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# The Association Between Indwelling Arterial Catheters and Mortality in Hemodynamically Stable Patients With Respiratory Failure: A Propensity Score Analysis

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## ABSTRACT

**Background:** Indwelling arterial catheters (IAC) are used extensively in the Intensive Care Unit (ICU) for hemodynamic monitoring and for blood gas analysis. IAC use also poses potentially serious risks, including blood stream infections and vascular complications. The purpose of this study was to assess whether IAC use was associated with mortality in mechanically ventilated patients who do not require vasopressor support.

**Methods:** This study utilized the Multiparameter Intelligent Monitoring in Intensive Care II database, consisting of over 24,000 patients admitted to the Beth Israel Deaconess Medical Center ICU between 2001 – 2008. Patients requiring mechanical ventilation who did not require vasopressors or have a diagnosis of sepsis were identified, and the primary outcome was 28-day mortality. A model based on patient demographics, co-morbidities, vital signs, and laboratory results was developed to estimate the propensity for IAC placement. Patients were then propensity-matched, and McNemar's test was used to evaluate the association of IAC with 28-day mortality.

**Results:** We identified 1,776 mechanically ventilated patients that met inclusion criteria. There were no differences in the covariates included in the final propensity model between the IAC and non-IAC propensity-matched groups. For the matched cohort, there was no difference in 28-day mortality between the IAC group and the non-IAC group (14.7% vs 15.2%, OR 0.96, 95% CI [0.62, 1.47]).

**Conclusions:** In hemodynamically stable mechanically ventilated patients, the presence of an IAC is not associated with a difference in 28-day mortality. Validation in other datasets, as well as further analyses in other subgroups is warranted.

**ABBREVIATIONS LIST**

IAC = Indwelling arterial catheter

ICD-9-CM = International Classification of Diseases, 9th revision, Clinical Modification

ICU = Intensive care unit

IQR = Interquartile Range

LOS = Length-of-stay

MIMIC-II = Multiparameter Intelligent Monitoring in Intensive Care – II

ROC = Receiver operating characteristic

SOFA = Sequential Organ Failure Assessment score

PAC = Pulmonary arterial catheter

## INTRODUCTION

Indwelling arterial catheters (IAC) are used in the Intensive Care Unit (ICU) setting for continuous hemodynamic monitoring and for arterial blood sampling for blood gas analysis. IAC use in the ICU setting is widespread, occurring in approximately 30% of all ICU patients, with relatively stable IAC use over time.[1-3]

Despite widespread IAC use, there are rare but potentially serious complications that may arise. IAC-associated blood stream infections have been reported at a rate that, while not to the level of central venous catheters, is significantly higher than peripheral venous access. A systematic review of the risk of blood stream infections associated with intravascular catheters reports a pooled point estimate of 1.6 per 1,000 device days (95% CI 1.2, 2.3) for IAC compared with 0.5 (95% CI 0.2, 0.7) for peripheral venous access, and 2.7 (95% CI 2.6, 2.9) for central venous catheters.[4] Additionally, vascular complications associated with IAC use are more common than previously thought, including thrombosis, ischemia, hematoma, bleeding, and pseudoaneurysm.[5] The presence of IAC may promote an increased frequency of blood draws and laboratory testing, including arterial blood gas sampling.[6,7]

In the context of increased IAC-associated utilization and complications, there are scant outcomes data to support their widespread use. The purpose of this study was to examine the association between IAC use and outcomes in a large cohort of hemodynamically stable intensive care patients with respiratory failure undergoing mechanical ventilation.

## MATERIALS AND METHODS

### Study Population

We conducted a longitudinal, single center, retrospective cohort study of patients from the Multi Parameter Intelligent Monitoring of Intensive Care (MIMIC-II) database, which includes patients admitted between 2001- 2008. The database contains data from 24,581 ICU patients and includes physiologic information from bedside monitors and hospital information systems in the adult ICUs at Beth Israel Deaconess Medical Center, a tertiary care university academic medical center located in Boston, Massachusetts.[8] The data in MIMIC-II has been previously de-identified, and the Institutional Review Boards of the Massachusetts Institute of Technology (No. 0403000206) and Beth Israel Deaconess Medical Center (2001-P-001699/14) both approved the use of the database for research.

The MIMIC-II database was queried to identify adult patients requiring mechanical ventilation within the first 24 hours of medical or surgical ICU admission and lasting for at least 24 hours. The presence of an IAC was defined as placement of an invasive arterial catheter at any point in time after initiation of mechanical ventilation. Patients were excluded if they had a diagnosis of sepsis based on the Angus criteria[9] or required vasopressors while in the ICU, as well if IAC placement was performed prior to endotracheal intubation and initiation of mechanical ventilation (including pre-ICU admission IAC placement). As the majority of patients in the cardiac surgery recovery unit had an IAC placed prior to ICU arrival, all patients from the cardiac surgery ICU were also excluded from this analysis. Additionally, to ensure the independence of data, only the first ICU admission was included in patients that had multiple ICU admissions.

Co-incident diseases were obtained based on International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). The Sequential Organ Failure Assessment score (SOFA) was obtained at the time of ICU admission, and laboratory values immediately preceding onset of mechanical ventilation were used.

Outcome Measures:

The primary outcome was 28-day mortality. Secondary outcomes included ICU and hospital length-of-stay (LOS), duration of mechanical ventilation, and mean number of arterial and venous blood gas measurements performed per day while admitted to the ICU.

Statistical Analysis

A propensity score model was created to match baseline patient characteristics. 29 pre-IAC placement features including patient demographics, co-morbidities, vital signs, and pre-intervention laboratory results were selected from 53 available candidate variables (those without significant missing data) to estimate propensity for IAC insertion using a genetic algorithm (See Appendix).[10] Patients with or without IAC placement were then matched based on the estimated propensity scores using one-to-one matching without replacement with a caliper of 0.01. To ensure the robustness of the propensity score model and to avoid over-fitting, the goodness-of-fit of the prediction model was evaluated based on the average area under receiver operating characteristic (ROC) curve using 10-fold cross-validation, and the predictive model was also evaluated with the Hosmer–Lemeshow test.

The success of the propensity score model was evaluated by assessment of the differences in baseline covariates between IAC and non-IAC groups. As continuous variables were not normally distributed, median values and Interquartile Range (IQR) were used to summarize distributions. The Fisher's exact test and Wilcoxon rank-sum test were applied to statistically assess the differences in categorical and continuous variables between the unmatched IAC and non-IAC groups. Measures of association for baseline covariates in the propensity-matched cohorts were performed using either McNemar's test for categorical variables or Wilcoxon Signed Rank Test for continuous variables. The distributions of the propensity score before and after matching were also compared to further assess the degree of balance.

In univariate analyses, a McNemar's test was performed for binary outcomes, and paired t-tests for continuous outcomes. As mortality is a competing risk for ICU LOS, total LOS, and duration of mechanical ventilation, we used the cumulative incidence function to estimate the probability of the secondary outcome over 28 days while allowing for the possibility of alternative outcomes (e.g. death) to occur.[11]

Sensitivity Analyses

Sensitivity analyses were performed to evaluate the effects of varying both the inclusion criteria of time to mechanical ventilation (to include all patients undergoing endotracheal intubation at any point during their ICU course) and the caliper level for propensity matching on the association between IAC placement and 28-day mortality. 10 different caliper levels between 0.01 – 0.1 at 0.01 increments were used to match the positive and negative controls. We also performed a sensitivity analysis utilizing

propensity score weights to create an alternative propensity score model for IAC placement. This method optimizes post-weighting balance of covariates between groups, and a weighted regression model including any imbalanced covariates between the matched groups was estimated for 28-day mortality (see appendix).

## RESULTS

### Propensity Score Matching

Of the 24,581 MIMIC-II admissions reviewed, 24,443 patients remained after eliminating multiple admissions. A total of 1,776 patients met inclusion criteria (Figure 1), of which 44.6% had an IAC. Figure 2 shows the distribution of the propensity score of the IAC and the non-IAC groups before and after matching. The propensity score model for IAC placement yielded 0.79 for the area under ROC curve (over 10-fold cross-validation) and a p-value of 0.83 for the Hosmer–Lemeshow test. After 1:1 matching, the propensity-matched sample consisted of 696 patients (348 patients with respiratory failure who underwent IAC placement matched to 348 patients with respiratory failure who do no have an IAC placed). In the matched cohort, the median age for the IAC and non-IAC groups were 54 (IQR 38-73) and 53 (IQR 35-72), respectively. There were no differences between the IAC and non-IAC propensity-matched groups for covariates included in the final propensity score model, including chronic co-morbidities and acute respiratory diagnoses such as acute respiratory distress syndrome and pneumonia (Table 1, eFigure 1).

### Primary & Secondary Outcomes

After propensity score matching, there was no difference in 28-day mortality in the IAC (14.7%) versus non-IAC (15.2%) groups (OR 0.96, 95% CI [0.62, 1.47]; Table 2). Patients with an IAC had a significantly lower likelihood for discharge from the ICU (sub-hazard ratio 0.72, p<0.0001, 95% CI [0.61, 0.86]) or from the hospital (sub-HR 0.71, p<0.0001, 95% CI [0.6, 0.84]) at 28 days. Likewise, IAC patients had a lower likelihood of successful ventilator removal (sub-HR 0.74, p<0.0001, 95% CI [0.63, 0.87]) at 28 days. When survivors were separately analyzed, ICU LOS, hospital LOS, and duration of mechanical ventilation were significantly shorter among non-IAC patients (Table 2). Patients with an IAC had a mean difference of 1.44 more blood gas measurements performed per day (p<0.0001).

Sensitivity Analyses

The study cohort only included patients who were intubated within 24 hours of admission to the ICU. We performed a sensitivity analysis that included all patients who were intubated regardless of timing. No significant difference in 28-day mortally between the IAC and non-IAC group (p=0.4) was observed in this expanded cohort. Figure 3 summarizes the results of the sensitivity analyses using various matching caliper levels. As shown in Part A, the odds ratios for IAC placement and 28-day mortality are around 1.0 for all caliper levels. As shown in part B, measures of association for all caliper levels did not reach statistical significance (p>0.05). Utilizing the propensity score weight methodology, there remained no difference in 28-day mortality between the IAC and non-IAC groups (see appendix).

## DISCUSSION

In this propensity-matched cohort analysis of hemodynamically stable mechanically ventilated patients, we report no association between the placement of an invasive arterial catheter and 28-day mortality. Placement of IAC was, however, associated with a longer duration of mechanical ventilation, ICU and hospital LOS, and an increased frequency of blood gas sampling after matching patients for propensity to receive an IAC.

There are several potential explanations for the lack of association between IAC use and mortality in our analysis. First, the blood gas data and hemodynamic measurements obtained from IAC do not provide valuable clinical data that lead to changes in management that translate into a measurable impact on mortality. Alternatively, the results of this analysis may be attributed to unmeasured confounding, which we attempted to account for by using a propensity-matched cohort. Our findings from the MIMIC-II database are consistent with a recent study using the Project IMPACT database, which reported no association between IAC and mortality in ICU patients.[12] Our findings support the need for replication in additional large critical care databases, as well as future randomized controlled trials to investigate causation between IAC and patient outcomes.

The care of critically ill patients is an excellent case study in the adoption of technological advancement within healthcare. An example of this is the use of pulmonary arterial catheters (PAC) in critically ill patients, which was a widely accepted and used monitoring device before 13 subsequent randomized clinical trials and repeated meta-analyses demonstrated no improvement in patient outcomes[13,14] led to subsequent declines in PAC utilization over time.[15,16] Despite lessons learned, IAC use remains

common, and in recent years the development and utilization of other invasive and non-invasive modalities of hemodynamic monitoring has increased to include arterial waveform analysis, bedside echocardiography, esophageal Doppler, non-invasive bioimpedance/bioreactance, all with limited to no demonstrated benefit in patient outcomes. RCTs to investigate causal relationships between these monitoring devices and outcomes within specific patient subsets and clinical contexts are warranted, although there are often cost and logistical challenges to performing RCTs in the ICU. Research using highly granular databases such as MIMIC-II should be explored to identify sub-populations of critically ill patients that may benefit from specific technology application, thus allowing for more focused RCTs and more parsimonious application of technology.

Additionally, the MIMIC-II database contains comprehensive electronic health record data throughout the hospital course. Our analysis leverages the availability of time-stamped vital signs, laboratory results, and interventions to build a propensity score model by including predictors and confounders available at the time the clinical decision was made. Such granularity is important in creating propensity score models at the time when the decisions are made, especially in a highly dynamic setting such as the ICU. The granularity of these data are also particularly useful for decision analysis, evaluation of information gain, personalized dosage calculation,[17] or comparative effectiveness studies,[18] which have been traditionally performed using low-resolution data.

There are several limitations, however, that should be noted. First, as this is a single-center study from an academic tertiary care center, our findings may not be generalizable to other institutions. Residual confounding may also mar our findings, although we attempted to account for this through propensity matching. Potential

unmeasured confounders not accounted for in this analysis include relevant past medical history such as prior episodes of respiratory failure or prolonged mechanical ventilation, as well as treating physician(s). This raises the possibility that there may be negative confounding that contributed to our findings of no association between IAC placement and mortality. Additionally, the potential for immortal time bias and indication bias is present, as in all observational studies. We attempted to minimize interaction or effect modification by limiting our primary analysis to patients admitted to the ICU with acute respiratory failure without hemodynamic compromise requiring vasopressor support or concomitant sepsis, which are alternative reasons IAC placement may be considered. By limiting our study sample to a single indication for IAC placement, we are also attempting to optimize our propensity score model for assessment of IAC placement and 28-day mortality. There will be different relationships between covariates, IAC placement, and 28-day mortality based on indication for IAC placement, which will have effects on bias, variance, and mean squared error of the estimated exposure effect.[19] Of note, we plan on performing subsequent analyses in MIMIC-II and larger EHR-derived datasets for other ICU sub-groups with different indications for IAC placement. We are unable to report potential adverse events associated with IAC placement and use, including catheter-associated bloods stream infections or vascular complications, as these were not consistently captured in MIMIC-II. Finally, while our findings do not support an association between IAC use and mortality, only randomized controlled trials can establish a causal relationship.

## CONCLUSIONS

In this single center, retrospective study of hemodynamically stable patients requiring mechanical ventilation, the placement of invasive arterial catheters was not associated with a change in mortality as compared to propensity-matched patients without invasive arterial catheters. Invasive arterial catheters were associated with an increased ICU length-of-stay, total length-of-stay, duration of mechanical ventilation, and increased blood gas measurements.

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### Author Contributions:

LAC was the principal investigator and is the guarantor of this study; he takes full responsibility for the integrity of the submission as a whole, from inception to published article, including the data and analysis.

Conception and Design: DJH, LAC, MF
Analysis, data collection, and interpretation: DJH, MF, RK, HZ, KPC, LAC
Drafting Manuscript: DJH, MF, RK, HZ, KPC, LAC

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Table 1. Baseline covariates between IAC and non-IAC groups in unmatched cohorts and propensity-matched cohorts

| | Entire Cohort (1776) | | | Matched Cohort (696) | | |
|---|---|---|---|---|---|---|
| **Variables** | **Non-IAC (n=984)** | **IAC (n=792)** | **p-value** | **Non-IAC (n=348)** | **IAC (n=348)** | **p-value** |
| Age (year) | 51 (35-72) | 56 (40-73) | 0.009 | 53 (35-72) | 54 (38-73) | 0.8 |
| Female | 344 (43.5%) | 406 (41.3%) | 0.36 | 205 (58.9%) | 192 (55.2%) | 0.6 |
| SOFA | 5 (4-6) | 6 (5-8) | <0.0001 | 5 (4-7) | 6 (4-7) | 0.5 |
| **Service Unit** | | | <0.0001 | | | 0.3 |
| MICU | 504 (63.6%) | 290 (29.5%) | | 184 (52.9%) | 192 (55.2%) | |
| SICU | 288 (26.4%) | 694 (70.5) | | 164 (47.1%) | 156 (44.8%) | |
| **Co-incident Diseases** | | | | | | |
| Chronic obstructive pulmonary disease | 81 (10.23%) | 76 (7.72%) | 0.07 | 32 (9.2%) | 39 (11.2%) | 0.8 |
| Respiratory disease (non-COPD)[1] | 278 (35.1%) | 287 (29.2%) | 0.008 | 121 (34.7%) | 125 (35.9%) | 0.5 |
| Pneumonia | 147 (18.6%) | 152 (15.5%) | 0.005 | 67 (20%) | 68 (20.3%) | 0.7 |
| Congestive heart failure | 97 (12.5%) | 116 (11.8%) | 0.7 | 44 (12.6%) | 36 (10.3%) | 0.6 |
| Atrial fibrillation | 82 (10.4%) | 125 (12.7%) | 0.1 | 36 (10.3%) | 32 (9.2%) | 1 |
| Chronic kidney | 28 (3.5%) | 32 (3.3%) | 0.8 | 13 (3.8%) | 10 (2.9%) | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| disease | | | | | | |
| Chronic liver disease | 28 (4.8%) | 61 (6.2%) | 0.2 | 14 (4%) | 18 (5.2%) | 0.7 |
| Coronary artery disease | 51 (6.4%) | 72 (7.32%) | 0.5 | 23 (6.6%) | 21 (6%) | 0.2 |
| Stroke | 70 (8.8%) | 152 (15.5%) | 0.0001 | 32 (9.2%) | 33 (9.5%) | 0.9 |
| Malignancy | 92 (11.6%) | 164 (16.7%) | 0.003 | 44 (12.6%) | 51 (14.7%) | 0.4 |
| | | | | | | |
| **Laboratory Tests** | | | | | | |
| WBC | 10.6 (7.8-14.3) | 11.8 (8.5-15.9) | <0.0001 | 10.7 (8-14.8) | 11.5 (8.4-14.7) | 0.8 |
| Hemoglobin | 13 (11.3-14.4) | 12.6 (11-14.1) | 0.003 | 12.8 (11.2 -14.2) | 12.7 (11-14.1) | 0.8 |
| Platelet | 246 (190-304) | 237 (177-294) | 0.01 | 238 (184-303) | 238 (186-289) | 0.8 |
| Sodium | 140 (138-143) | 140 (137-142) | 0.007 | 140 (138-143) | 140 (137-142) | 0.6 |
| Potassium | 4 (3.6-4.5) | 4 (3.7-4.4) | 0.77 | 4 (3.6-4.5) | 4 (3.7-4.4) | 0.9 |
| Bicarbonate | 24 (22-27) | 24 (21-27) | 0.05 | 24 (22-27) | 24 (21-27) | 0.3 |
| Chloride | 104 (100-107) | 104 (101-108) | 0.0003 | 104 (100-107) | 104 (100-107) | 0.3 |
| BUN | 15 (11-21) | 16 (12-22) | 0.02 | 15 (11-22) | 16 (12-22) | 0.7 |
| Creatinine | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) | 0.6 | 0.9 (0.7-1.2) | 0.9 (0.7-1.1) | 0.6 |
| $PO_2$ | 206 (96-375) | 200 (108-337) | 0.5 | 180 (104-340) | 187 (106-300) | 0.8 |
| $PCO_2$ | 42 (37-50) | 41 (36-48) | 0.02 | 41.5 (37-47) | 40 (35-46.5) | 0.6 |
| | | | | | | |
| DNR at Admission | 65 (8.2%) | 39 (4%) | <0.0001 | 20 (5.8%) | 12 (3.5%) | 0.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Change in code status during ICU admission[2] | 41 (5.2%) | 95 (9.7%) | <0.0001 | 35 (10.4%) | 34 (10.1%) | 0.9 |

1 ICD-9-CM code 518*, which includes acute respiratory distress syndrome (ARDS).

2 Defined as code status change to Do Not Resuscitate or Comfort Measures Only

Table 2: Primary and secondary outcomes for propensity-matched IAC and non-IAC groups

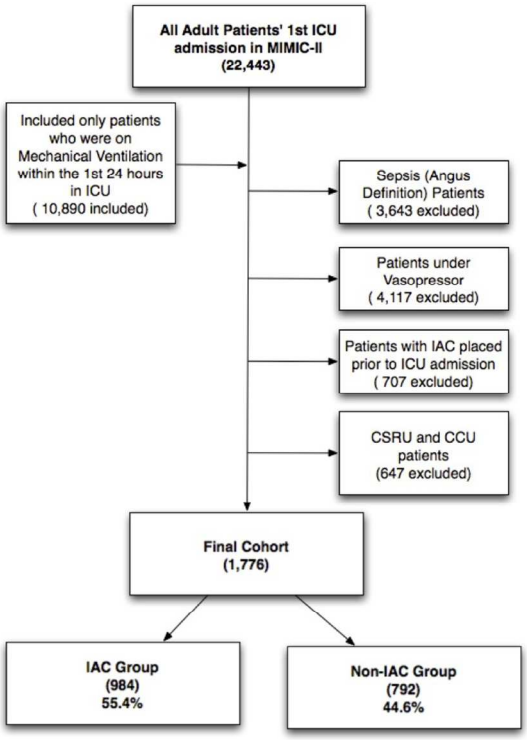
| **Primary Outcome** | **Non-IAC** | **IAC** | **p-value** | **Odds Ratio (95% CI)** |
|---|---|---|---|---|
| 28-day mortality | 15.20% | 14.70% | 0.83 | 0.96 (0.62, 1.47) |
| | | | | |
| **Secondary Outcomes** | **Non-IAC** | **IAC** | **p-value** | **Mean Difference (95% CI)** |
| ICU LOS (survivors) | 2.2 (1.4)[1] | 3.7 (3.1) | <0.0001 | 1.65 (1.24, 2.07) |
| Hospital LOS (survivors) | 5.7 (4.8) | 9.4 (7.5) | <0.0001 | 3.47 (2.34, 4.59) |
| Mechanical ventilation time (survivors) | 1 (1) | 2.1 (2.6) | <0.0001 | 1.1 (0.76, 1.42) |
| Blood gas measurements (per 24 hours) | 1 (0.8) | 2.4 (1.4) | <0.0001 | 1.44 (1.27, 1.62) |

1 All continuous variables reported as mean with standard deviation

Figure 1. Flowchart of patient inclusion.

Figure 2. Propensity score distribution plot comparing IAC and non-IAC groups before and after matching.

Figure 3. Sensitivity analyses of various matching caliper levels.

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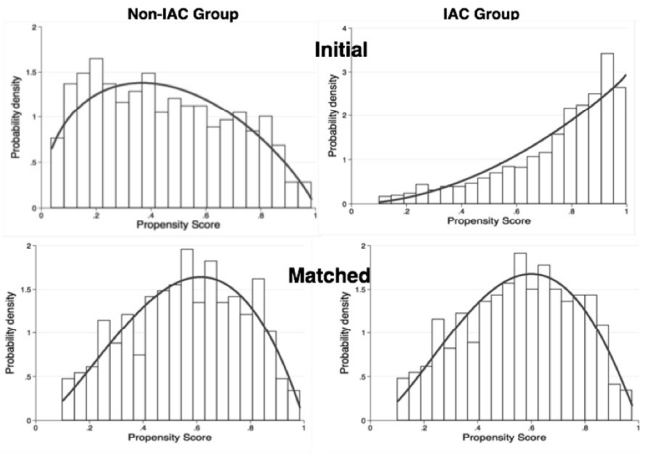


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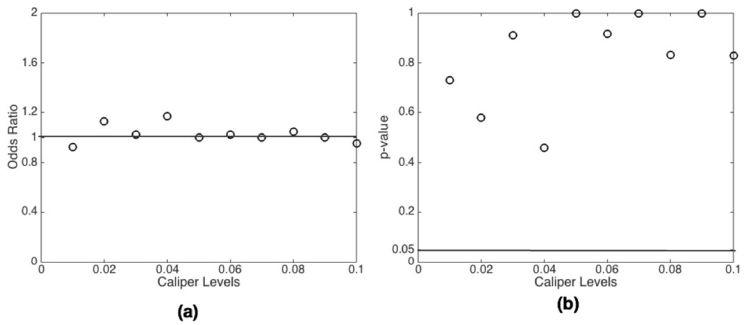


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**Appendix: The Association Between Indwelling Arterial Catheters and Mortality in Hemodynamically Stable Patients With Respiratory Failure: A Propensity Score Analysis**

## A. Construction of Propensity Score Model

In this study, a propensity score model was developed to estimate likelihood of getting an IAC placement. To construct the model, we first identified an initial set of 53 covariates that potentially influence the decision for IAC placement. We then employed a Genetic Algorithm (GA) based method to shortlist a subset of covariates that optimize the performance of the propensity score model.

### A.1 Covariates Identification based on Clinical Knowledge

The initial set of 53 covariates is as follows.

Demographic: Admission age, gender, race, daytime admission (7am to 7pm), day of admission and service unit (medical or surgical ICU), and admission Sequential Organ Failure Assessment (SOFA) score.

Co-morbidities (ICD-9): Congestive Heart Failure 398.91 428.0 428.1 428.20 428.21 428.22 428.23 428.30 428.31 428.32 428.33 428.40 428.41 428.42, 428, 428.2, 428.3, 428.4, 428.43, 428.9; Atrial fibrillation 427.3*; Chronic renal disease 585.*; Chronic liver disease 571*; Chronic Obstructive Pulmonary Disease 490-496; Coronary Artery Disease 414.*; Stroke 440-434; Malignancy 140-239; non-COPD lung disease (including acute respiratory distress syndrome) 518*, and Pneumonia 482*.

Vital sign/Hemodynamic variables: Data include weight, mean arterial pressure (MAP), temperature, heart rate, oxygen saturation ($SpO_2$) and central venous pressure (CVP).

Laboratory test results: White blood cell (WBC) count, hemoglobin, platelet count, sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, magnesium, phosphate, aspartate Aminotransferase (AST), alanine Aminotransferase (ALT), lactic acid dehydrogenase (LDH), total bilirubin, alkaline phosphatase, albumin, troponin T, creatinine kinase, brain natriuretic peptide (BNP), lactate, pH, central venous oxygen saturation ($ScVO_2$), arterial partial pressure of oxygen ($PaO_2$) and arterial partial pressure of carbon dioxide ($PCO_2$).

Sedative medication use, including midazolam, fentanyl, and propofol.

### A.2 Genetic Algorithm-based Covariate Selection and Model Optimization

A GA-based algorithm was employed to select the subset of covariates that optimizes the performance of the propensity score model.

The genetic algorithm (GA) is a heuristic algorithm inspired by a natural “survival of the fittest” selection process [1]. The GA is commonly adopted for optimization and variable selection problems, and has a wide application in computational biology, engineering, economics, manufacturing, physicals, and mathematics. This method starts with a population of candidate solutions to an optimization problem, and then gradually evolves towards better solutions through an iterative process. Through the iterative process, the “fitness” of all candidate solutions or variable subsets is evaluated based on optimization criteria, and “fitter” solutions will be selected to remain and contribute to the next generation of solutions. The selected solutions based on the fitness function then randomly “mutate” (change a variable) or “breed” (exchange smaller subsets of variables with one another) to generate a new set of candidate solutions for the next iteration. The evolution/optimization process stops when the maximum numbers of iterations or best possible solution has been achieved.

In our study, the GA R package was used to implement the optimization method [2]. We allowed the GA algorithm to evolve over 3000 iterations with 50 candidate solution sets. The GA-based optimization was guided by the following criteria:

- Maximize the average area under the receiver operating characteristic (ROC) curves of the model over a 10-fold cross validation.
- Select a minimum set of covariates for the optimum performance
- Covariates with large amount of missing data are less favorable

### A.3 Final Propensity Score Model

The final propensity score model consists of 29 covariates as shown in eTable 1. Covariates used in the propensity model building process in pre- and post- matched IAC and non-IAC groups are displayed in eTable 2 and eFigure 1. eFigure 2 demonstrates that, over a 10-fold cross validation, the average area under the ROC curve of the final model is 0.81. This indicates a stable performance of the final model.

### eTable 1. Final Propensity Score Model

| | **Odds Ratio** | **[95% Conf.** | **Interval]** | **p-value** |
|---|---|---|---|---|
| **Age** | 0.997 | 0.988 | 1.005 | 0.426 |
| **Weight** | 1.001 | 0.995 | 1.007 | 0.761 |
| **SOFA** | 1.591 | 1.469 | 1.723 | 0.000 |
| **MICU (ref) vs CSRU** | 7.216 | 5.310 | 9.805 | < 0.0001 |
| **ICU Admission Day (Reference – Sunday)** | | | | |
| Monday | 1.504 | 0.923 | 2.450 | 0.101 |
| Tuesday | 1.183 | 0.737 | 1.899 | 0.486 |
| Wednesday | 1.575 | 0.970 | 2.558 | 0.066 |
| Thursday | 1.492 | 0.922 | 2.415 | 0.104 |
| Friday | 1.904 | 1.151 | 3.148 | 0.012 |
| Saturday | 1.128 | 0.710 | 1.793 | 0.611 |
| **Co-incident Diseases** | | | | |
| Congestive Heart Failure | 1.780 | 1.091 | 2.904 | 0.021 |
| Atrial fibrillation | 0.978 | 0.623 | 1.535 | 0.922 |
| Chronic Renal Disease | 1.537 | 0.703 | 3.360 | 0.281 |
| End-stage Liver Disease | 0.360 | 0.192 | 0.676 | 0.001 |
| Chronic obstructive pulmonary disease | 0.784 | 0.488 | 1.259 | 0.314 |
| Coronary artery disease | 0.958 | 0.544 | 1.688 | 0.883 |
| Stroke | 1.382 | 0.873 | 2.189 | 0.168 |
| Malignancy | 1.160 | 0.785 | 1.713 | 0.456 |

| | | | | |
|---|---|---|---|---|
| Respiratory Failure (non-COPD)[1] | 1.016 | 0.746 | 1.385 | 0.918 |
| **Vital Signs** | | | | |
| Mean Arterial Pressure | 1.007 | 1.000 | 1.015 | 0.054 |
| Heart Rate | 1.006 | 0.999 | 1.014 | 0.098 |
| $SpO_2$ | 0.974 | 0.947 | 1.001 | 0.063 |
| Temperature | 1.000 | 0.972 | 1.029 | 0.988 |
| **Laboratory Tests** | | | | |
| White Blood Cell | 1.032 | 1.009 | 1.056 | 0.006 |
| Hemoglobin | 0.954 | 0.888 | 1.024 | 0.191 |
| Platelet | 1.000 | 0.998 | 1.001 | 0.726 |
| Sodium | 0.930 | 0.892 | 0.969 | 0.001 |
| Potassium | 1.022 | 0.863 | 1.211 | 0.799 |
| Bicarbonate | 1.023 | 0.990 | 1.058 | 0.177 |
| Chloride | 1.055 | 1.018 | 1.093 | 0.003 |
| BUN | 1.006 | 0.993 | 1.019 | 0.376 |
| Creatinine | 0.763 | 0.637 | 0.915 | 0.003 |
| $PO_2$ | 1.001 | 1.000 | 1.002 | 0.134 |
| $PCO_2$ | 0.996 | 0.984 | 1.007 | 0.462 |

1 ICD-9-CM code 518*, which includes acute respiratory distress syndrome (ARDS)

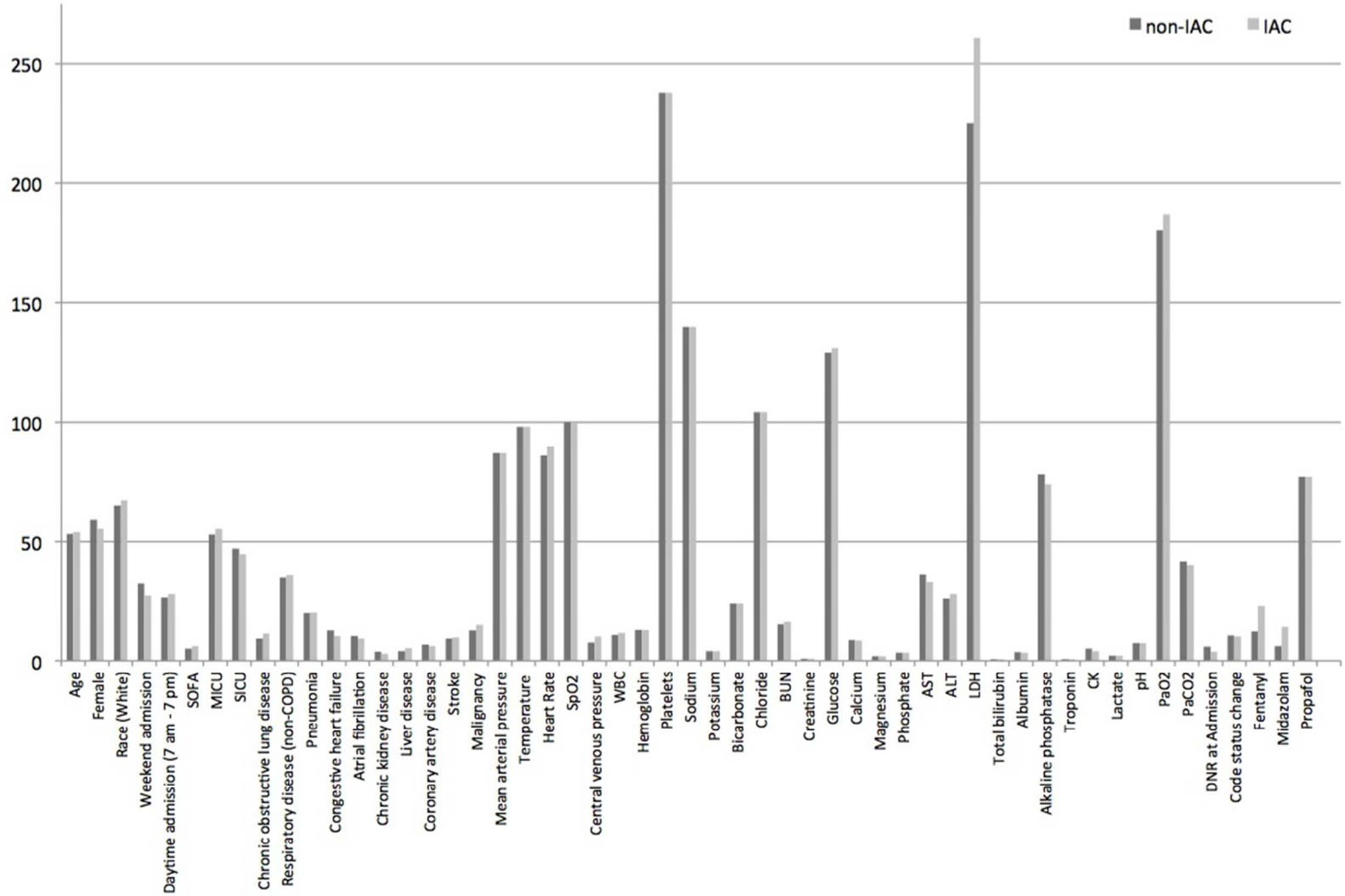
eTable 2. Candidate covariates considered in propensity model building

| Variables | Entire Cohort (1776) | | | Matched Cohort (696) | | |
|---|---|---|---|---|---|---|
| | Non-IAC (n=984) | IAC (n=792) | p-value | Non-IAC (n=348) | IAC (n=348) | p-value |
| Age (year) | 51 (35-72) | 56 (40-73) | 0.009 | 53 (35-72) | 54 (38-73) | 0.8 |
| Female | 344 (43.5%) | 406 (41.3%) | 0.36 | 205 (58.9%) | 192 (55.2%) | 0.6 |
| White race | 558 (70.5%) | 690 (70.1%) | 0.9 | 225 (64.7%) | 234 (67.3%) | 0.5 |
| Daytime admission (7am-7pm) | 240 (30.3%) | 287 (29.2%) | 0.6 | 92 (26.4%) | 97 (27.9%) | 0.7 |
| Weekend admission | 252 (31.8%) | 256 (26%) | 0.008 | 112 (32.2%) | 95 (27.3%) | 0.2 |
| SOFA Score | 5 (4-6) | 6 (5-8) | <0.0001 | 5 (4-7) | 6 (4-7) | 0.5 |
| **Service Unit** | | | | | | |
| MICU | 504 (63.6%) | 290 (29.5%) | <0.0001 | 184 (52.9%) | 192 (55.2%) | 0.3 |
| SICU | 288 (26.4%) | 694 (70.5) | | 164 (47.1%) | 156 (44.8%) | |
| **Co-incident Diseases** | | | | | | |
| Congestive heart failure | 97 (12.5%) | 116 (11.8%) | 0.7 | 44 (12.6%) | 36 (10.3%) | 0.6 |
| Atrial fibrillation | 82 (10.4%) | 125 (12.7%) | 0.1 | 36 (10.3%) | 32 (9.2%) | 1.0 |
| Chronic kidney disease | 28 (3.5%) | 32 (3.3%) | 0.8 | 13 (3.8%) | 10 (2.9%) | 1.0 |
| Liver Disease | 28 (4.8%) | 61 (6.2%) | 0.2 | 14 (4%) | 18 (5.2%) | 0.7 |
| Chronic obstructive pulmonary disease | 81 (10.23%) | 76 (7.72%) | 0.07 | 32 (9.2%) | 39 (11.2%) | 0.8 |
| Coronary artery disease | 51 (6.4%) | 72 (7.32%) | 0.5 | 23 (6.6%) | 21 (6%) | 0.2 |
| Stroke | 70 (8.8%) | 152 (15.5%) | 0.0001 | 32 (9.2%) | 33 (9.5%) | 0.9 |
| Malignancy | 92 (11.6%) | 164 (16.7%) | 0.003 | 44 (12.6%) | 51 (14.7%) | 0.4 |
| Respiratory disease (non-COPD) | 278 (35.1%) | 287 (29.2%) | 0.008 | 121 (34.7%) | 125 (35.9%) | 0.5 |
| Pneumonia | 147 (18.6%) | 152 (15.5%) | 0.005 | 67 (20%) | 68 (20.3%) | 0.9 |
| **Vital Signs** | | | | | | |
| Weight (Kg) | 76 (65-90) | 78 (67-90) | 0.08 | 76 (76-90) | 78 (65-90) | 0.4 |
| Mean arterial pressure (mmHg) | 86 (77-98) | 88 (76-100) | 0.2 | 87 (77-98) | 87 (75-98) | 0.8 |
| Temperature (F) | 98 (97-99) | 98 (97-99) | 0.6 | 98 (97-99) | 98 (97-99) | 0.6 |
| Heart Rate | 87 (75-100) | 88 (74-99) | 0.5 | 86 (74-100) | 90 (77-99) | 0.3 |
| $S_pO_2$ (%) | 100 (98-100) | 100 (98-100) | 0.5 | 100 (98-100) | 100 (99-100) | 0.6 |
| Central venous | 8 (6-11) | 10 (6-13) | 0.4 | 7.5 (6-12) | 10 (6-13) | 0.1 |

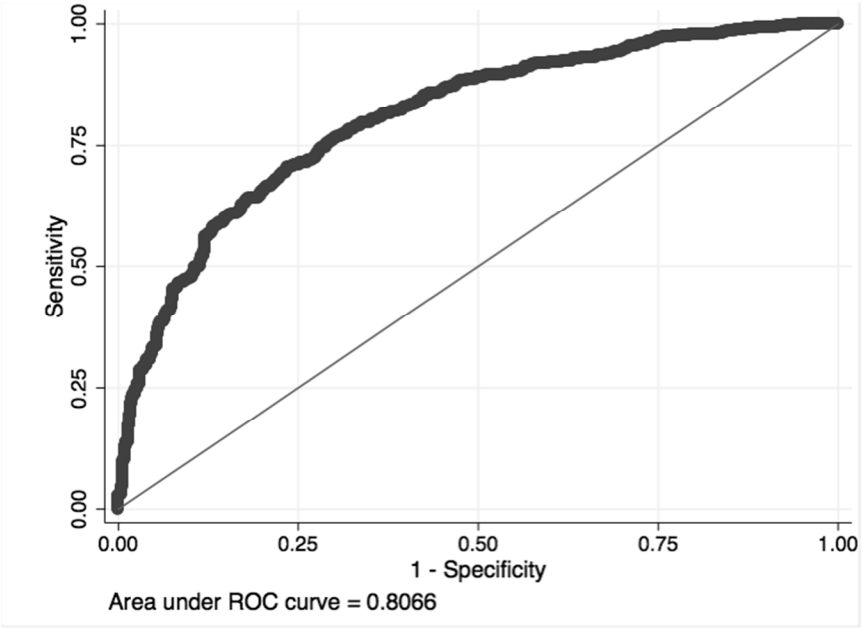
| | | | | | | |
|---|---|---|---|---|---|---|
| pressure (mmHg) | | | | | | |
| **Laboratory Tests** | | | | | | |
| White blood cell count (K/uL) | 10.6 (7.8-14.3) | 11.8 (8.5-15.9) | <0.0001 | 10.7 (8-14.8) | 11.5 (8.4-14.7) | 0.8 |
| Hemoglobin (g/dL) | 13 (11.3-14.4) | 12.6 (11-14.1) | 0.003 | 12.8 (11.2 - 14.2) | 12.7 (11-14.1) | 0.8 |
| Platelets (K/uL) | 246 (190-304) | 237 (177-294) | 0.01 | 238 (184-303) | 238 (186-289) | 0.8 |
| Sodium (mEq/L) | 140 (138-143) | 140 (137-142) | 0.007 | 140 (138-143) | 140 (137-142) | 0.6 |
| Potassium (mEq/L) | 4 (3.6-4.5) | 4 (3.7-4.4) | 0.77 | 4 (3.6-4.5) | 4 (3.7-4.4) | 0.9 |
| Bicarbonate (mEq/L) | 24 (22-27) | 24 (21-27) | 0.05 | 24 (22-27) | 24 (21-27) | 0.3 |
| Chloride (mEq/L) | 104 (100-107) | 104 (101-108) | 0.0003 | 104 (100-107) | 104 (100-107) | 0.3 |
| Blood urea nitrogen (mg/dL) | 15 (11-21) | 16 (12-22) | 0.02 | 15 (11-22) | 16 (12-22) | 0.7 |
| Creatinine (mg/dL) | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) | 0.6 | 0.9 (0.7-1.2) | 0.9 (0.7-1.1) | 0.6 |
| Glucose (mg/dL) | 126 (105-161) | 136 (111-171) | 0.0001 | 129 (107-157) | 131 (109-171) | 0.3 |
| Calcium (mg/dL) | 8.6 (8.1-9) | 8.4 (7.9-8.9) | 0.0001 | 8.5 (8-9) | 8.4 (7.9-8.9) | 0.3 |
| Magnesium (mg/dL) | 1.9 (1.7-2.1) | 1.8 (1.5-2) | <0.0001 | 1.8 (1.6-2) | 1.8 (1.6-2.1) | 0.8 |
| Phosphate (mg/dL) | 3.3 (2.7-4) | 3.4 (2.8-4.1) | 0.02 | 3.3 (2.7-4) | 3.4 (2.7-4.1) | 0.5 |
| Aspartate transaminase (IU/L) | 32 (22-56) | 38 (23-83) | 0.0008 | 36 (23-67) | 33 (21-67) | 0.05 |
| Alanine transaminase (IU/L) | 26 (16-45) | 29 (17-60) | 0.004 | 26 (17-48) | 28 (17-51) | 0.1 |
| Lactate dehydrogenase (IU/L) | 226 (187-297) | 268 (207-383) | <0.0001 | 225 (188-319) | 261 (199-377) | 0.9 |
| Total Bilirubin (mg/dL) | 0.5 (0.3-0.8) | 0.6 (0.4-1) | <0.0001 | 0.5 (0.3-1) | 0.6 (0.3-0.9) | 0.13 |
| Alkaline phosphatase (IU/L) | 78 (60-106) | 77 (58-103) | 0.8 | 78 (59-108) | 74 (57-99) | 0.2 |
| Albumin (g/dL) | 3.6 (3.2-4) | 3.3 (2.8-3.7) | <0.0001 | 3.6 (3.1-3.9) | 3.4 (2.9-3.8) | 0.1 |
| Troponin T (ng/mL) | 0.045 (0.02-0.11) | 0.05 (0.02-0.12) | 0.97 | 0.05 (0.03-0.15) | 0.04 (0.02-0.16) | 0.3 |
| Creatinine kinase (ng/mL) | 5 (3-8) | 5 (4-10) | 0.0007 | 5 (3-9) | 4 (3-8.5) | 0.7 |
| Brain natriuretic peptide (pg/mL) | 2269 (1076-6199) | 2636 (1230-4228) | 0.9 | --- | --- | --- |
| Lactate (mmol/L) | 2.1 (1.4-3) | 2 (1.4-3.2) | 0.7 | 2 (1.3-2.9) | 2.2 (1.5-3.4) | 0.2 |
| pH | 7.4 (7.3-7.4) | 7.4 (7.3-7.4) | 0.6 | 7.37 (7.32-7.43) | 7.37 (7.3-7.42) | 0.07 |
| $SvO_2$ | 70 (59-90) | 81 (76-84) | 0.6 | --- | --- | --- |
| $PaO_2$ (mmHg) | 206 (96-375) | 200 (108-337) | 0.5 | 180 (104-340) | 187 (106-300) | 0.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| $PaCO_2$ (mmHg) | 42 (37-50) | 41 (36-48) | 0.02 | 41.5 (37-47) | 40 (35-46.5) | 0.6 |
| **Sedative Medications Used** | 554 (70%) | 819 (83%) | <0.0001 | 269 (80%) | 279 (83%) | 0.3 |
| Fentanyl | 83 (11%) | 224 (23%) | <0.0001 | 43 (12%) | 79 (23%) | 0.002 |
| Midazolam | 55 (7%) | 95 (10%) | 0.05 | 22 (6%) | 48 (14%) | 0.001 |
| Propofol | 524 (66%) | 774 (79%) | <0.0001 | 259 (77%) | 259 (77%) | 1 |

* Insufficient number matched pairs for brain natriuretic peptide and SvO2 comparisons




eFigure 1. Baseline covariate distributional balance in propensity-matched cohorts




eFigure 2. Average ROC curve of the finalized Propensity Score Model over 10-fold cross-validation.

**A.4 Sensitivity Analyses – Propensity Score Weight Method**

We used propensity score weights (PSW) to do a weighted regression for outcome estimation [4, 5]. The PSW were generated by an algorithm that aimed at optimizing post-weighting balance of covariates between the treatment and the control group. Some covariates stayed imbalanced after weighting, and were adjusted for in the weighted regression model without further variable selection, thus providing a robust estimation for the outcome.

A machine learning-based generalized boosted model (GBM) was used for the estimation and evaluation of propensity scores and associated PSW. GBM fitted a piecewise constant model to predict a dichotomous outcome, i.e. the treatment assignment. The iterative fitting algorithm built a regression tree that provided increasing log likelihood for the data with increasing iteration. During the iterative process, the PSW generated after each iteration were evaluated by calculating the standardized bias across all covariates of the weighted data. An iteration number that minimized the mean standardized bias across all covariates, i.e. maximized the balancing of covariates between the treatment and the control group, was chosen for generating the final PSW.

**A.5 Sensitivity Analyses – Multivariate Logistic Regression**

Utilizing both the original GA-derived matched cohorts, as well as the PSW-derived matched cohorts, we then estimated logistic regression models for 28-day mortality including any imbalanced baseline covariates (including those not retained in final propensity score models). There was no significant differences in 28-day mortality between the IAC and non-IAC groups (eTable 2).

**eTable 3. Weighted logistic regression model for 28-day mortality**

| | OR | 95% Confidence Interval | p-value |
|---|---|---|---|
| GA Method | 0.93 | 0.61, 1.44 | 0.75 |
| PSW Method | 1.39 | 0.63, 3.06 | 0.41 |

* Reference group - Non-IAC

**eTable 4. Comparison of candidate covariates between matched and unmatched cohorts**

| | Non-IAC | | | IAC | | |
|---|---|---|---|---|---|---|
| **Variables** | **Matched (n=348)** | **Unmatched (n=636)** | **p-value** | **Matched (n=348)** | **Unmatched (n=444)** | **p-value** |
| Age (year) | 53 (35-72) | 49 (34-71) | 0.1 | 54 (38-73) | 58 (41-74) | 0.1 |
| Female | 205 (58.9%) | 256 (56.1%) | 0.8 | 192 (55.2%) | 394 (60.7%) | 0.1 |
| White race | 225 (64.7%) | 333 (72.8%) | 0.2 | 234 (67.3%) | 459 (70.7%) | 0.8 |
| Daytime admission (7am-7pm) | 92 (26.4%) | 148 (32.3%) | 0.1 | 97 (27.9%) | 190 (29.2%) | 0.9 |
| Weekend admission | 112 (32.2%) | 140 (30.6%) | 0.4 | 95 (27.3%) | 161 (24.8%) | 0.3 |
| SOFA Score | 5 (4-7) | 4 (3-5) | <0.0001 | 6 (4-7) | 7 (5-8) | <0.0001 |
| **Service Unit** | | | | | | |
| MICU | 184 (52.9%) | 328 (71.7%) | <0.0001 | 192 (55.2%) | 103 (15.9%) | <0.0001 |
| SICU | 164 (47.1%) | 129 (28.2%) | | 156 (44.8%) | 546 (84.1%) | |
| **Co-incident Diseases** | | | | | | |
| Congestive heart failure | 44 (12.6%) | 60 (13.1%) | 0.4 | 36 (10.3%) | 75 (11.6%) | 0.8 |
| Atrial fibrillation | 36 (10.3%) | 45 (9.9%) | 0.6 | 32 (9.2%) | 88 (13.6%) | 0.3 |
| Chronic renal disease | 13 (3.8%) | 18 (4%) | 0.6 | 10 (2.9%) | 22 (3.4%) | 0.9 |
| Liver Disease | 14 (4%) | 20 (4.4%) | 0.6 | 18 (5.2%) | 45 (6.9%) | 0.2 |
| Chronic obstructive pulmonary disease | 32 (9.2%) | 43 (9.4%) | 0.4 | 39 (11.2%) | 40 (6.2%) | 0.02 |
| Coronary artery disease | 23 (6.6%) | 27 (6%) | 0.6 | 21 (6%) | 56 (8.6%) | 0.03 |
| Stroke | 32 (9.2%) | 37 (8.1%) | 0.4 | 33 (9.5%) | 118 (18,2%) | 0.001 |
| Malignancy | 44 (12.6%) | 46 (10.1%) | 0.1 | 51 (14.7%) | 125 (19.3%) | 0.0002 |
| Respiratory disease (non- | 121 (34.7%) | 157 (34.4%) | 0.7 | 125 (35.9%) | 158 (24.4%) | <0.0001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| COPD) | | | | | | |
| Pneumonia | 67 (20%) | 89 (17.5%) | 0.4 | 68 (20.3%) | 84 (12.9%) | 0.003 |
| **Vital Signs** | | | | | | |
| Weight (Kg) | 75 (65-90) | 76 (65-89) | 0.9 | 78 (65-90) | 78 (67-90) | 0.7 |
| Mean arterial pressure (mmHg) | 87 (77-98) | 86 (77-97) | 0.99 | 87 (75-98) | 88 (76-101) | 0.2 |
| Temperature (F) | 98 (97-99) | 98 (97-99) | 0.2 | 98 (97-99) | 98 (97-99) | 0.3 |
| Heart Rate | 86 (74-100) | 88 (76-101) | 0.2 | 90 (77-99) | 86 (73-100) | 0.1 |
| $S_pO_2$ (%) | 100 (98-100) | 100 (98-100) | 0.1 | 100 (99-100) | 100 (99-100) | 0.3 |
| Central venous pressure (mmHg) | 7.5 (6-12) | 8.5 (6-11) | 0.7 | 10 (6-13) | 10 (6-13) | 0.5 |
| **Laboratory Tests** | | | | | | |
| White blood cell count (K/uL) | 10.7 (8-14.8) | 10.6 (7.6-14.1) | 0.3 | 11.5 (8.4-14.7) | 11.8 (8,7-16.4) | 0.2 |
| Hemoglobin (g/dL) | 12.8 (11.2 - 14.2) | 13 (11.4-14.4) | 0.1 | 12.7 (11-14.1) | 12.3 (10.8-13.9) | 0.02 |
| Platelets (K/uL) | 238 (184-303) | 247 (199-307) | 0.09 | 238 (186-289) | 228 (165-291) | 0.05 |
| Sodium (mEq/L) | 140 (138-143) | 140 (138-143) | 0.12 | 140 (137-142) | 139 (137-142) | 0.01 |
| Potassium (mEq/L) | 4 (3.6-4.5) | 4 (3.7-4.4) | 0.5 | 4 (3.7-4.4) | 4 (3.6-4.4) | 0.5 |
| Bicarbonate (mEq/L) | 24 (22-27) | 25 (22-28) | 0.02 | 24 (21-27) | 24 (21-27) | 0.22 |
| Chloride (mEq/L) | 104 (100-107) | 103 (100-106) | 0.1 | 104 (100-107) | 105 (101-108) | 0.02 |
| Blood urea nitrogen (mg/dL) | 15 (11-22) | 15 (11-21) | 0.5 | 16 (12-22) | 16 (12-22) | 0.6 |
| Creatinine (mg/dL) | 0.9 (0.7-1.2) | 0.9 (0.7-1.1) | 0.2 | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) | 0.2 |
| Glucose (mg/dL) | 129 (107-157) | 124 (104-164 | 0.4 | 131 (109-171) | 137 (112-171) | 0.2 |
| Calcium (mg/dL) | 8.5 (8-9) | 8.6 (8.1-9.1) | 0.1 | 8.4 (7.9-8.9) | 8.4 (7.8-8.9) | 0.4 |
| Magnesium (mg/dL) | 1.8 (1.6-2) | 1.9 (1.7-2.1) | 0.01 | 1.8 (1.6-2.1) | 1.7 (1.5-2) | 0.03 |
| Phosphate (mg/dL) | 3.3 (2.7-4) | 3.3 (2.7-3.9) | 0.8 | 3.4 (2.7-4.1) | 3.4 (2.9-4.1) | 0.3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Aspartate transaminase (IU/L) | 36 (23 -67) | 29 (21-51) | 0.01 | 33 (21-67) | 40 (24-92) | 0.02 |
| Alanine transaminase (IU/L) | 26 (17-48) | 34 (16-42) | 0.3 | 28 (17-51) | 30 (17-64) | 0.3 |
| Lactate dehydrogenase (IU/L) | 225 (188-319) | 230 (184-291) | 0.5 | 261 (199-377) | 270 (210-384) | 0.3 |
| Total Bilirubin (mg/dL) | 0.5 (0.3-1) | 0.5 (0.3-0.7) | 0.2 | 0.6 (0.3-0.9) | 0.7 (0.4-1.2) | 0.0007 |
| Alkaline phosphatase (IU/L) | 78 (59-108) | 78 (61-101) | 0.9 | 74 (57-99) | 78 (59-112) | 0.13 |
| Albumin (g/dL) | 3.6 (3.1-3.9) | 3.7 (3.2-4.1) | 0.05 | 3.4 (2.9-3.8) | 3.1 (2.8-3.7) | 0.01 |
| Troponin T (ng/mL) | 0.05 (0.03-0.15) | 0.04 (0.02-0.1) | 0.1 | 0.04 (0.02-0.16) | 0.05 (0.02-0.11) | 0.9 |
| Creatinine kinase (ng/mL) | 5 (3-9) | 5 (3-8) | 0.7 | 4 (3-8.5) | 5 (4-10) | 0.2 |
| Brain natriuretic peptide (pg/mL) | NA | NA | NA | NA | NA | NA |
| Lactate (mmol/L) | 2 (1.3-2.9) | 2.2 (1.5-3.1) | 0.1 | 2.2 (1.5-3.4) | 1.9 (1.4-3.1) | 0.1 |
| pH | 7.37 (7.32-7.43) | 7.4 (7.3-7.4) | 0.3 | 7.37 (7.3-7.42) | 7.38 (7.3-7.4) | 0.1 |
| $SvO_2$ | NA | NA | NA | NA | NA | NA |
| $PaO_2$ (mmHg) | 180 (104-340) | 174 (87-341) | 0.2 | 187 (106-300) | 205 (122-326) | 0.2 |
| $PaCO_2$ (mmHg) | 41.5 (37-47) | 42 (37-49) | 0.06 | 40 (35-46.5) | 40 (35-45) | 0.2 |
| **Sedative Medications Used** | 269 (80%) | 285 (63%) | <0.0001 | 279 (83%) | 540 (22%) | 1 |
| Fentanyl | 43 (12%) | 40 (9%) | 0.08 | 79 (23%) | 145 (22%) | 0.7 |
| Midazolam | 22 (6%) | 33 (7%) | 0.8 | 48 (14%) | 47 (7%) | 0.001 |
| Propofol | 259 (77%) | 265 (58%) | <0.0001 | 259 (77%) | 515 (79%) | 0.5 |

* Insufficient number of matched pairs for brain natriuretic peptide and SvO2 comparisons

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