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Transthoracic Echocardiography and Mortality in Sepsis: Analysis of the MIMIC-III Database

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Abstract:

Purpose: While the use of transthoracic echocardiography (TTE) in the ICU is rapidly expanding, the contribution of TTE to altering patient outcomes among ICU patients with sepsis has not been examined. This study was designed to examine the association of TTE with 28-day mortality specifically in that population.

Methods and Results: The MIMIC-III database was employed to identify patients with sepsis who had and had not received transthoracic echocardiography. The statistical approaches utilized included multi-variate regression, propensity score analysis, doubly robust estimation, the gradient boosted model and an inverse probability-weighting model to ensure the robustness of our findings. Significant benefit in terms of 28-day mortality was observed among the TTE patients compared to the control ('no TTE') group (Odds Ratio = 0.78, 95% CI = 0.68~0.90 and $p<0.001$). The amount of fluid administered (2.5 liters vs. 2.1 liters on day 1, $p<0.001$), use of dobutamine (2% vs. 1%, $p=0.007$) and the maximum dose of norepinephrine (1.4 vs. 1 mg/min, $p=0.001$) were significantly higher for the TTE patients. Importantly, the TTE patients were weaned off vasopressors more quickly than those in the 'no TTE' group (vasopressor-free days on day 28 of 21 vs. 19, $p=0.004$).

Conclusion: In a general population of critically ill patients with sepsis, use of TTE is associated with an improvement in 28-day mortality.

Keywords: echocardiography, sepsis, value, critical care

List of Acronyms

CI = Confidence Interval

GBM = Gradient Boosting Model

IPW = Inverse Probabilities Weighting

IQR = Interquartile Range

LOS = Length-of-stay

MICU = Medical Intensive Care Unit

MIMIC-II = Medical Information Mart for Intensive Care-II

PAC= Pulmonary artery catheter

SAPS = Simplified Acute Physiology Score

SICU = Surgical Intensive Care Unit

SOFA = Sequential Organ Failure Assessment score

SSMD = Standardized Mean Difference

TTE = Transthoracic Echocardiography

Introduction:

The clinical value of many tests and interventions used in the care of critically ill patients is unproven. While this circumstance is frequently observed throughout the healthcare system, it is particularly so in the ICU where randomized controlled trial data is sparse [1, 2]. This lack of supportive evidence is well recognized, and persists for a number of reasons including difficulty in obtaining informed consent, pathophysiologic variability in patients with superficially similar clinical presentations, and the pitfalls of interpreting treatment effects and outcomes in a very complex setting. Understanding the clinical value of interventions performed for critically ill patients is enormously important. Beyond the epidemiologic significance of the ICU, a care setting in which six million Americans are treated per year, including one in five Americans at the end of life [3, 4], identifying interventions that have clinical value--and distinguishing them from those that do not--lays a solid foundation for effective clinical and health policy decision-making. It also promises to improve quality of care, increase cost-effectiveness, and enhance the experience of patients and their families in the ICU. Such knowledge may also reduce clinician burnout by reassuring providers that their interventions have clear-cut benefits [5].

Unsuspected cardiac abnormalities are frequently detected by echocardiography in critically ill patients [6]. While there is evidence that bedside transthoracic echocardiography (TTE) leads to management changes in up to 54% of critically ill patients, the importance and impact of these changes on patient outcomes have not been examined [7–9]. Recent evidence not limited to the critical care setting demonstrates that less than one third of TTEs lead to an active change in care, with inpatient TTE studies even less likely to result in a change in management [10]. Similarly, in a recent large retrospective cohort study, preoperative echocardiography was not associated with improved mortality or shorter length of stay following non-cardiac surgery [11]. In contrast, a recent study using the National Inpatient Sample suggested that for specific diagnostic purposes, performance of TTE is associated with lower odds of inpatient mortality [12]. Studies thus far have primarily focused on management changes due to TTEs, but the outcome impact of these changes is not clear. While the widespread availability and noninvasive nature of TTE make it an appealing diagnostic tool, the marked increase in the use of TTE in the past ten years has significant financial implications. Use of TTE increased by 90% from 1999 to 2008, accounting for over $1.1 billion of Medicare spending in 2010 [10, 13]. Given the increasing attention being placed on value-added care and excessive costs in the ICU,

the impact of this expanding technology on patient care warrants further investigation.

Although professional societies have published guidelines for appropriate use of TTE based on expert consensus, many clinicians are not familiar with these guidelines [14]. Notably, approximately 15% of studies are inappropriate according to these guidelines [15]. It has been argued that TTE use in the surgical intensive care unit (SICU) is not cost effective due to a high failure rate, and addition of TTE variables to the APACHE II score does not improve prediction of mortality [16, 17]. In response to these many issues and questions, the current study was carried out to investigate the impact of TTE performance on the outcomes of critically ill adult patients with sepsis.

Methods:

Study Cohort

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [18]. We conducted a longitudinal, single center, retrospective study of adult patients from the medical (MICU) and surgical (SICU) intensive care units with a diagnosis of sepsis based on the method established by Angus and colleagues to retrospectively identify patients using billing codes [19].

The study was designed to investigate whether formal TTE, performed by an echocardiography technologist and interpreted by a cardiologist, independently contributes to improvements in mortality and clinically important changes in the management of septic patients in the ICU. The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (BIDMC) and was granted a waiver of informed consent.

We utilized the Medical Information Mart for Intensive Care (MIMIC) database, which was developed and is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology [20]. MIMIC-III contains data from 38,605 ICU patients and includes physiologic information from bedside monitors in the adult ICUs of BIDMC, a tertiary care university hospital, located in Boston, Massachusetts, USA. The database includes information from 2002 to 2011. Hourly physiologic readings from bedside monitors, validated by ICU nurses, were recorded. The database also contains records of demographics, labs, nursing progress notes, intravenous (IV) medications, fluid balance, and other clinical variables. Specialists evaluated radiologic films at the time of patient care, and written evaluations were stored in the database along with the corresponding time stamps. International Classification of Diseases, Ninth Revision (ICD-9) codes were also

documented for specific diseases by hospital staff on patient discharge. The database has extensive documentation of how data elements are captured as well as their fidelity. The documentation is provided not only by clinicians, data scientists and information technology personnel at both BIDMC and MIT, but contributed to by the community of users who connect with those who generate the data in the context of research projects. Discussions around reliability of specific data elements are captured in a community white board to guide future investigators who may be interested in exploring similar concept [21]. During the study period, the decision to perform a TTE was based on the clinical judgment of the medical team. There was no protocol in place or guidelines employed regarding performance of TTE in patients with sepsis.

Only the data of each patient's first ICU admission were used in this study. The patients who had TTE performed fewer than 24 hours before their ICU admission or during their ICU stay were categorized as the "TTE" group, with the remaining patients making up the "Non-TTE" group.

Primary outcome and secondary outcomes

The primary outcome of the study was 28-day mortality from the date of ICU admission. Patient mortality information for discharged patients was gathered from the US Social Security Death Index. Secondary

outcomes included number of mechanical ventilation and vasopressor free days within 28 days after ICU admission; use of dobutamine; maximum dose of norepinephrine; IV fluid totals given to patients during their first, second, and third day in the ICU; and reduction in serum lactate and serum creatinine. The reduction in serum lactate and creatinine were calculated as follows: For the TTE patients, the difference between the last measurement before TTE and the first measurement 48 hours after the TTE was calculated; for the non-TTE patients, the difference between the first measurement after ICU admission and the first measurement 48 hours after the initial measurement was calculated.

Statistical Methods

The doubly robust estimation method was applied to infer the independent associations between TTE and patients' primary and secondary outcomes. "Doubly robust estimation combines a multivariate regression model with a propensity score model to estimate the association and causal effect of an exposure on an outcome" [22, 23]. Conventionally, when one applies the regression model or the propensity score model individually to estimate a causal effect, both outcome regression and propensity score methods are unbiased only if both of the statistical models are correctly specified. The doubly robust estimator combines the two

approaches such that only one of the two models needs to be correctly specified to obtain an unbiased effect estimator.

The Gradient Boosted Model (GBM) was employed for the estimation of patients' propensity scores for TTE, so that covariate imbalance between the TTE and no TTE groups was minimized. GBM is a machine learning algorithm that consecutively constructs new models and forms an ensemble of models to provide a more accurate estimate of the response variable. The principal idea is to construct the new base-learners to be maximally correlated with the negative gradient of the pre-defined loss function. In our study, regression tree was used as the base learner of the GBM, and a total of thirty-nine covariates were used in the model.

Using the estimated propensity scores as weights, a weighted cohort was generated based on an inverse probabilities weighting (IPW) model [24]. A logistic regression was then performed on the weighted cohort, adjusting for the variables that remained unbalanced between the groups with and without a TTE in the propensity score model, thus the term doubly robust analysis.

To evaluate the effectiveness of the propensity score model in balancing the two comparing groups, the imbalance of covariates for the original and the adjusted (weighted) cohorts were compared. The standardized mean difference (SSMD) between the TTE and non-TTE

groups were calculated. The Wilcoxon signed rank test, a non-parametric test, was used to statistically test the differences among the continuous covariates. A Chi-square test was used to test the differences among the categorical covariates.

For the comparison of the secondary outcomes, the TTE and non TTE patients were matched based on estimated propensity scores. The SSMD and statistical significance of the observed differences were then calculated with the paired t-test for continuous outcomes and McNemar's test for categorical outcomes.

Sensitivity Analysis

We conducted a series of sensitivity analyses to evaluate the robustness of the findings of the study and how our conclusions can be affected by applying various association inference models. In the sensitivity analysis, we applied four more association inferences models: a doubly robust model adjusting for all covariates, a propensity score based IPW model, a propensity score based patient matching model, and a logistic regression based multivariate analysis model. The calculated effect sizes and p-values from all these models were reported and compared.

We have also conducted a sensitivity analysis focusing only on those patients who had TTE performed within the first 48 hours of their ICU stays.

Covariates

Demographic and admission information: age, gender, weight, day of the week of admission, time of admission, and severity at admission measured by SAPS score, SOFA score and the Elixhauser co-morbidity score [25–27].

Co-morbidities: Congestive heart failure (CHF), atrial fibrillation (AFIB), chronic renal disease, liver disease, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), stroke, and malignant tumor. All of the co-morbidities were identified on the basis of the recorded ICD9 codes. (A detailed table of ICD9 codes used for each co-morbidity is included in the Appendix.)

Vital Signs: Mean Arterial Pressure (MAP), Heart Rate, Temperature (^{o}F) and Central Venous Pressure (CVP) readings at ICU admission.

Interventions: Use of mechanical ventilation, inotropic and vasopressor agents, and sedative drugs during the first 24 hours of ICU admission.

Laboratory results: White blood cell (WBC) count, hemoglobin, platelet count, sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), lactate, creatinine, pH, partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2), B-type natriuretic peptide (BNP), troponin and creatinine kinase.

We observed that CVP values were not collected for more than half of the patients in our cohort. If we directly used the CVP readings as the co-variate, we would have had a large number of missing values. Instead, we utilized the presence or absence of CVP values as the covariate. Thus, a flag indicating whether CVP was recorded was included as a co-variate in our models. Similarly, laboratory tests for BNP, troponin and creatinine kinase were not ordered in more than half of the cohort. Therefore, flags indicating whether these tests were obtained were used as covariates. (Details around missing values can be found in the Appendix).

The source codes for all analyses can be found at https://github.com/nus-mornin-lab/echo-mimiciii.

Results

After reviewing 38,605 MIMIC-III adult admissions, sepsis was identified in 17,420 admissions based on the Angus methodology [19]. After including only patients' first ICU admissions, and excluding admissions to the CCU and the cardiac surgical unit, 6,361 patients were included in our study cohort (Fig 1). TTE was ordered for 51.3% of patients during or in the period less than 24 hours before their ICU admission. The characteristics of the cohort are summarized in Table 1. The TTE patients had significantly higher severity scores on admission:

SAPS-I score 20.75 (+/- 5.44) vs. 14.63 (+/-5.78), and SOFA score 6.3 (+/- 3.8) vs. 5.3 (+/- 3.62). A larger percentage of the TTE patients received mechanical ventilation (58% vs. 47%) and vasopressor treatment (38% vs 27%) during the first 24 hours of their ICU stay.

Doubly Robust Analysis

A propensity score model was first constructed employing the thirty-nine covariates with the Gradient Boosting Model (GBM). The contributions of individual covariates to the final propensity score are illustrated in Fig 2. The top covariates include age, history of atrial fibrillation, presence of CHF, heart rate, and SOFA score: unsurprisingly, these covariates represent common factors influencing physicians' decisions regarding whether to perform TTE.

Based on the estimated propensity scores, inverse probability weighting (IPW) was applied to standardize the differences between the TTE and no TTE cohorts [24]. As shown in Table 1, most of the covariates of the weighted cohorts were similar or 'balanced' between the groups with and without echocardiograms. The exceptions were SOFA score; mechanical ventilation; use of inotropic, vasopressor and/or sedative medications; the availability of BNP, troponin and creatinine kinase values; and two co-morbid conditions (CHF and atrial fibrillation). Under the doubly robust estimation framework, a regression model was

developed to adjust for these unbalanced covariates on the weighted cohort.

Primary Outcome and Sensitivity Studies

The doubly robust analysis demonstrated a significant beneficial effect of TTE in terms of the 28-day mortality. The propensity score matched mortalities rates for TTE and non-TTE were 25% vs 30%. The adjusted odds ratio was 0.78 (95% confidence interval=0.67 to 0.89, $p<0.001$). For the sensitivity analysis, as summarized in Table 2, all five estimation models led to the same conclusion: patients who had TTE had lower 28-day mortalities.

We also conducted a sensitivity study to include only patients with TTE performed within the first 48 hours and observed the same findings (appendix).

Secondary Outcomes Studies with Propensity Score Matching

We evaluated a number of secondary outcomes to investigate potential factors that might account for the beneficial effects of TTE. Several key differences in secondary outcomes were observed. First, the amount of fluid administered to the TTE group was significantly higher on day 1 (2.5 liters vs. 2.1 liters, $p<0.001$), day 2 (1.3 liters vs. 0.9 liter, $p<0.001$) and day 3 (0.8 liter vs. 0.3 liter, $p<0.001$). Second, the use of dobutamine (2% vs. 1%, $p=0.007$) and, when administered, the maximum

dose of norepinephrine (1.4 vs. 1 mg/min, p=0.001) were significantly higher for the TTE patients. Third, the TTE group had a significantly shorter duration of vasopressor use (vasopressor-free days on day 28 of 21 vs. 19, p=0.004). The duration of mechanical ventilation did not significantly differ between the 2 groups. Differences in the reduction of lactate and creatinine values were not significant. These comparisons are for those values recorded nearest the time stamp of the TTE with those from 48 hours later for the TTE group, and the values recorded on days 1 and 3 for the non TTE group. The detailed results are summarized in Table 3.

Discussion

Identifying clinical value is challenging when innovations in healthcare are studied [28, 29]. This challenge only increases in complex, dynamic environments like the ICU. At times, new technologies diffuse rapidly based on theoretical benefits from our understanding of disease pathophysiology, but before rigorous evaluations of benefits and harms are performed. Similarly, innovations which have been found to be beneficial in specific patient populations may be applied to other populations in which they have not been adequately studied, potentially exposing patients to harm (and added expense) without commensurate benefit [5]. Notable examples of this phenomenon include the initial enthusiasm for and

subsequent decline in pulmonary artery catheter utilization, routine use of invasive cardiac catheterization in the initial evaluation of patients with stable coronary disease, and utilization of cardiac computed tomography angiography [30–38]. Examples of other technologies that are commonly used in the ICU but have received little formal utility assessment include electrolyte repletion to restore normal range values, insertion of central venous catheters, and the use of indwelling arterial catheters [39].

The advent of electronic medical records provides a powerful tool for investigating the clinical effectiveness of technologies using real-world data [40]. In light of the uncertainty surrounding the value of most diagnostic tests and interventions used in the ICU, as well as the implications that this evidence gap has for practice and policy, we describe a novel framework that exemplifies how big data can be employed for measuring impact on clinical and/or patient-centered outcomes.

While the use of TTE has steadily increased over the past decade, the implications for patient outcomes remain unknown [12]. There is limited data available in the literature regarding the utility of TTE in critically ill, septic patients: A recent study by Papolos et al. found that use of TTE was associated with lower odds of in hospital mortality among patients hospitalized for five specific diagnoses, including sepsis [12].

In our study, patients who had TTE had higher severity of illness scores, more co-morbid conditions, and were more likely to receive mechanical ventilation, inotropic, vasopressor and sedative agents. Despite these factors pointing to a sicker group of patients, we found a significantly lower 28-day mortality among patients who had TTE after adjustment for confounding. Considering the factors displayed in figure two, clinicians may particularly want to consider TTE early in the ICU stay for patients with sepsis.

We tested several hypotheses to account for the mortality benefit, and compared several variables between the patients with and without TTE. More fluids were administered to the TTE group on days 1, 2 and 3 in the ICU. Dobutamine was used more often in the group who received TTE, but this might be because a history of CHF was more frequent among this group i.e. it is not certain whether the TTE triggered the use of dobutamine or if it had already been in place. Those who had TTE also had a higher maximum dose of norepinephrine, but surprisingly, were weaned off vasopressors earlier compared to the no TTE group. Whether the mortality improvements are entirely due to the differences in the volume of fluid administered, dobutamine use and/or maximum dose of norepinephrine is impossible to assess given the sample size.

Our findings raise the possibility that TTE provides information to physicians that may aid in the management of critically ill septic patients. We fully realize that observational, database studies of this kind require careful, multifaceted, and rigorous statistical approaches in order to produce valid, reliable, and actionable results. We believe that we have done so in this regard for the subject at hand, and intend to pursue further such analyses in the future in order to minimize the ambiguity of clinical decision-making in the confounding and complex environment posed by the ICU.

The findings should in no way be taken as the final and definitive word with regard to the value of TTE in the management of sepsis in the ICU. As an observational single center study retrospectively performed on electronic health record data, the potential issues of residual confounding by variables not captured in the EHR, as well as generalizability of the findings to other institutions, require additional investigation. The outcomes were not adjusted for year of ICU admission, which is a limitation of the analysis as practice patterns may have changed during the study period. Additionally, the lack of a standardized protocol related to performance of a TTE in septic patients during this study period may limit the generalizability of these results. This paper was undertaken to exemplify the way secondary analysis of EHR data can be utilized to

evaluate tests and treatments that have been widely adopted into practice based on theoretical or limited (with respect to patient cohort and/or surrogate outcome) benefits. Some analyses will require prospective randomized trials for confirmation as was the case of pulmonary artery catheter use in the ICU, but in some cases, retrospective studies are adequate, as in the case of rofecoxib withdrawal from the market or to convince the public of the cancer risk of smoking.

Conclusions

The performance of TTE is associated with a 28-day mortality benefit in a general population of septic, critically ill patients. The mechanism of this benefit remains to be explored but may be related to the increased use of fluids and vasoactive agents as indicated and guided by TTE results. Given that for most of ICU practice, randomized controlled trial (RCT)-based data are lacking and no RCT will likely be performed to provide evidence in the future, the application of the real-world data that is captured in EHRs is necessary to assess the clinical effectiveness of interventions such as TTE. While these investigations must be performed with full awareness of and attention to the complexity, and possible confounding by indication, of such data applications, they are now quite

feasible and we feel, absolutely necessary, in the future development and evolution of optimal clinical care.

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Legends

Fig 1: Study cohort. Illustration of exclusion and inclusion criteria as utilized to select the final cohort of 6361 patients.

Fig 2: Relative influence factor of co-variates. The relative influence factor measures how discriminative are the 39 co-variates of the propensity score model when predicting the likelihood of echocardiogram performance.

Table 1. Comparison of the basic demographics, co-morbidity conditions and day of ICU admissions between the original cohort and the adjusted (weighted) cohort. For all continuous covariates, the mean values and standard deviations are reported. For both cohorts, those covariate entries that are bolded have p-values <0.05.

Covariate	Original Cohort			Matched Cohort			Missing Data %
	Non-TTE	TTE	SSMD	Non-TTE	TTE	SSMD	
n	3099	3262		1626	1626		NA
Age	**66.69 (17.21)**	**65.74 (16.55)**	**0.056**	66.58 (16.54)	65.84 (17.07)	0.044	0.0%
Gender (Female)	**50.80%**	**47.80%**	**0.061**	48.00%	49.00%	0.021	0.0%
Service Unit (MICU %)	**77.60%**	**79.50%**	**0.047**	78.40%	78.90%	0.014	0.0%
Weight (Kg)	**78.56 (23.58)**	**83.17 (26.87)**	**0.182**	81.35 (24.69)	79.50 (23.11)	0.077	9.4%
SAPS Score	**19.63 (5.79)**	**20.76 (5.44)**	**0.202**	20.29 (5.42)	19.80 (5.17)	0.092	0.0%
SOFA Score	**5.31 (3.62)**	**6.33 (3.79)**	**0.277**	**5.99 (3.74)**	**5.55 (3.50)**	**0.123**	0.0%
Elixhauser Score	**8.51 (7.45)**	**10.07 (7.67)**	**0.207**	9.54 (7.67)	8.82 (7.52)	0.096	0.0%
Interventions							
Mechanical Ventilation Use (1st 24 Hours)	**47.10%**	**58.30%**	**0.226**	**52.30%**	**49.60%**	**0.055**	0.0%
Vasopressor Use (1st 24 Hours)	**27.10%**	**37.60%**	**0.227**	**32.70%**	**31.20%**	**0.032**	0.0%
Sedative Use (1st 24 Hours)	**40.20%**	**49.80%**	**0.192**	43.80%	42.80%	0.021	0.0%
Co-morbidities							
CHF	**18.20%**	**40.00%**	**0.495**	**28.80%**	**19.40%**	**0.221**	0.0%
AFIB	**20.10%**	**32.40%**	**0.282**	**27.60%**	**24.80%**	**0.062**	0.0%
RENAL	**14.10%**	**16.40%**	**0.066**	15.40%	14.30%	0.031	0.0%
LIVER	10.10%	11.20%	0.034	11.40%	11.90%	0.013	0.0%
COPD	**15.20%**	**17.50%**	**0.063**	17.80%	15.60%	0.061	0.0%
CAD	**11.90%**	**15.80%**	**0.113**	13.20%	13.20%	0.002	0.0%
STROKE	**7.70%**	**10.80%**	**0.106**	8.80%	8.70%	0.002	0.0%
MALIGNANCY	**25.20%**	**22.30%**	**0.068**	25.00%	25.20%	0.003	0.0%
Vital Signs							
MAP	79.91 (19.44)	80.03 (20.48)	0.006	80.13 (19.95)	80.31 (20.05)	0.009	1.2%
Heart Rate	**93.01 (19.81)**	**95.07 (21.79)**	**0.099**	94.88 (20.77)	93.88 (20.04)	0.049	1.2%
Temperature (C)	**36.75 (1.05)**	**36.85 (1.90)**	**0.07**	36.81 (1.06)	36.86 (1.85)	0.031	1.6%
CVP	**11.88 (17.09)**	**13.74 (20.45)**	**0.099**	12.41 (19.95)	11.86 (11.63)	0.033	64.5%
Lab Tests							
WBC	13.48 (14.03)	13.76 (12.41)	0.021	13.71 (15.17)	13.70 (13.84)	0.001	4.1%
HEMOGLOBIN	**10.55 (1.98)**	**10.60 (2.04)**	**0.021**	10.56 (2.01)	10.57 (2.02)	0.009	4.0%
PLATELET	**223.96 (134.79)**	**211.55 (128.46)**	**0.094**	215.31 (130.72)	216.43 (129.90)	0.009	4.1%
SODIUM	**139.09 (6.45)**	**138.56 (5.89)**	**0.086**	138.75 (5.88)	138.52 (6.08)	0.039	2.6%
POTASSIUM	**4.10 (0.79)**	**4.15 (0.84)**	**0.061**	4.12 (0.79)	4.09 (0.76)	0.033	2.4%
BICARBONATE	22.28 (5.40)	22.35 (5.71)	0.012	22.39 (5.67)	22.30 (5.33)	0.018	2.9%
CHLORIDE	**106.21 (7.45)**	**105.14 (7.20)**	**0.145**	**105.50 (7.14)**	**105.47 (7.21)**	**0.004**	2.6%
BUN	**32.02 (26.34)**	**36.01 (27.38)**	**0.149**	34.05 (26.40)	32.41 (25.57)	0.063	2.8%
LACTATE	2.62 (2.35)	2.51 (2.27)	0.047	2.58 (2.21)	2.47 (2.14)	0.049	38.2%
CREATININE	**1.60 (1.66)**	**1.83 (1.81)**	**0.132**	1.72 (1.68)	1.63 (1.64)	0.053	2.8%
PH	**7.35 (0.11)**	**7.34 (0.11)**	**0.043**	7.34 (0.11)	7.35 (0.11)	0.086	30.5%
PO2	**147.61 (107.49)**	**133.24 (93.89)**	**0.142**	135.33 (98.90)	139.78 (100.24)	0.045	33.1%
PCO2	**41.48 (13.34)**	**42.77 (14.83)**	**0.091**	42.18 (13.69)	41.46 (13.81)	0.053	33.1%
BNP (tested)	**1.20%**	**4.40%**	**0.196**	**2.20%**	**1.50%**	**0.05**	0.0%
TROPONIN (tested)	**20.40%**	**40.70%**	**0.451**	**31.90%**	**24.10%**	**0.173**	0.0%
CREATININE KINASE (tested)	**37.20%**	**59.30%**	**0.452**	**51.80%**	**44.00%**	**0.157**	0.0%
Day of ICU Admission			**0.148**			0.093	
SUNDAY	12.70%	14.20%		14.40%	12.90%		
MONDAY	13.40%	14.60%		13.00%	13.70%		
TUESDAY	13.80%	15.10%		13.70%	15.70%		
WEDNESDAY	13.60%	15.80%		15.40%	13.80%		
THURSDAY	15.00%	15.30%		14.60%	14.50%		
FRIDAY	17.40%	13.70%		15.70%	17.10%		
SATURDAY	14.10%	11.40%		13.20%	12.20%		0.0%

Table 2. Primary outcome analysis with 5 different models: 1) Doubly robust model with unbalanced co-variates 2) Doubly robust model with all co-variates 3) Propensity Score IPW model 4) Propensity Score Matching model 5) Multivariate logistic regression model.

Method	OR	Confidence Interval		P-value
		2.5%	97.5%	
Doubly Robust with Unbalanced Covariates	**0.78**	**0.68**	**0.90**	**<0.001**
Doubly Robust with All Covariates	0.64	0.52	0.78	<0.001
Propensity Score IPW	0.84	0.78	0.92	<0.001
Propensity Score Matching	0.78	0.66	0.92	<0.001
Multivariate	0.64	0.53	0.78	<0.001

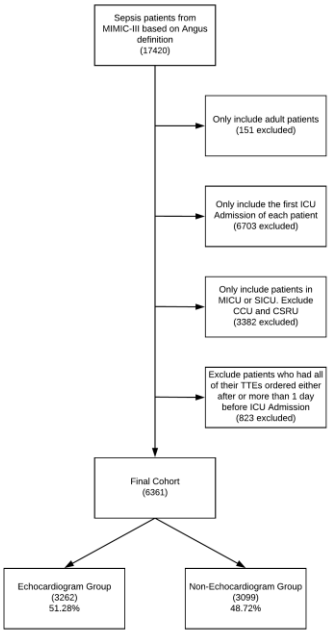
Table 3 Secondary outcome analysis with propensity score matched cohorts. For the use of dobutamine, the difference in the percentage of patients was calculated as the effect size. For the other secondary outcomes, mean values and standard deviations were reported, and the standardized mean differences (SSMD) were calculated as the effect size.

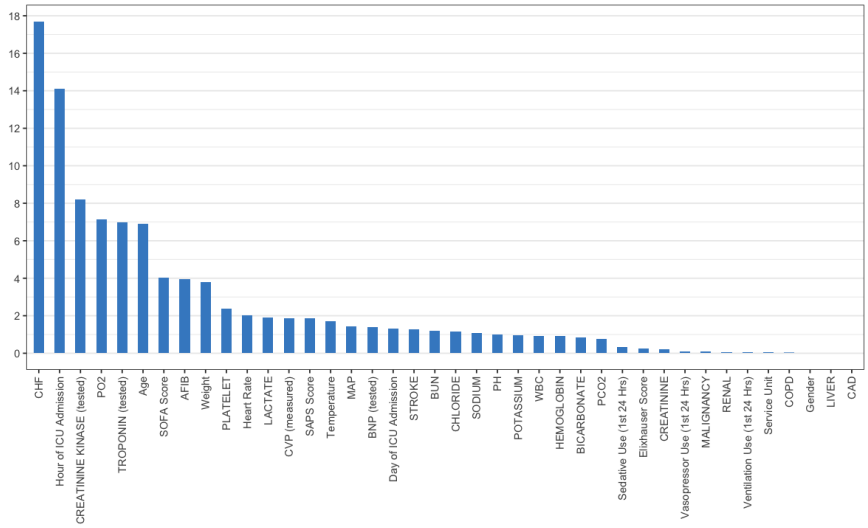
Secondary Outcomes	Non TTE	TTE	Effect Size	p-value	Missing Data %
Ventilation free days in 28 days	18 (14.70)	20 (32.64)	0.06	0.1	0%
Vasopressor free days in 28 days	19 (12.73)	21 (16.95)	0.1	<0.001	0%
Dobutamine Use	1%	2.1%	1.1%	<0.001	0%
Norepinephrine (maximum dosage mg/min)	1.04 (2.68)	1.38 (3.13)	0.117	<0.001	0%
IV Fluid day 1 (mL)	2112.35 (3372.21)	2492.39 (3768.86)	0.089	<0.001	10%
IV Fluid day 2 (mL)*	900.41 (2557.54)	1275.30 (2872.91)	0.138	<0.0001	18%
IV Fluid day 3 (mL)*	253.25 (2147.55)	771.78 (2683.65)	0.213	<0.0001	34%
Serum Lactate	0.23	0.53	0.06	0.5	68.9%

Reduction#	(1.94)	(2.4)			
Serum Creatinine Reduction#	0.08 (0.65)	0.12 (0.58)	0.003	0.3	9.3%

*Patients, who were dead or discharged from the hospital before day 2 or day 3 were excluded.

#Patients who were dead or discharged from the hospital within 48 hours of TTE (TTE group) or initial lab value (non TTE group) were excluded.




18
16
14
12
10
8
6
4
2
0
CHF
Hour of ICU Admission
CREATININE KINASE (tested)
PO2
TROPONIN (tested)
Age
SOFA Score
AFIB
Weight
PLATELET
Heart Rate
LACTATE
CVP (measured)
SAPS Score
Temperature
MAP
BNP (tested)
Day of ICU Admission
STROKE
BUN
CHLORIDE
SODIUM
PH
POTASSIUM
WBC
HEMOGLOBIN
BICARBONATE
PCO2
Sedative Use (1st 24 Hrs)
Elixhauser Score
CREATININE
Vasopressor Use (1st 24 Hrs)
MALIGNANCY
RENAL
Ventilation Use (1st 24 Hrs)
Service Unit
COPD
Gender
LIVER
CAD