The Effect of Right Heart Catheterization (RHC) During the First 24 Hours on 30-day Mortality of Critically Ill Patients in Intensive Care Units

Taehoon Ha, Jingjing Qi

Background

It is a popular belief that right heart catheterization (RHC) is necessary to guide therapy for certain critically ill patients that might lead to better patient outcomes. However, the benefit of RHC has not been demonstrated in RCT because physicians cannot ethically randomize the patients. Therefore, observational studies have been used to evaluate its effectiveness.

A multi-center observational study, includes 5 medical centers was conducted. The data was centralized and the data quality has been checked. Study inclusion criteria: all patients that met severity and other entry criteria in 1 or more of 9 disease categories on admission to the hospital ICU stay consented. Exclusion criteria included age less than 18 years, death or discharge within 48 hours, inability to speak English, acute psychiatric disorders, pregnancy, acquired immunodeficiency syndrome (AIDS), acute burns, and head trauma or other trauma. RHC is recorded if the procedure was performed within the first 24 hours after study entry. (detected by abstraction of charts and bedside flow sheets in the ICU by specially trained nurses.)

Study dataset includes 5735 subjects, 2184 patients with RHC (38%) and 3551 patients non-RHC patients (62%). The outcome variable was calculated by taking two-stage

process: First, the difference between admission date and death date were calculated. Second, the minimum between 30 days and the difference was considered as the outcome. 50 covariates were grouped into four by similarities: (1) Socio-demographics, (2) presentation at admission to ICU units, diagnosis on day 1, comorbid illness, and transfer status, (3) day 1 summary measures of presentation and severity of illness, and (4) day 1 Lab results. The table below summarizes the covariates by the outcome variable, 30-day mortality.

[Table1] Data summarized by 30-day mortality status

	Alive N=3843	Dead N=1892	p-value
Treatment:			<0.001
RHC	1363 (35.5%)	821 (43.4%)	
No RHC	2480 (64.5%)	1071 (56.6%)	
Age	60.3 (16.8)	63.6 (16.3)	<0.001
Sex:			0.716
Male	2132 (55.5%)	1060 (56.0%)	
Female	1711 (44.5%)	832 (44.0%)	
Education In Years	11.7 (3.13)	11.6 (3.17)	0.318
Income Category:			<0.001
Under $11k	2087 (54.3%)	1139 (60.2%)	
$11-$25k	799 (20.8%)	366 (19.3%)	
$25-$50k	639 (16.6%)	254 (13.4%)	
> $50k	318 (8.27%)	133 (7.03%)	
Insurnace Category:			<0.001
Private	1181 (30.7%)	517 (27.3%)	
Private & Medicare	785 (20.4%)	451 (23.8%)	
Medicare	940 (24.5%)	518 (27.4%)	
Medicare & Medicaid	253 (6.58%)	121 (6.40%)	
Medicaid	476 (12.4%)	171 (9.04%)	
No insurance	208 (5.41%)	114 (6.03%)	

Table 1 – *continued from previous page*

	Alive N=3843	Dead N=1892	p-value
Race:			0.697
white	2987 (77.7%)	1473 (77.9%)	
black	624 (16.2%)	296 (15.6%)	
other	232 (6.04%)	123 (6.50%)	
Primary disease category:			.
ARF	1755 (45.7%)	735 (38.8%)	
CHF	403 (10.5%)	53 (2.80%)	
Cirrhosis	130 (3.38%)	94 (4.97%)	
Colon Cancer	6 (0.16%)	1 (0.05%)	
Coma	150 (3.90%)	286 (15.1%)	
COPD	378 (9.84%)	79 (4.18%)	
Lung Cancer	27 (0.70%)	12 (0.63%)	
MOSF w/Malignancy	186 (4.84%)	213 (11.3%)	
MOSF w/Sepsis	808 (21.0%)	419 (22.1%)	
Do Not Resuscitate status, day 1:			<0.001
No	3581 (93.2%)	1500 (79.3%)	
Yes	262 (6.82%)	392 (20.7%)	
Weight in kg, day 1	68.4 (29.3)	66.6 (28.6)	0.029
Heart rate, day 1	115 (39.7)	116 (44.3)	0.443
Mean Blood Pressure, day 1	81.1 (37.7)	73.3 (38.1)	<0.001
Respiratory rate, day 1	28.3 (13.7)	27.7 (14.9)	0.128
Temperature, C, day 1	37.7 (1.72)	37.5 (1.88)	0.018
Cardiovascular diagnosis:			0.001
No	2491 (64.8%)	1313 (69.4%)	
Yes	1352 (35.2%)	579 (30.6%)	
Gastrointestinal diagnosis:			<0.001
No	3282 (85.4%)	1511 (79.9%)	
Yes	561 (14.6%)	381 (20.1%)	
Hematologic diagnosis:			<0.001
No	3669 (95.5%)	1712 (90.5%)	
Yes	174 (4.53%)	180 (9.51%)	
Metabolic diagnosis:			0.289
No	3657 (95.2%)	1813 (95.8%)	
Yes	186 (4.84%)	79 (4.18%)	

Table 1 – *continued from previous page*

	Alive N=3843	Dead N=1892	p-value
Gastrointestinal diagnosis:			<0.001
No	3282 (85.4%)	1511 (79.9%)	
Yes	561 (14.6%)	381 (20.1%)	
Hematologic diagnosis:			<0.001
No	3669 (95.5%)	1712 (90.5%)	
Yes	174 (4.53%)	180 (9.51%)	
Metabolic diagnosis:			0.289
No	3657 (95.2%)	1813 (95.8%)	
Yes	186 (4.84%)	79 (4.18%)	
Neurological diagnosis:			<0.001
No	3443 (89.6%)	1599 (84.5%)	
Yes	400 (10.4%)	293 (15.5%)	
Orthopedic diagnosis:			0.438
No	3837 (99.8%)	1891 (99.9%)	
Yes	6 (0.16%)	1 (0.05%)	
Renal diagnosis:			0.122
No	3658 (95.2%)	1782 (94.2%)	
Yes	185 (4.81%)	110 (5.81%)	
Respiratory diagnosis:			0.002
No	2374 (61.8%)	1248 (66.0%)	
Yes	1469 (38.2%)	644 (34.0%)	
Sepsis diagnosis:			<0.001
No	3201 (83.3%)	1503 (79.4%)	
Yes	642 (16.7%)	389 (20.6%)	
Trauma diagnosis:			0.168
No	3803 (99.0%)	1880 (99.4%)	
Yes	40 (1.04%)	12 (0.63%)	
Definite Myocardial Infarction	0.04 (0.19)	0.03 (0.17)	0.055
Cancer:			<0.001
No	3064 (79.7%)	1315 (69.5%)	
Yes	567 (14.8%)	405 (21.4%)	
Metastatic	212 (5.52%)	172 (9.09%)	
Acute MI and CVD	0.19 (0.40)	0.14 (0.35)	<0.001
Congestive Heart Failure	0.20 (0.40)	0.14 (0.35)	<0.001
Chronic Pulmonary Disease and etc.	0.20 (0.40)	0.16 (0.37)	<0.001
Dementia and etc.	0.09 (0.29)	0.12 (0.32)	0.002

Table 1 – *continued from previous page*

	Alive N=3843	Dead N=1892	p-value
Upper GI Bleeding	0.03 (0.16)	0.04 (0.20)	0.008
Immunosupperssion and etc.	0.27 (0.44)	0.27 (0.44)	0.802
Cirrhosis, Hepatic Failure	0.06 (0.23)	0.10 (0.30)	<0.001
Solid Tumor and etc.	0.20 (0.40)	0.29 (0.46)	<0.001
Psychiatric History and etc.	0.08 (0.26)	0.05 (0.22)	<0.001
Chronic Renal Disease and etc.	0.04 (0.20)	0.05 (0.21)	0.602
Transfer(>24Hs) from Another Hospital	0.12 (0.32)	0.11 (0.31)	0.457
APACHE III score ignoring Coma, day 1	51.4 (18.5)	61.2 (21.1)	<0.001
DASI, day 1	20.7 (5.72)	20.0 (4.35)	<0.001
Support Coma score, day 1	16.1 (26.0)	30.9 (35.4)	<0.001
SUPPORT: Prob(surviving 2 months)	0.65 (0.17)	0.48 (0.20)	<0.001
Albumin	3.13 (0.81)	3.01 (0.72)	<0.001
Bilirubin	1.70 (3.17)	3.41 (6.90)	<0.001
Serum Creatinine	2.05 (2.10)	2.29 (1.94)	<0.001
Hematocrit	32.3 (8.59)	30.9 (7.80)	<0.001
PaCo2	39.6 (13.4)	37.1 (12.6)	<0.001
PaO2/(.01 FIO2)	226 (112)	215 (119)	0.001
Serum PH	7.39 (0.10)	7.38 (0.12)	0.021
Serum Potassium	4.06 (1.01)	4.09 (1.07)	0.345
Serum Sodium	137 (7.52)	137 (7.92)	0.220
White blood cell count	15.4 (11.0)	16.2 (13.5)	0.032

Scientific Question

What is the causal effect of RHC during the first 24 hours of care in the intensive care unit (ICU) on the patients' mortality in 30 days?

Causal Model

- Endogenous variables: $X \leftarrow (W_1,\ W_2,\ W_3,\ W_4,\ A,\ Y)$
- Exogenous variables: $U \leftarrow (U_{W_1},\ U_{W_2},\ U_{W_3},\ U_{W_4},\ U_A,\ U_Y)$

$$U = (U_{W_1},\ U_{W_2},\ U_{W_3},\ U_{W_4},\ U_A,\ U_Y) \sim P^*$$

- Structural equations:

$$W1 \leftarrow f_{W_1}(U_{W_1})$$

$$W2 \leftarrow f_{W_2}(W1,\ U_{W_2})$$

$$W3 \leftarrow f_{W_3}(W1,\ W2,\ U_{W_3})$$

$$W4 \leftarrow f_{W_4}(W1,\ W2,\ W3,\ U_{W_4})$$

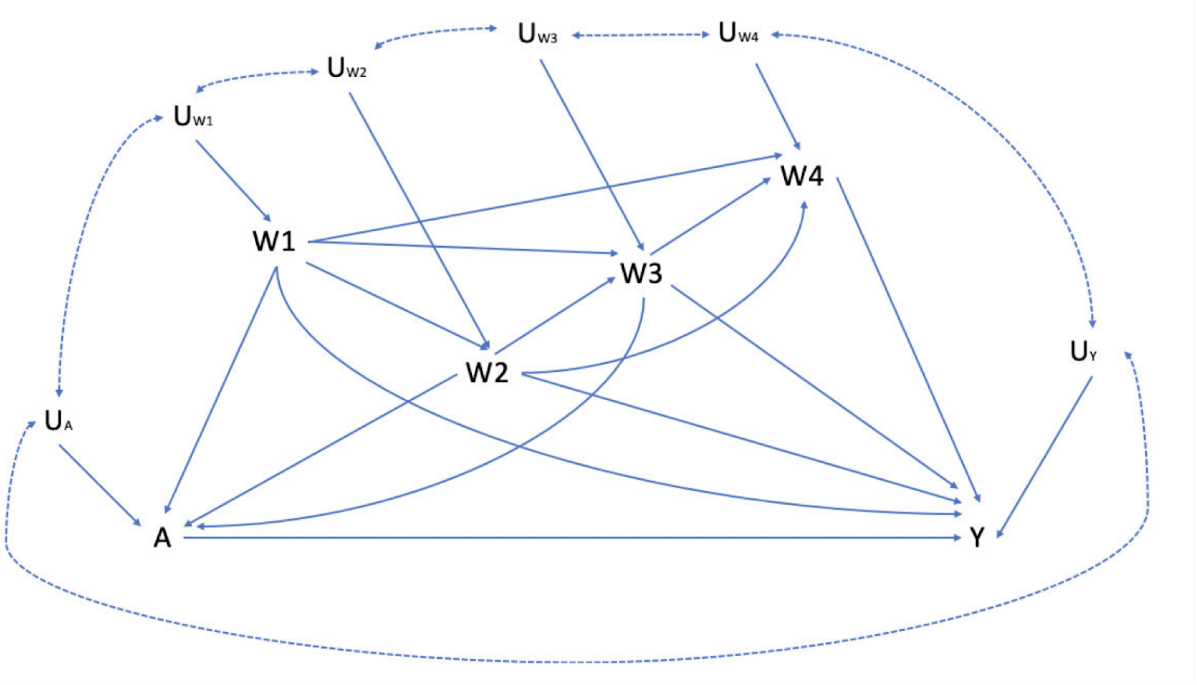
$$A \leftarrow f_A(W1,\ W2,\ W3,\ U_{W_A})$$

$$Y \leftarrow f_Y(W1,\ W2,\ W3, W4, A,\ U_{W_Y})$$

- No independent assumptions
- Exclusion restriction: $W4$ on A

For endogenous variables, there are 4 covariates: from $W1$ to $W4$, with treatment (A, RHC during the first 24 hours of care in the intensive care unit) and outcome (Y, mortality in 30 days). When it comes to the exogenous variables, there are 6 and there is no assumption placed on the distribution P^*. First, $W1$ includes Socio-demographics information of each patient such as age, sex, education in years, income level, insurance type, and race. Second, $W2$ covers presentation at admission to ICU units, diagnosis on day 1, comorbid illness, and transfer status. Based on $W2$, $W3$ can be calculated such as APACHE III score, DASI (Duke Activity Status Index prior to admission), support coma score based on Glasgow on day 1, SUPPORT model estimate of Prob(surviving 2 months). Thus, $W3$ demonstrates day 1 summary measures of presentation and severity of illness. Lastly, $W4$ summarizes the day 1 Lab results. One thing we have to keep in mind is that the results come out later than 24 hours since admission. Therefore, $W4$ covariate does not influence on the decision making of whether to apply RHC or not. This is the reason that there is an exclusion restriction: $W4$ on A. This relationship was visualized in [Figure 1].

[Figure 1] Directed Acyclic Graph of Causal Model



Causal Parameter

$A = \{0,\ 1\}$, with or without RHC treatment during the first 24 hours of care in ICU units

Link Between Structural Causal Model (SCM) and Observed Data

$$O = (W_1,\ W_2,\ W_3,\ W_4,\ A,\ Y) \sim P$$

The statistical model $\mathcal{M}$ is non-parametric, assumes observed data is compatible with the causal structural model.

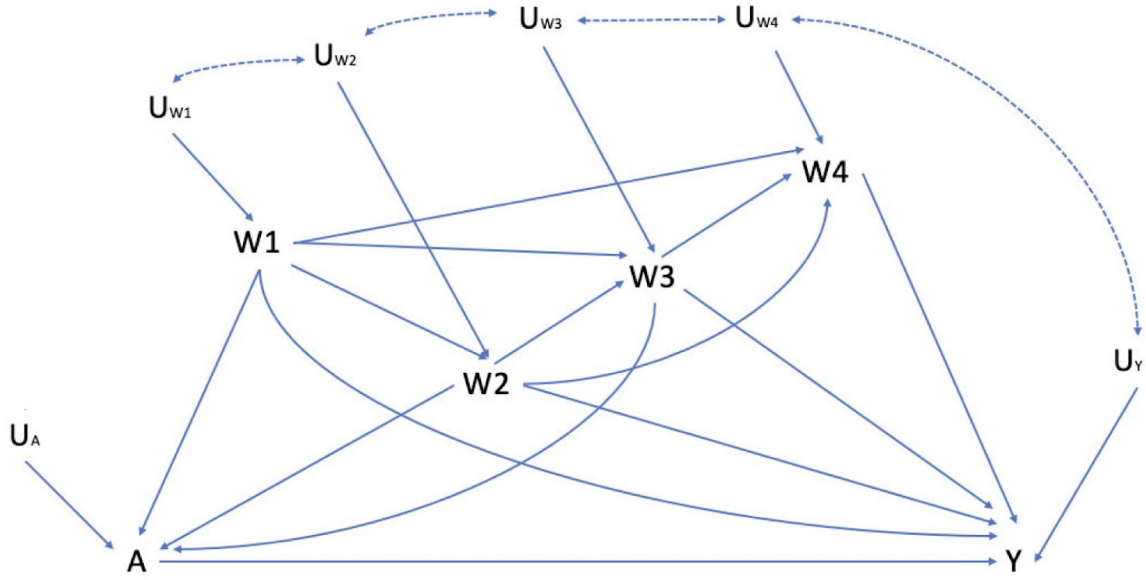
Identifiability and Positivity

Further assumptions are required to make the causal structural model identifiable:

$$A \perp Y \mid W1,\ W2,\ W3$$

Many possible scenarios that hold the backdoor criteria sufficient but not minimal for the conditional independence of $A \perp Y$. One of the scenarios meeting identifiability is no unmeasured link between U_A and U_Y; no unmeasured link between U_A and U_{W_1}, where $W = \{W1,\ W2,\ W3\}$. Under the scenario, since it is about ICU units, we could assume that all possible measurements and tests were performed in order to determine whether to apply the RHC treatment. Thus, we could say no unmeasured link between U_A and U_{W_1}. This scenario was graphically summarized in [Figure 2].

[Figure 2] One of DAGs that Satisfies Identifiability



Identifiability also requires the positivity assumption to hold:

$$\min_{a \in A} P_o(A = a | W = w) > 0 \text{ for } P(W = w) > 0, \quad W = \{W1, W2, W3\}$$

The positivity assumption was evaluated. However, the empirical probability of treatment is impossible to check due to the high-dimensional setting of the dataset. For this reason, further analysis assumes that the positivity assumption holds.

Statistical Model and Estimand

We are interested in estimating the causal effect of right heart catheterization (RHC) during the first 24 hours of care in the intensive care unit (ICU) on the patients' mortality in 30 days. Multiple statistical estimands have been utilized in order to estimate the causal effect. Below are the estimands used in the analysis:

- Unadjusted Average Treatment Effect:

$$\theta^*_{ATE} = \mathrm{E}^*(Y_1) - \mathrm{E}^*(Y_0) = \mathrm{P}^*(Y_1 = 1) - \mathrm{P}^*(Y_0 = 1)$$

- G-computation:

$$\theta^*_{G-comp} = E[E(Y|A = 1, W = w) - E(Y|A = 0, W = w)], W = \{W1, W2, W3\}$$

- IPTW:

$$\theta^*_{IPTW} = E\left(\frac{I(A = 1)}{\hat{P}(A = 1, W)}Y\right) - E\left(\frac{I(A = 0)}{\hat{P}(A = 0, W)}Y\right)$$

- AIPTW:

$$\theta^*_{\mathrm{APTW}} = E\left[\frac{I(A = 1)}{\widehat{P}(A = 1, W)}[Y - E(Y|A = 1, W)] + E(Y|A = 1, W)\right] - E\left[\frac{I(A = 0)}{\hat{P}(A = 0, W)}[Y - E(Y|A = 0, W)] + E(Y|A = 0, W)\right]$$

- TMLE:

$$\theta *_{TMLE} = E[\tilde{E}(Y|A = 1, W = w) - \tilde{E}(Y|A = 0, W = w)]$$

Method

Data adaptation method was used to face the high dimensional setting of the dataset. **`SuperLearner`** R package was used to implement the data adaption method to

estimate the propensity score $E[P(A = a \mid W = w)]$, where $W = \{W1,\ W2,\ W3\}$ and the counterfactual treatment effect $E[P(Y|A = a,\ W = w)]$, where $W = \{W1,\ W2,\ W3\}$. Random forest, glm, elastic net, LASSO, and gradient boosting were included in the **`SuperLearner`** algorithm library. 5-fold cross-validation was used to determine each algorithm's performance; 5-fold cross-validation was used to identify each algorithm's coefficient in the ensemble estimator. Each of the estimand listed above was computed, and bootstrapping mean and variance were calculated across the 10 random samplings.

Result

Estimate of Propensity Score

[Table 2] 5-fold Cross-Validation Result of Each Algorithm in **`SuperLearner`** library

Algorithm	Average	Standard Error
SuperLearner	0.1786340	0.002320295
Discrete SuperLearner	0.1791010	0.002296465
SuperLearner GLM	0.1851796	0.002663659
SuperLearner Step AIC	0.1889587	0.002638942
SuperLearner GLMnet	0.1848636	0.002522264
SuperLearner GBM	**0.1791010**	**0.002296465**

It appears that gradient boosting estimate performs slightly better than the other discrete learner, and is comparable to the ensemble learner. Gradient boosting alone, it was chosen to estimate the propensity score for simplicity.

Estimate of Counterfactual Treatment Effect

[Table 3] 5-fold Cross-Validation Result of Each Algorithm in `SuperLearner` library

Algorithm	Average
SuperLearner	0.1777546
Discrete SuperLearner	0.1771588
SuperLearner GLM	0.1797952
SuperLearner Step AIC	0.1828585
SuperLearner GLMnet	0.1792970
SuperLearner GBM	**0.1750503**

Gradient boosting alone, it was chosen to estimate the propensity score for simplicity, which is the same reason with the above.

Estimate of Causal Effect

The point estimate of the causal effect of G-computation, IPTW, AIPW, and TMLE was compared to the unadjusted crude average treatment effect (ATE).

[Table 3] Point Estimate of Causal Effect Estimator

Method	Average
Unadjusted ATE	0.0743
G-computation	0.0346
IPTW	0.0283
AIPW	0.0429
TMLE	0.0345

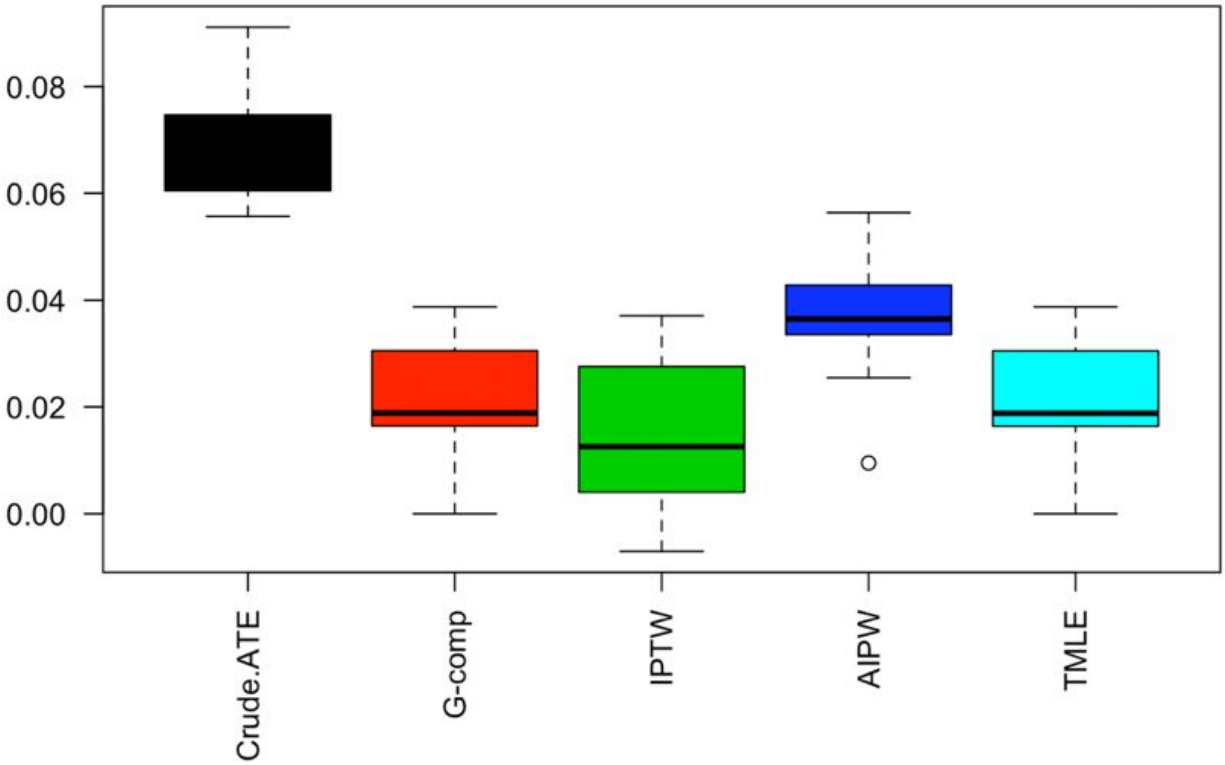
Estimators' Mean and SD form Bootstrap sampling

The causal effect of the abovementioned estimators was compared by ten bootstrap sampling. The mean and standard deviation were summarized in [Table 4], and the distribution was visualized in [Figure 4].

[Table 4] Mean and SD of Causal Estimators From 10 Bootstrapping

Method	Mean	SD
Crude ATE	0.0672	0.0114
G-computation	0.0206	0.0119
IPTW	0.0151	0.0141
AIPW	0.0362	0.0125
TMLE	0.0206	0.0119

[Figure 4] Boxplot of Causal Estimators from 10 Bootstrapping



Discussion

The study is observational due to ethics; therefore, the covariates are not randomization. Also, due to the high-dimensional setting of the dataset, the complete conditional probability of treatment given adjusted covariates is not possible to check. No guarantee that the positivity assumption was met.

The treatment selection is biased, considering the treatment is more likely to be performed on critically ill patients that are highly associated with mortality, which is the outcome of interest. The crude ATE is higher than the adjusted estimators also implied the existence of confounding factors within the covariates in the dataset.

32 out of 40 covariates are nominal with few levels. The performance of glm with all-covariates did not differ much from the algorithms with a variable selection like LASSO or gbm. The confounding effect might not be adequately captured by binary or nominal factors.

Though the estimated distribution of propensity score was evaluated, no truncation or weight stabilization was applied to the causal effect analysis, consider that the weight factor does not have extreme value, and the study dataset includes over 5000 observation.

IPTW is more sensitive to the near-zero treatment probabilities and gives larger SD of counterfactual effect estimation in bootstrap sampling. AIPW also use inverse propensity score weighting but is less sensitive to violation of piratical positivity.

Appendix

W1: Socio-demographics

Variable	Definition	Values
age	Age in years	18.04 to 101.85
sex	Sex	Female (44%) or Male (56%)
edu	Years of Education	0 to 30
income	Income Category	4 categories: Under $11k (56%), $11-$25k (20%), $25-$50k (16%), > $50k (8%)
ninsclas	Insurance Category	6 categories: Private (30%), Private & Medicare (22%), Medicare (25%), Medicare & Medicaid (7%), Medicaid (11%), No insurance (6%)
race	Self-Reported Race	3 categories: white (78%), black (16%), other (6%)

W2: Presentation at Admission and Diagnosis, Comorbid Illness and Transfer Status

Variable	Definition	Values
cat1	Primary disease category	9 categories: ARF, CHF, Cirrhosis, Colon Cancer, Coma, COPD, Lung Cancer, Multi-Organ System Failure (MOSF) w/Malignancy, MOSF w/Sepsis
dnr1	Do Not Resuscitate status, day 1	No (89%) or Yes (11%)
wtkilo1	Weight in kg, day 1	0 to 244, with 515 subjects having a value of 0
hrt1	Heart rate, day 1	0 to 250, with 159 subjects having a value of 0
meanbp1	Mean Blood Pressure, day 1	0 to 259, with 80 subjects having a value of 0
resp1	Respiratory rate, day 1	0 to 100, with 136 subjects having a value of 0
temp1	Temperature, C, day 1	27 to 43
card	Cardiovascular diagnosis	No or Yes, occurs in 34% of subjects
gastr	Gastrointestinal diagnosis	No or Yes, occurs in 16% of subjects
hema	Hematologic diagnosis	No or Yes, occurs in 6% of subjects
meta	Metabolic diagnosis	No or Yes, occurs in 5% of subjects
neuro	Neurological diagnosis	No or Yes, occurs in 12% of subjects
ortho	Orthopedic diagnosis	No or Yes, occurs in only 7 subjects
renal	Renal diagnosis	No or Yes, occurs in 5% of subjects
resp	Respiratory diagnosis	No or Yes, occurs in 37% of subjects
seps	Sepsis diagnosis	No or Yes, occurs in 18% of subjects
trauma	Trauma diagnosis	No or Yes, occurs in 1% of subjects
amihx	Definite Myocardial Infarction	0 = No, 1 =Yes, occurs in 3% of subjects
ca	Cancer	Metastatic (7%), Yes (17%) or No (76%)
cardiohx	Acute MI, Peripheral Vascular Disease, Severe Cardiovascular Symptoms (NYHA-Class III), Very Severe Cardiovascular Symptoms (NYHA- IV)	0 = No, 1 =Yes, Yes in 18% of subjects
chfhx	Congestive Heart Failure	0 = No, 1 =Yes, Yes in 18% of subjects

`chrpulhx`	Chronic Pulmonary Disease, Severe or Very Severe Pulmonary Disease	0 = No, 1 =Yes, Yes in 19% of subjects
`dementhx`	Dementia, Stroke or Cerebral Infarct, Parkinson's Disease	0 = No, 1 =Yes, Yes in 10% of subjects
`gibledhx`	Upper GI Bleeding	0 = No, 1 =Yes, Yes in 3% of subjects
`immunhx`	Immunosupperssion, Organ Transplant, HIV Positivity, Diabetes Mellitus Without End Organ Damage, Diabetes Mellitus With End Organ Damage, Connective Tissue Disease	0 = No, 1 =Yes, occurs in 27% of subjects
`liverhx`	Cirrhosis, Hepatic Failure	0 = No, 1 =Yes, occurs in 7% of subjects
`malighx`	Solid Tumor, Metastatic Disease, Chronic Leukemia/Myeloma, Acute Leukemia, Lymphoma	0 = No, 1 =Yes, Yes for 23% of subjects. `malighx` = Yes for all `ca` = Metastatic, plus 96% of those with `ca` = Yes, and 0% of those with `ca` = No.
`psychhx`	Psychiatric History, Active Psychosis or Severe Depression	0 = No, 1 =Yes, Yes in 7% of subjects
`renalhx`	Chronic Renal Disease, Chronic Hemodialysis or Peritoneal Dialysis	0 = No, 1 =Yes, Yes in 4% of subjects
`transhx`	Transfer (> 24 Hours) from Another Hospital	0 = No, 1 =Yes, Yes in 12% of subjects

W3: Day 1 Summary Measures / Severity

Variable	Definition	Values
`aps1`	APACHE III score ignoring Coma, day 1	3 to 147
`das2d3pc`	DASI (Duke Activity Status Index prior to admission)	11 to 33
`scoma1`	Support Coma score based on Glasgow, day 1	0 to 100, with 54% of subjects at 0, all others at 9, 26, 37, 41, 44, 55, 61, 89, 94 or 100
`surv2md1`	SUPPORT model estimate of Prob(surviving 2 months)	0.000 to 0.962

W4: Day 1 Lab Result

Variable	Definition	Values
`alb1`	Albumin	0.3 to 29
`bili1`	Bilirubin	0.1 to 58.2
`crea1`	Serum Creatinine	0.1 to 25.1
`hema1`	Hematocrit	2 to 66.2
`paco21`	PaCo2	1 to 156
`pafi1`	PaO2(.01 FIO2)	11.6 to 937.5
`ph1`	Serum PH (arterial)	6.6 to 7.8
`pot1`	Serum Potassium	1.1 to 11.9
`sod1`	Serum Sodium	101 to 178
`urin1`	Urine output	0 to 9000, with 60 subjects at 0 **3,028 missing values**
`wblc1`	White blood cell count	0 to 192, with 4 subjects having a value of 0

* **`urin1`** was excluded from the analysis due to many missings.

References

Connors et al. (1996): The effectiveness of RHC in the initial care of critically ill patients. J American Medical Association 276:889-897