechanical ventilation independently contributes to improvements in mortality in mechanically ventilated patients in the ICU.

Methods

This study was reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[15]. We collected data from Medical Information Mart for Intensive Care (MIMIC)-III v1.4[16] and the eICU Collaborative Research Database (eICU-CRD) v2.0[17]. Both are extensive, free, public databases containing hospitalization information. MIMIC covers 61,532 ICU admissions for 46,476 patients at the Beth Israel Deaconess Medical Center in Boston, MA, USA. The eICU-CRD covers 200,859 ICU admissions from 139,226 patients at 208 U.S. hospitals. We completed the required courses for the use of the database and obtained the corresponding certificate (researcher certification number 1605699 and record id 27752407).

Study cohort

We conducted a retrospective study of mechanically ventilated adult patients from medical intensive care units (MICUs) and surgical intensive care units (SICUs) based on the method established by Serpa Neto et al[18]. We used only the first ICU admission data for the first hospitalization and patients 16 years of age or older who had been continuously ventilated for at least 48 hours. Patients who had incomplete datasets were excluded. Patients who underwent echocardiography less than 24 hours before mechanical ventilation or within 24 hours after mechanical ventilation were classified as the early TTE group, and the remaining patients constituted the group without earlier TTE (non-TTE).

Data were extracted from the database using structured query language (SQL). The following demographic data (using data from the first 24 hours of admission) were collected: age, sex, weight, race, comorbidities (chronic obstructive pulmonary disorder [COPD], asthma, sepsis, acute respiratory distress syndrome [ARDS]), Sequential Organ Failure Assessment (SOFA) score, Oxford Acute Severity of Illness Score (OASIS), vital signs (mean arterial pressure [MAP], heart rate [HR]) and laboratory values (white

blood cell [WBC] count, haemoglobin [Hb], blood urea nitrogen [BUN], pH, pO₂, pCO₂, lactate). In addition, we also collected management data for the first day of mechanical ventilation (total IV fluid; ventilator settings; use of dobutamine and norepinephrine).

Outcomes

The primary outcome of the study was in-hospital mortality. Secondary outcomes were 30-day mortality from the date of ICU admission; days free of mechanical ventilation and vasopressors 30 days after ICU admission; use of vasoactive drugs; total IV fluid; and ventilator settings during the first day of MV.

Statistical methods

To control for confounding factors, propensity score matching (PSM) was performed. The baseline characteristics of the original cohort were stratified by TTE. The propensity score for an individual was determined based on the covariates age, sex, weight, race, HR, COPD, asthma, ARDS, sepsis, SOFA score, OASIS, WBC, Hb, pH, pO₂, pCO₂ and lactate using a standard software package (matching package) with a PSM methodology. These variables were selected due to their clinical relevance. This method consisted of ranking the MV patients with TTE and non-TTE, then selecting the TTE patients who had the highest propensity score and finding the non-TTE patient with the closest propensity score (maximum calliper, 0.2). Both patients were then removed from consideration for matching, and the next highest patient was selected (matched 1:1 using the nearest-neighbor algorithm).

After matching, to assess the balance between the two groups, the standardized mean differences (SMDs) between the TTE cohort and the non-TTE cohort were calculated. SMDs eliminate not only the influence of the absolute values from a study but also the influence of the unit of measurement on the results[19]. Continuous variables are shown as the means and standard deviation, and categorical variables are represented as the total and proportion. For continuous variables, we used a nonparametric test or the Wilcoxon rank-sum test. For the categorical variables, we used a chi-square test or Fisher's exact test.

Secondary outcomes were observed after matching as well. We used paired t tests for continuous outcomes and chi-square tests for categorical outcomes.

We used the random forest model to impute missing data (Additional file 1, eFig.1 and eFig.2)[20].

Sensitivity analysis

We conducted a series of sensitivity analyses with the cohort with missing data, the cohort after imputation, and the cohort after PSM to assess the outcomes. In addition, we used multiple logistic regression, the inverse probability of treatment weight (IPTW)[21] and the covariate balancing propensity score (CBPS)[22] to further validate the primary outcome. To adjust for these covariates, the doubly robust estimation method[23] was used to deduce the independent associations between TTE and in-hospital mortality and 30-day mortality (details about the IPTW and CBPS can be found in the Additional

file 2). In addition, we used multiple logistic regression to analyse the impact of TTE during different time periods on the outcome (echo time I: patients who had TTE but the TTE time was not in echo time II; echo time II: TTE time \geq MV time+24 hours and TTE \leq MV time+24 hours). Finally, we carried out a sensitivity analysis through multivariate logistic regression focusing on patients with ARDS and sepsis.

Statistical significance was assessed to be determined by a two-sided $p < 0.05$. All statistical analyses mentioned above were performed using R version 3.5.3.

Results

After reviewing 46476 unique patients from the MIMIC-III database and excluding those with readmission, age <16 years, and ventilation duration <48 hours, and those receiving tracheostomy, 2790 patients from the MICU and SICU were enrolled (Fig.1). In the eICU-CRD, of the 139226 unique patients, 6076 patients in the MICU and SICU were included after the exclusion of patients aged <16 years, those receiving invasive ventilation for less than 48 h or tracheostomy and those missing hospital discharge information (Fig.1). The in-hospital mortality of MV patients was 32.11% in the MIMIC database and 28.74% in the eICU-CRD. Patients who died were older and lighter and had higher OASIS and SOFA scores, higher lactate, and lower MAP (eTable.1).

The original cohort baseline in the MIMIC database showed that patients who underwent TTE on the first day of mechanical ventilation had a more severe status in terms of SOFA score, MAP, pH, pO_2 , and pCO_2 (Table.1); however, there was no statistically significant difference between the TTE and non-TTE groups in the eICU-CRD (Table.1).

Primary Outcomes

Univariate logistic regression analysis results of in-hospital mortality are shown in Additional file 1(eTable.8) and the details of multiple logistic regression are shown in Additional file 1(eTable.9). Then, we used PSM to standardize the differences between the TTE and non-TTE cohorts (eTable.2 and eTable.3). All covariates were balanced in the PSM cohort (eFig.3 and eFig.4). After that, logistic regression was used. The adjusted odds ratio (OR) [MIMIC: OR 0.77, 95% CI (0.63–0.94), ($P=0.01$); eICU-CRD: OR 0.78, 95% CI (0.68–0.89), ($P<0.01$)] in both cohorts showed that the use of TTE was beneficial to improve the in-hospital mortality of patients undergoing mechanical ventilation (Fig. 2).

Secondary outcomes

After PSM, TTE was also associated with 30-day mortality in the MIMIC database [OR 0.74, 95% CI (0.6–0.92), $P=0.01$] (eFig.5). Since the eICU-CRD only contains in-hospital mortality data, we had no way to assess the association between TTE and 30-day mortality in the eICU-CRD cohort. In addition, we found that those who had TTE had both more ventilation-free days and more vasopressor-free days in 30 days than the non-TTE group (eTable.7), which might be related to the management changes brought by TTE, including the amount of IV fluid (only in the eICU-CRD), the use of vasoactive drugs and the ventilator

setting parameters (only in the MIMIC database). However, this conclusion should be regarded cautiously as far as the generalization of results is concerned.

Sensitivity studies

We performed some sensitivity analyses, as summarized in Fig.2 (in-hospital mortality) and additional file 1: eFig.5 (30-day mortality). We analysed all three cohorts, including the matched cohort, the original cohort with missing data, and the cohort after imputation, and found similar results: in-hospital mortality and 30-day mortality were improved in mechanically ventilated patients undergoing TTE. In addition, early TTE was more conducive to patient prognosis than TTE during other time periods (eFig.6), and the subgroup analysis also showed that TTE was beneficial in improving in-hospital mortality in the ARDS cohort (in the MIMIC sample only) and the sepsis cohort (eTable.5).

Discussion

In our study, the results provided evidence to support our hypotheses. After we adjusted for important confounding factors through PSM analysis, the results showed that TTE was associated with a reduced risk of in-hospital mortality and 30-day mortality in these patients. The above results were verified by the data from the MIMIC III and eICU-CRD databases. We also tested several hypotheses to account for the mortality benefit. It may be that TTE caused a change in management and improved the patient's prognosis, but based on current research, we cannot be completely sure.

We consider the following possible reasons for the improvement in in-hospital mortality and 30-day mortality with echocardiography: The lung is not only a ventilatory organ but also a blood-flow-related organ[4], and mechanical ventilation affects haemodynamics as well as the respiratory system[24]. The effect of ventilation on the haemodynamics of the heart is mainly due to changes in pleural pressure (Ppl), and Ppl affects both the inflow of the right ventricle and the outflow of the left ventricle[25]. While reducing the vena cava return, resulting in abnormal filling of the right ventricle, it will also increase the resistance of the pulmonary vascular vessels and affect the outflow function of the right ventricle. While affecting the right ventricle, it also affects the function of the left ventricle. These effects lead to acute cardiac strain and functional and even organic lesions. Intuitive assessment of cardiac function can help clinicians adjust ventilator settings to minimize the occurrence of cardiovascular dysfunction while maintaining ventilation[26].

TTE is a valuable tool for monitoring haemodynamics bedside[27]; it can easily provide dynamic haemodynamic parameters[28] and information about heart–lung interactions in mechanically ventilated patients[29]. It can comprehensively assess the structure and function of the heart and valves, stroke volume, ejection fraction, etc., provide physicians with specific and direct information about left and right ventricular functions, and provide many other options to assess fluid status or pharmacological demand[30, 31]. It can provide the clinician with reliable information for making the correct clinical decision[11]. Recently, similar to our study, Dessap et al. found that early identification of diastolic dysfunction may allow the intensivist to design an intervention that might improve acute respiratory

distress syndrome patient mortality[32], and Feng et al. also showed that early transthoracic echocardiography could improve the prognosis of sepsis patients by changing their management[33]. These findings increase the possibility that TTE can provide physicians with useful information in the ICU. In addition, echocardiography is non-invasive and provides reliable information in most cases. Thus, although the effect of echocardiography on patient outcomes has not yet been established, experts recommend that patients undergo mechanical ventilation for echocardiography. They suggested that echocardiography should be performed early in the course of management to quickly obtain information on ventricular dimensions and function and to assess changes in cardiac output in response to therapy[4, 28]. Our findings provide evidence for the early use of echocardiography in mechanically ventilated patients and the possibility that TTE can be better applied in the ICU.

The present analysis had some limitations. First, since this was a retrospective study, to rule out the impact of professional physicians on the success of TTE, only patients from the MICU and SICU were selected. Second, although we tried to control the confounding factors as much as possible, the addition of other variables may have affected the results. Third, as this was a retrospective study, we cannot know whether the management differed between the TTE group and the non-TTE group with regards to TTE, and there is insufficient evidence to show that different management is associated with the mortality of MV patients. Fourth, we used PSM to adjust some of the potential selection biases. Although we performed a sensitivity analysis to make the results more reliable, some biases are inevitable. Finally, although our study suggested that the in-hospital mortality of MV patients was associated with TTE, further prospective randomized controlled trials are still needed to validate our results.

Conclusions

To the best of our knowledge, this is the first report to determine the clinical value of TTE for patients undergoing MV. Early application of echocardiography during mechanical ventilation is beneficial for the prognosis of patients. However, further prospective, multicentre, randomized controlled studies are needed to validate our results.

Abbreviations

Acute respiratory distress syndrome	ARDS
Blood urea nitrogen	BUN
Covariate balancing propensity score	CBPS
eICU Collaborative Research Database	eICU-CRD
Chronic obstructive pulmonary disorder	COPD
Haemoglobin	Hb
Heart rate	HR
Intensive care units	ICUs
Inverse probability of treatment weight	IPTW
Mean arterial pressure	MAP
Mechanical ventilation	MV
Medical Information Mart for Intensive Care III	MIMIC-III
Medical intensive care units	MICUs
Oxford Acute Severity of Illness Score	OASIS
Propensity score matching	PSM
Sequential Organ Failure Assessment	SOFA
Structured query language	SQL
Surgical intensive care units	SICUs
Transthoracic echocardiography	TTE
White blood cell	WBC

Declarations

Ethics approval and consent to participate:

This study was in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional review boards of MIT and the Beth Israel Deaconess Medical Center (researchers certification number 1605699, record id 27752407). MIMIC-III and eICU-CRD were retrospective with lack of patient intervention and all patients' data were de-identified, thus individual patient informed consent was not required.

Consent for publication:

Not Applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: XSY designed this study, analysed data, and drafted the manuscript; HJ designed this study, and drafted the manuscript; WJC and LLP collected, compiled and analysed the data; ZDF analysed the data, interpreted the results and reviewed the manuscript; XWZ contributed with the study design and interpreted results; ZQC and JS interpreted the results and reviewed the manuscript; YCY collected and compiled data; and JYP designed and supervised this study and obtained funding. All authors read and approved the final manuscript.

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Tables

Table 1: Baseline characteristics of the original cohort.

Variables	MIMIC cohort			eICU-CRD cohort		
	non-TTE	TTE	SMD	non-TTE	TTE	SMD
N	1922	868		4014	2058	
Sex (%)						0.06
F	928 (48.3)	418 (48.2)	<0.01	1758 (43.8)	963 (46.8)	
M	994 (51.7)	450 (51.8)		2256 (56.2)	1095 (53.2)	
Age (mean (SD))	62.23 (15.66)	62.23 (16.47)	<0.01	62.11 (15.48)	61.79 (15.82)	0.02
Race (%)						0.13
Black	156 (8.1)	74 (8.5)	0.08	390 (9.7)	212 (10.3)	
Hispanic	51 (2.7)	26 (3)		113 (2.8)	34 (1.7)	
White	1297 (67.5)	606 (69.8)		3307 (82.4)	1655 (80.4)	
Other	418 (21.7)	162 (18.7)		204 (5.1)	157 (7.6)	
Weight (mean (SD))	79.31 (20.31)	81.65 (20.91)	0.11	83.61 (22.19)	83.13 (22.76)	0.02
HR (mean (SD))	90.94 (17.28)	92.23 (18.79)	0.07	94.76 (17.34)	93.90 (17.13)	0.05
MAP (mean (SD))	79.49 (11.36)	77.79 (11.4)	0.15	81.28 (12.1)	82.47 (12.34)	0.1
COPD (%)						0.1
0	1807 (94)	810 (93.3)	0.03	3200 (79.7)	1554 (75.5)	
1	115 (6)	58 (6.7)		814 (20.3)	504 (24.5)	
Asthma (%)						0.08
0	1784 (92.8)	797 (91.8)	0.04	3928 (97.9)	2035 (98.9)	
1	138 (7.2)	71 (8.2)		86 (2.1)	23 (1.1)	
ARDS (%)						0.09
0	1720 (89.5)	717 (82.6)	0.2	3529 (87.9)	1868 (90.8)	
1	202 (10.5)	151 (17.4)		485 (12.1)	190 (9.2)	
Sepsis (%)						0.51
0	545 (28.4)	174 (20)	0.2	2752 (68.6)	1824 (88.6)	
1	1377 (71.6)	694 (80)		1262 (31.4)	234 (11.4)	

SOFA (mean (SD))	5.99 (3.89)	7.65 (3.96)	0.42	6.28 (3.64)	6.07 (3.37)	0.06
OASIS (mean (SD))	38.23 (8.02)	40.87 (8.11)	0.33	33.30 (10.39)	32.78 (10.51)	0.05
Hb (mean (SD))	10.82 (2.06)	10.92 (2.15)	0.05	11.76 (2.69)	11.57 (2.66)	0.07
WBC (mean (SD))	12.07 (5.76)	12.58 (6.21)	0.09	12.76 (5.93)	12.74 (5.88)	<0.01
BUN (mean (SD))	29.59 (25.02)	34.03 (25.46)	0.18	7.33 (0.11)	7.34 (0.1)	0.09
pH (mean (SD))	7.36 (0.1)	7.32 (0.12)	0.34	30.02 (24.60)	29.06 (23.45)	0.04
pO ₂ (mean (SD))	143.38 (74.06)	130.03 (74.6)	0.18	121.51 (62.31)	121.75 (59.87)	<0.01
pCO ₂ (mean (SD))	40.68 (9.04)	40.91 (10)	0.02	43.39 (11.52)	43.76 (11.74)	0.03
Lactate (mean (SD))	2.09 (0.98)	2.24 (1.12)	0.15	3.09 (2.54)	2.88 (2.37)	0.09

SMD standardized mean difference, HR heart rate, MAP mean arterial pressure, COPD chronic obstructive pulmonary disorder, ARDS acute respiratory distress syndrome, SOFA sequential organ failure assessment, OASIS Oxford Acute Severity Of Illness Score, Hb haemoglobin, WBC white blood cell, BUN blood urea nitrogen.

Data are reported as the mean (standard deviation) or no./total (%).

All data were extracted in the first 24 hours of ICU admission.

Figures

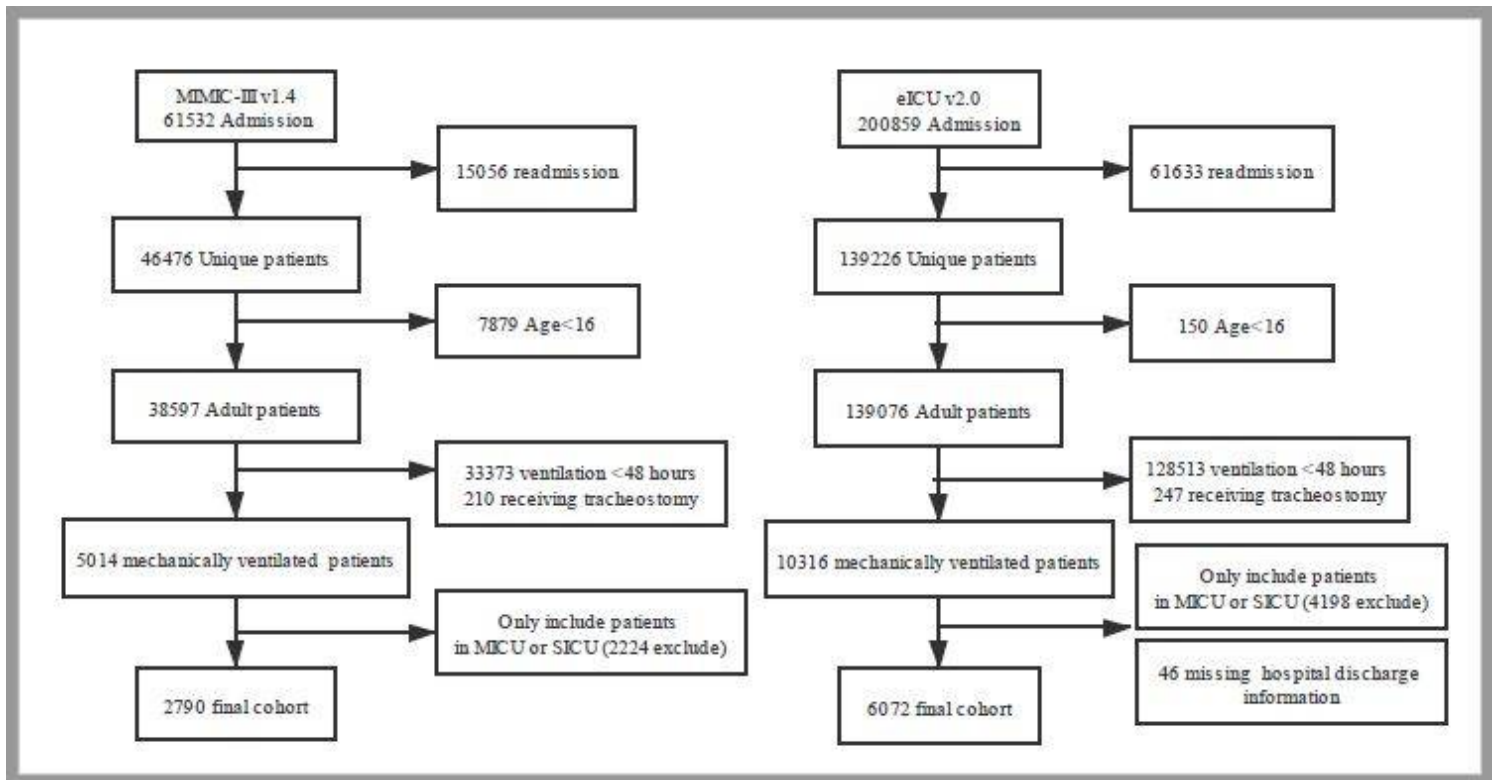


Figure 1

Flow chart illustrating the inclusion and exclusion criteria of the study.

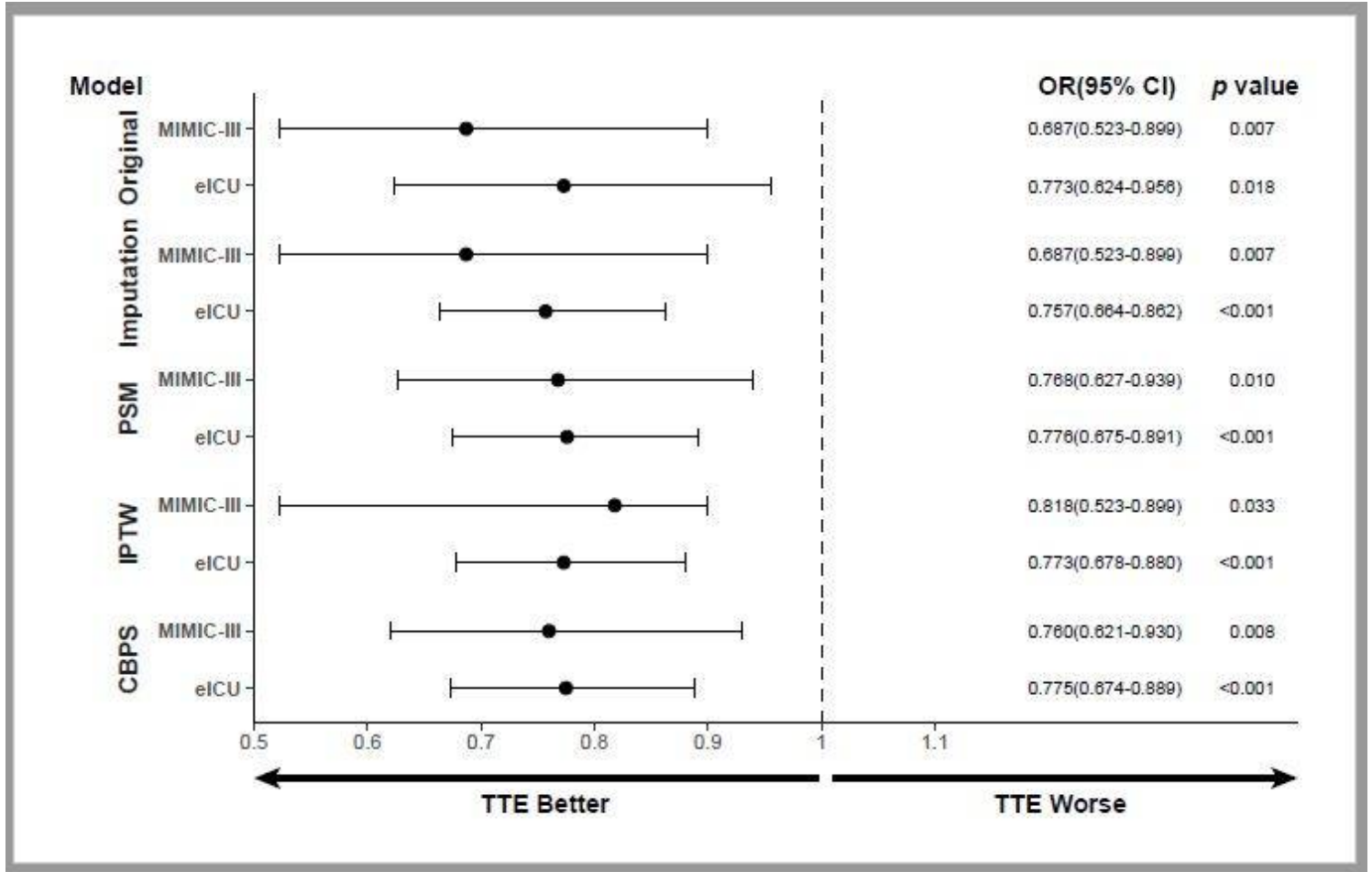


Figure 2

Primary outcomes and sensitivity analyses. The results showed that early use of TTE was beneficial in improving the in-hospital mortality of patients undergoing mechanical ventilation. Sensitivity analyses were performed to determine whether the results were dependent on the method of covariate adjustment. Original, the cohort with missing data; Imputation, the cohort after imputation; PSM, the cohort after propensity score matching; IPTW, the cohort after inverse probability of treatment weight; CBPS, the cohort after covariate balancing propensity score.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile2.docx](#)
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