**Supplementary Material**

**Title:**

Early Antibiotic Therapy in Sepsis Without Shock: A Multimethod Study of Heterogeneous Treatment Effects in ICU Patients

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## Supplementary Methods

## Supplementary Methods 1. Definitions and Operationalization of Clinical Variables

- **Definition of acute organ dysfunction**

Acute organ dysfunction was identified using data from the 24 hours prior to intensive care unit (ICU) admission through 48 hours after ICU admission. Baseline laboratory values were defined as the patient's best value recorded during the index hospitalization prior to this observation window (and imputed as normal if not measured during that timeframe):

- Acute renal dysfunction: creatinine >1.2 mg/dL and a 50% increase from baseline. Patients with pre-existing end-stage renal disease, as identified by diagnostic codes, were not eligible to have acute renal dysfunction.
- Acute liver dysfunction: total bilirubin >2.0 mg/dL and a 100% increase from baseline. Patients with prior mild or severe liver disease, as identified by diagnostic codes, were not eligible to have acute liver dysfunction.
- Acute hematologic dysfunction: platelet count <100 cells/μL and a 50% decrease from baseline.
- Abnormal lactate: >2.0 mmol/L.
- Acute lung/respiratory dysfunction: receipt of invasive mechanical ventilation.

- **Patient characteristics evaluated**

Comorbidities were defined using the Charlson Comorbidity Index (CCI) and were ascertained from ICD-9-CM/ICD-10-CM diagnosis codes in database recorded on or before the index hospital admission.

**Acute organ dysfunctions:**

- Lactate elevation
- Kidney
- Hematologic
- Liver
- Respiratory

**Chronic conditions:**

- Congestive heart failure
- Chronic pulmonary disease
- Renal disease
- Myocardial infarction
- Diabetes, uncomplicated
- Liver disease
- Peripheral vascular disease
- Malignant cancer
- Cerebrovascular disease
- Diabetes, complicated
- Metastatic cancer
- Paraplegia
- Peptic ulcer disease
- Rheumatic disease
- Dementia
- AIDS

- **Definition of acute cardiovascular dysfunction (shock)**

Acute cardiovascular dysfunction (shock) was operationally defined as receipt of any intravenous vasopressor therapy during the peri-sepsis observation period. This definition was aligned with that used in prior large observational analyses of heterogeneity of treatment effects of antibiotic timing in sepsis published in the American Journal of Respiratory and Critical Care Medicine, as well as with the U.S. Centers for Disease Control and Prevention Adult Sepsis Event framework, in which acute cardiovascular dysfunction is identified based on vasopressor use.

Vasopressor exposure was ascertained from medication administration records. Patients with any documented vasopressor administration within the peri-sepsis observation period (from 24 hours before to 48 hours after sepsis onset) were classified as having acute cardiovascular dysfunction and were excluded from the analytic cohort.

- **Definition of intravenous fluid volume**

Intravenous fluid volume was defined as the cumulative volume (mL) of intravenously administered fluids received during the 24 hours preceding sepsis onset. Sepsis onset was used as the analytic time zero.

Fluid administration data were extracted from the database inputevents table. Only intravenous fluids and blood products were included. Enteral, oral, dialysis-related, irrigation, and nutritional fluids were excluded based on order category and description fields.

For continuous infusions, fluid volume was calculated as infusion rate multiplied by the duration overlapping the −24-hour to 0-hour window relative to sepsis onset. For intermittent bolus administrations, the documented administered volume was included if the administration time occurred within the observation window.

All volumes were converted to milliliters and summed at the ICU stay level. Extreme values were truncated to minimize the influence of implausible recordings. Patients without documented intravenous fluid administration during the observation window were assigned a value of zero.

## Supplementary Methods 2. Variable Derivation for the Risk-Based Heterogeneity of Treatment Effect Model

- **Derivation of risk score for risk-based heterogeneity of treatment effect model.**

We developed an internal risk prediction model for 28-day mortality using cumulative logistic regression. The model was based on a preselected set of candidate predictors, all of which were collected within 24 hours before to 48 hours after sepsis diagnose. We chose the final variables by identifying the model with the lowest Bayesian Information Criterion (BIC) among all possible combinations of the following factors: age, gender, ethnicity, Acute Physiology Score III (APS III), Charlson comorbidity index (CCI), infection site, admission type, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, liver disease, chronic pulmonary disease, diabetes without complications, diabetes with complications, renal disease, nonmetastatic cancer, metastatic cancer, number of acute organ dysfunctions and acute organ dysfunction (respiratory, lactate elevation, kidney, hematologic, and liver).

## Supplementary Methods 3. Variable Derivation for the Effect-Based Heterogeneity of Treatment Effect Model

- **Derivation of effect-based heterogeneity of treatment effect model.**

To estimate heterogeneity of treatment effects at the individual level, we applied a causal forest approach. Candidate effect-modifying variables were prespecified based on clinical relevance and availability at the time of sepsis diagnosis. All variables were collected within 24 hours before to 48 hours after sepsis diagnosis.

The candidate effect-modifying variable set included age, gender, ethnicity, Acute Physiology Score III (APS III), Charlson comorbidity index (CCI), admission type, infection site, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes without complications, diabetes with complications, renal disease, nonmetastatic cancer, metastatic cancer, and acute organ dysfunction indicators, including respiratory dysfunction, lactate elevation, acute kidney dysfunction, acute hematologic dysfunction, and acute liver dysfunction.

This variable set was derived from the same candidate variable pool used for development of the risk-based mortality model but was specified to capture clinically meaningful effect modification rather than overall mortality risk. In particular, the number of acute organ dysfunctions was not included as a candidate effect modifier. These prespecified covariates were used as inputs to the causal forest to estimate individualized treatment effects.

## Supplementary Methods 4. Bayesian model implementation

Bayesian logistic and ordinal regression models were implemented using the rmsb package in R. Weakly informative priors were applied as normal priors centered at 0 on the log-odds scale for regression coefficients (Normal [0, 2.5]) to provide mild regularization and improve numerical stability. The model intercept was assigned a broader normal prior (Normal [0, 5]). Posterior summaries were obtained from full posterior distributions. Unless otherwise specified, rmsb default MCMC settings were used for sampling and convergence was assessed using standard diagnostics (trace plots and effective sample sizes).

# Supplementary Tables

## Table S1: Definitions and data sources of study variables

| | Supplementary information |
|---|---|
| Age | Provided in MIMIC-IV module “hosp” table “patients” |
| Male patients | Provided in MIMIC-IV module “hosp” table “patients” |
| Female patients | Provided in MIMIC-IV module “hosp” table “patients” |
| **Ethnicity** | Provided in MIMIC-IV module “hosp” table “admissions” |
| **Admission type** | Provided in MIMIC-IV module “hosp” table “admissions” |
| **Comorbidities** | Based on the International Classification of Diseases 9 and 10 codes |
| Congestive heart failure | Provided in MIMIC-IV module “derived” table “charlson” |
| Chronic pulmonary disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Myocardial infarction | Provided in MIMIC-IV module “derived” table “charlson” |
| Diabetes, uncomplicated | Provided in MIMIC-IV module “derived” table “charlson” |
| Peripheral vascular disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Renal disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Liver disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Malignant cancer | Provided in MIMIC-IV module “derived” table “charlson” |
| Cerebrovascular disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Diabetes, complicated | Provided in MIMIC-IV module “derived” table “charlson” |
| Metastatic cancer | Provided in MIMIC-IV module “derived” table “charlson” |
| Paraplegia | Provided in MIMIC-IV module “derived” table “charlson” |
| Peptic ulcer disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Rheumatic disease | Provided in MIMIC-IV module “derived” table “charlson” |
| Dementia | Provided in MIMIC-IV module “derived” table “charlson” |
| AIDS | Provided in MIMIC-IV module “derived” table “charlson” |
| CCI | Provided in MIMIC-IV module “derived” table “charlson” |
| SOFA score | Provided in MIMIC-IV module “derived” table “sofa” |
| APS III | Provided in MIMIC-IV module “derived” table “apsiii” |
| **Initial life support** | |
| Use of RRT | Provided in MIMIC-IV module “derived” table “rrt” |
| Intravenous Fluids | Provided in MIMIC-IV module “ICU” table “inputevents” |
| **Outcomes** | |
| 28-day mortality | Provided in MIMIC-IV module “hosp” table “patients” |
| Length of ICU stay | Provided in MIMIC-IV module “derived” table “icustay_detail” |
| Length of hospital stay | Provided in MIMIC-IV module “derived” table “icustay_detail” |

CCI: Charlson comorbidity index; SOFA: Sequential Organ Failure Assessment Score; APS III: Acute Physiology Score III; RRT: Renal replacement therapy; IMV: Invasive mechanical ventilation; ICU: Intensive care unit.

**Table S2 Additional Baseline characteristic of patients before and after overlap weighting**

| | Before weighting | | SMD | After weighting | | SMD |
|---|---|---|---|---|---|---|
| | Shorter Time (≤3h) (n=2891) | Longer Time (>3-12h) (n=5509) | | Shorter Time (≤3h) (n=4170) | Longer Time (>3-12h) (n=4230) | |
| Time-to-antibiotics, h, median (IQR) | 0.7 (0.0, 1.8) | 7.0 (5.2, 9.0) | 3.403 | 1.0 (0.0, 2.0) | 6.6(5.0, 8.8) | 3.172 |
| Female patients, n (%) | 1160 (40.1) | 2458 (44.6) | 0.091 | 1777 (42.6) | 1748 (41.3) | 0.026 |
| **Ethnicity, n (%)** | | | 0.227 | | | 0.054 |
| White | 1930 (66.8) | 3706 (67.3) | | 2806 (67.3) | 2782 (65.8) | |
| Black | 226 (7.8) | 741 (13.5) | | 423 (10.1) | 400 (9.5) | |
| Asian | 80 (2.8) | 166 (3.0) | | 122 (2.9) | 134 (3.2) | |
| Other | 655 (22.7) | 896 (16.3) | | 819 (19.6) | 914 (21.6) | |
| **Comorbidities, n (%)** | | | | | | |
| Congestive heart failure | 728 (25.2) | 1831 (33.2) | 0.178 | 1235 (29.6) | 1178 (27.9) | 0.039 |
| Diabetes, uncomplicated | 684 (23.7) | 1543 (28.0) | 0.099 | 1074 (25.8) | 1130 (26.7) | 0.022 |
| Renal disease | 584 (20.2) | 1577 (28.6) | 0.197 | 1000 (24.0) | 1015 (24.0) | 0.000 |
| Liver disease | 413 (14.3) | 901 (16.4) | 0.057 | 626 (15.0) | 671 (15.9) | 0.024 |
| Cerebrovascular disease | 372 (12.9) | 774 (14.0) | 0.035 | 565 (13.6) | 593 (14.0) | 0.014 |
| Nonmetastatic cancer | 293 (10.1) | 541 (9.8) | 0.010 | 392 (9.4) | 404 (9.6) | 0.005 |
| Diabetes, complicated | 233 (8.1) | 698 (12.7) | 0.152 | 405 (9.7) | 426 (10.1) | 0.012 |
| Peptic ulcer disease | 99 (3.4) | 171 (3.1) | 0.018 | 153 (3.7) | 160 (3.8) | 0.006 |
| Paraplegia | 108 (3.7) | 272 (4.9) | 0.059 | 169 (4.1) | 192 (4.5) | 0.024 |
| Rheumatic disease | 83 (2.9) | 223 (4.0) | 0.064 | 131 (3.1) | 138 (3.3) | 0.007 |
| Dementia | 74 (2.6) | 381 (6.9) | 0.206 | 177 (4.2) | 157 (3.7) | 0.027 |
| AIDS | 14 (0.5) | 69 (1.3) | 0.083 | 27 (0.7) | 26 (0.6) | 0.004 |
| **Number of acute organ dysfunctions** | | | | | | |
| 1 | 640 (22.1) | 1497 (27.2) | 0.117 | 1004 (24.1) | 1020 (24.1) | 0.001 |
| 2 | 811 (28.1) | 1662 (30.2) | 0.047 | 1199 (28.8) | 1237 (29.2) | 0.011 |
| 3+ | 859 (29.7) | 1490 (27.0) | 0.059 | 1180 (28.3) | 1167 (27.6) | 0.016 |
| **Initial life support** | | | | | | |
| RRT, n (%) | 0 (0.0) | 1 (0.0) | 0.019 | 0 (0.0) | 0 (0.0) | 0.000 |
| Intravenous Fluids, L, median (IQR) | 0.00 [0.00, 16.67] | 0.00 [0.00, 0.00] | 0.197 | 0.0 (0.0, 13.5) | 0.0 (0.0, 0.0) | 0.000 |

Definition of abbreviations: SMD =standardized mean difference; IQR = interquartile range; RRT renal replacement therapy.

**Table S3: Risk model for 28-day mortality used in risk-based heterogeneity of treatment effect analysis.**

| | Risk model coefficients | |
|---|---|---|
| **Model variable** | **Odds ratio (95% CI)** | **Log odds ratio** |
| Age, years | 1.01 (1.01–1.02) | 0.01 |
| **Infection site** | | |
| Lung | Reference | |
| Abdominal | 0.75 (0.57–0.97) | -0.29 |
| Genitourinary | 0.39 (0.24–0.60) | -0.93 |
| Other | 0.72 (0.47–1.07) | -0.33 |
| Unknown | 1.43 (1.18–1.73) | 0.36 |
| **Comorbidities** | | |
| Cerebrovascular Disease | 1.94 (1.56–2.39) | 0.66 |
| Diabetes, uncomplicated | 0.54 (0.44–0.66) | -0.61 |
| Diabetes, complicated | 0.44 (0.32–0.62) | -0.81 |
| Metastatic cancer | 2.86 (2.09–3.90) | 1.05 |
| **Acute organ dysfunction** | | |
| Lactate elevation | 2.46 (2.05–2.97) | 0.90 |
| Hematologic | 1.57 (1.26-1.95) | 0.45 |
| **Admission type** | | |
| Emergency | Reference | |
| Urgent | 1.25 (1.03–1.51) | 0.22 |
| Elective | 0.11 (0.05–0.23) | -2.18 |
| Other | 1.65 (1.25–2.17) | 0.50 |
| APS III | 1.03 (1.03–1.04) | 0.03 |
| CCI | 1.11 (1.06–1.16) | 0.11 |

APS III: Acute Physiology Score III; CCI: Charlson comorbidity index.

**Table S4: The clinical characteristics between patients in the training and validation cohorts.**

| | Training cohort (n=4148) | Validation cohort (n=4252) | P value |
|---|---|---|---|
| Age, years, median (IQR) | 66 (54, 78) | 65 (54, 77) | 0.194 |
| **Gender, n (%)** | | | 0.831 |
| Male patients | 2402 (57.9) | 2473 (58.2) | |
| Female patients | 1746 (42.1) | 1779 (41.8) | |
| Time-to-antibiotics, h, median (IQR) | 3.1 (0.9, 6.7) | 3.1 (1.0, 6.7) | 0.798 |
| **Ethnicity, n (%)** | | | 0.766 |
| White | 2776 (66.9) | 2812 (66.1) | |
| Black | 396 (9.5) | 427 (10.0) | |
| Asian | 130 (3.1) | 126 (3.0) | |
| Other | 846 (20.4) | 887 (20.9) | |
| **Admission type, n (%)** | | | 0.346 |
| Emergency | 2437 (58.8) | 2431 (57.2) | |
| Urgent | 1061 (25.6) | 1103 (25.9) | |
| Elective | 352 (8.5) | 401 (9.4) | |
| Other | 298 (7.2) | 317 (7.5) | |
| **Infection site, n (%)** | | | 0.292 |
| Lung | 1423 (34.3) | 1526 (35.9) | |
| Abdominal | 803 (19.4) | 806 (19.0) | |
| Genitourinary | 286 (6.9) | 300 (7.1) | |
| Other | 230 (5.5) | 258 (6.1) | |
| Unknown | 1406 (33.9) | 1362 (32.0) | |
| **Comorbidities, n (%)** | | | |
| Chronic pulmonary disease | 1193 (28.8) | 1172 (27.6) | 0.232 |
| Congestive heart failure | 1190 (28.7) | 1223 (28.8) | 0.959 |
| Diabetes, uncomplicated | 1104 (26.6) | 1100 (25.9) | 0.453 |
| Renal disease | 966 (23.3) | 1049 (24.7) | 0.145 |
| Liver disease | 630 (15.2) | 667 (15.7) | 0.547 |
| Myocardial infarction | 599 (14.4) | 614 (14.4) | 1.000 |
| Cerebrovascular disease | 560 (13.5) | 598 (14.1) | 0.473 |
| Peripheral vascular disease | 448 (10.8) | 477 (11.2) | 0.564 |
| Diabetes, complicated | 406 (9.8) | 425 (10.0) | 0.778 |
| Nonmetastatic cancer | 388 (9.4) | 408 (9.6) | 0.733 |
| Metastatic cancer | 314 (7.6) | 347 (8.2) | 0.334 |
| Paraplegia | 178 (4.3) | 183 (4.3) | 1.000 |
| Dementia | 168 (4.1) | 166 (3.9) | 0.774 |
| Peptic ulcer disease | 168 (4.1) | 145 (3.4) | 0.136 |
| Rheumatic disease | 127 (3.1) | 142 (3.3) | 0.508 |
| AIDS | 29 (0.7) | 24 (0.6) | 0.521 |
| CCI, median (IQR) | 5 (3, 7) | 5 (3, 7) | 0.739 |
| APS III, median (IQR) | 43 (33, 55) | 44 (33, 55) | 0.502 |

| | | | |
|---|---|---|---|
| SOFA score, median (IQR) | 2 (2, 3) | 2 (2, 4) | 0.656 |
| **Acute organ dysfunction, n (%)** | | | |
| Respiratory | 1680 (40.5) | 1746 (41.1) | 0.616 |
| Lactate elevation | 2290 (55.2) | 2354 (55.4) | 0.904 |
| Kidney | 1180 (28.4) | 1178 (27.7) | 0.463 |
| Liver | 1520 (36.6) | 1592 (37.4) | 0.463 |
| Hematologic | 555 (13.4) | 610 (14.3) | 0.211 |
| **Number of acute organ dysfunctions** | | | |
| 1 | 987 (23.8) | 1037 (24.4) | 0.541 |
| 2 | 1222 (29.5) | 1214 (28.6) | 0.372 |
| 3+ | 1141 (27.5) | 1206 (28.4) | 0.395 |
| **Initial life support** | | | |
| RRT, n (%) | 0 (0.00) | 0 (0.00) | 1.000 |
| Intravenous Fluids, L, median (IQR) | 0.00 (0.00, 5.08) | 0.00 (0.00, 4.52) | 0.333 |
| **Outcomes, n (%)** | | | |
| 28-day mortality, n (%) | 340 (8.2) | 371 (8.7) | 0.406 |
| Length of hospital stay, days | 7.0 (5.0, 13.0) | 8.0 (5.0, 14.0) | 0.018 |
| Length of ICU stay, days | 2.3 (1.6, 4.0) | 2.3 (1.6, 4.3) | 0.173 |

IQR = interquartile range; CCI: Charlson comorbidity index; SOFA: sequential organ failure assessment Score; APS III: Acute Physiology Score III; RRT: renal replacement therapy; ICU: intensive care unit.

**Table S5: Comparison of baseline characteristics between a group consisting of the highest 25% of predicted cARD from Effect-Based Modeling and a group consisting of all patients.**

| | Highest cARD quartile group (n=1063) | All patients (n=4252) | SMD* |
|---|---|---|---|
| Age, years, median (IQR) | 79 (68, 88) | 65 (54, 77) | 0.774 |
| **Gender, n (%)** | | | 0.063 |
| Male patients | 585 (55.0) | 2473 (58.2) | |
| Female patients | 478 (45.0) | 1779 (41.8) | |
| CCI, median (IQR) | 7 (5, 9) | 5 (3, 7) | 0.741 |
| APS III, median (IQR) | 53 (41, 62) | 44 (33, 55) | 0.378 |
| SOFA score, median (IQR) | 3 (2, 4) | 2 (2, 4) | 0.076 |
| **Ethnicity, n (%)** | | | |
| White | 717 (67.5) | 2812 (66.1) | 0.028 |
| Black | 103 (9.7) | 427 (10.0) | 0.012 |
| Asian | 42 (4.0) | 126 (3.0) | 0.054 |
| Other | 201 (18.9) | 887 (20.9) | 0.049 |
| **Admission Type, n (%)** | | | |
| Emergency | 638 (60.0) | 2431 (57.2) | 0.058 |
| Urgent | 320 (30.1) | 1103 (25.9) | 0.093 |
| Elective | 62 (5.8) | 401 (9.4) | 0.136 |
| Other | 43 (4.0) | 317 (7.5) | 0.147 |
| **Infection site, n (%)** | | | |
| Lung | 436 (41.0) | 1526 (35.9) | 0.106 |
| Abdominal | 147 (13.8) | 806 (19.0) | 0.139 |
| Genitourinary | 72 (6.8) | 300 (7.1) | 0.011 |
| Other | 74 (7.0) | 258 (6.1) | 0.036 |
| Unknown | 334 (31.4) | 1362 (32.0) | 0.013 |
| **Acute organ dysfunctions, n (%)** | | | |
| Respiratory | 315 (29.6) | 1746 (41.1) | 0.241 |
| Lactate elevation | 496 (46.7) | 2354 (55.4) | 0.175 |
| Kidney | 217 (20.4) | 1178 (27.7) | 0.171 |
| Hematologic | 133 (12.5) | 610 (14.3) | 0.054 |
| Liver | 562 (52.9) | 1592 (37.4) | 0.314 |
| **Comorbidities, n (%)** | | | |
| Congestive heart failure | 467 (43.9) | 1223 (28.8) | 0.319 |
| Chronic pulmonary disease | 373 (35.1) | 1172 (27.6) | 0.163 |
| Renal disease | 447 (42.1) | 1049 (24.7) | 0.375 |
| Myocardial infarction | 253 (23.8) | 614 (14.4) | 0.240 |
| Diabetes, uncomplicated | 277 (26.1) | 1100 (25.9) | 0.004 |
| Liver disease | 140 (13.2) | 667 (15.7) | 0.072 |
| Peripheral vascular disease | 170 (16.0) | 477 (11.2) | 0.140 |
| Nonmetastatic cancer | 91 (8.6) | 408 (9.6) | 0.036 |

| | | | |
|---|---|---|---|
| Cerebrovascular disease | 134 (12.6) | 598 (14.1) | 0.043 |
| Diabetes, complicated | 162 (15.2) | 425 (10.0) | 0.158 |
| Metastatic cancer | 173 (16.3) | 347 (8.2) | 0.250 |
| 28-day mortality, n (%) | 127 (11.9) | 371 (8.7) | 0.106 |

Comparison between the highest ARD decile group and all patients

cARD: Conditional absolute rate difference; SMD: Standardized mean difference; IQR interquartile range; CCI: Charlson comorbidity index; SOFA: Sequential Organ Failure Assessment Score; APS III: Acute Physiology Score III.

## Supplementary Figures

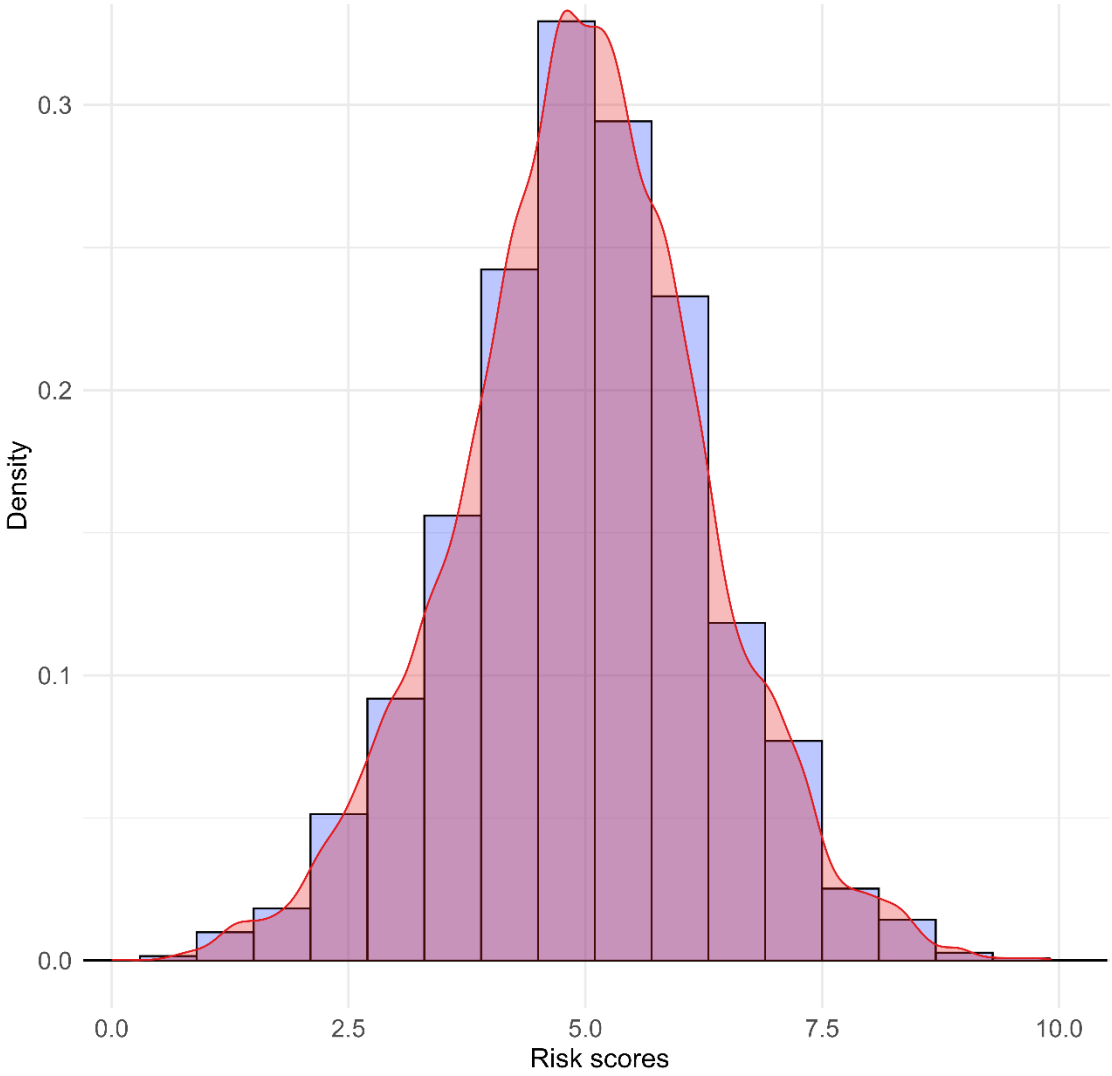


**Fig. S1:** Risk score distribution derived from the computed risk model for analyzing heterogeneous treatment effects.

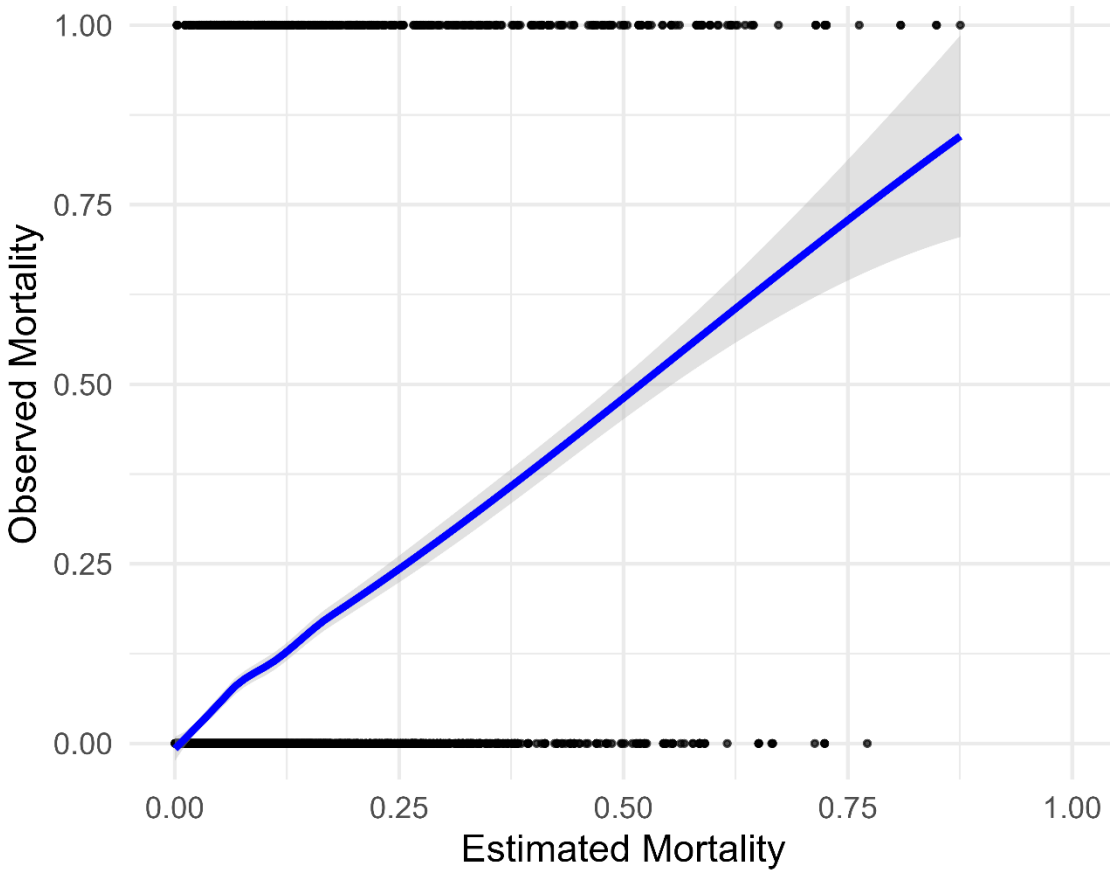


**Fig. S2** The calibration curves of risk model used in Risk-based heterogeneity of treatment effect analysis.

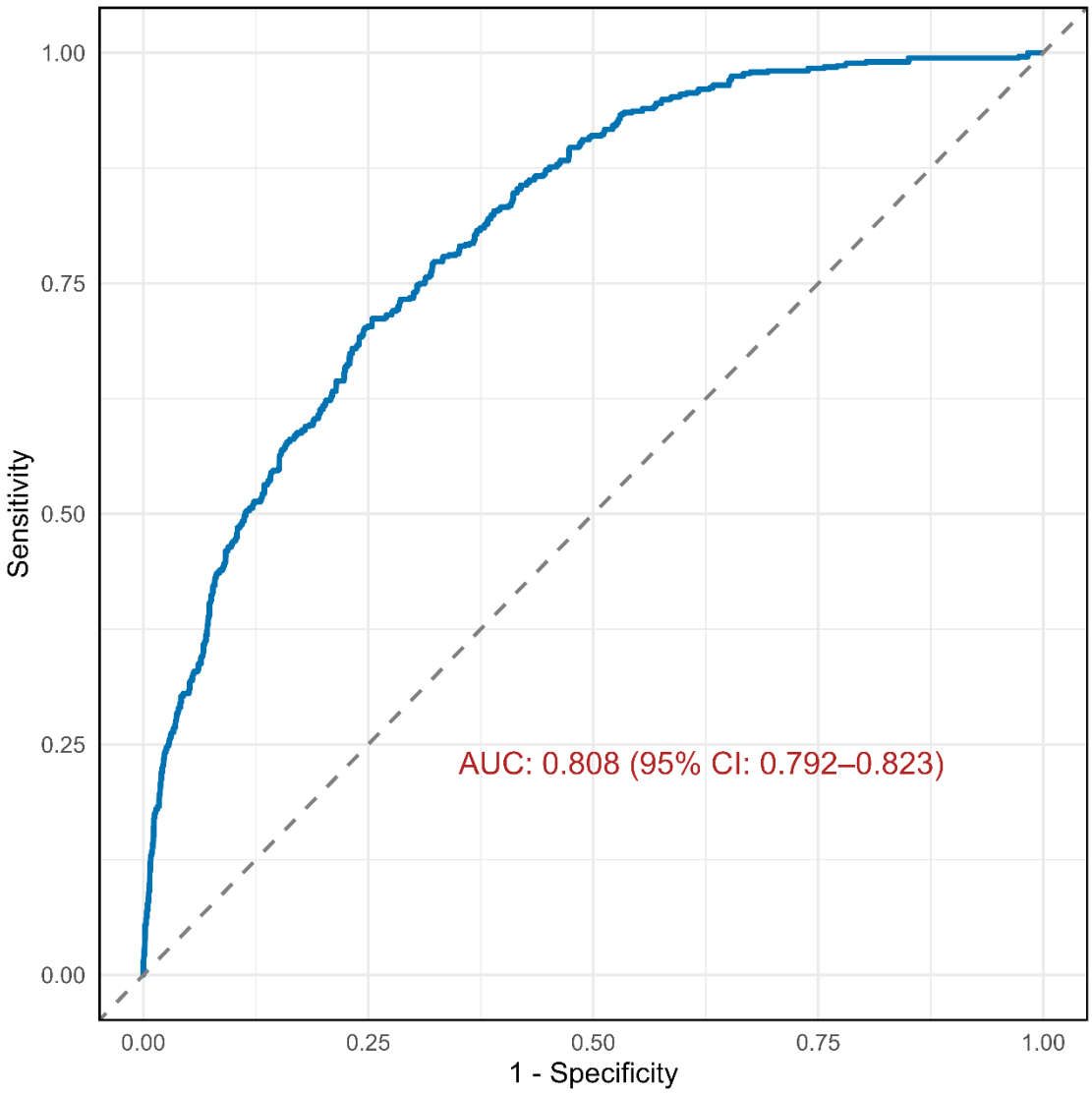


**Fig. S3** The predictive performance of the risk model used in Risk-based heterogeneity of treatment effect analysis. AUC: area under the curve; CI confidence interval.

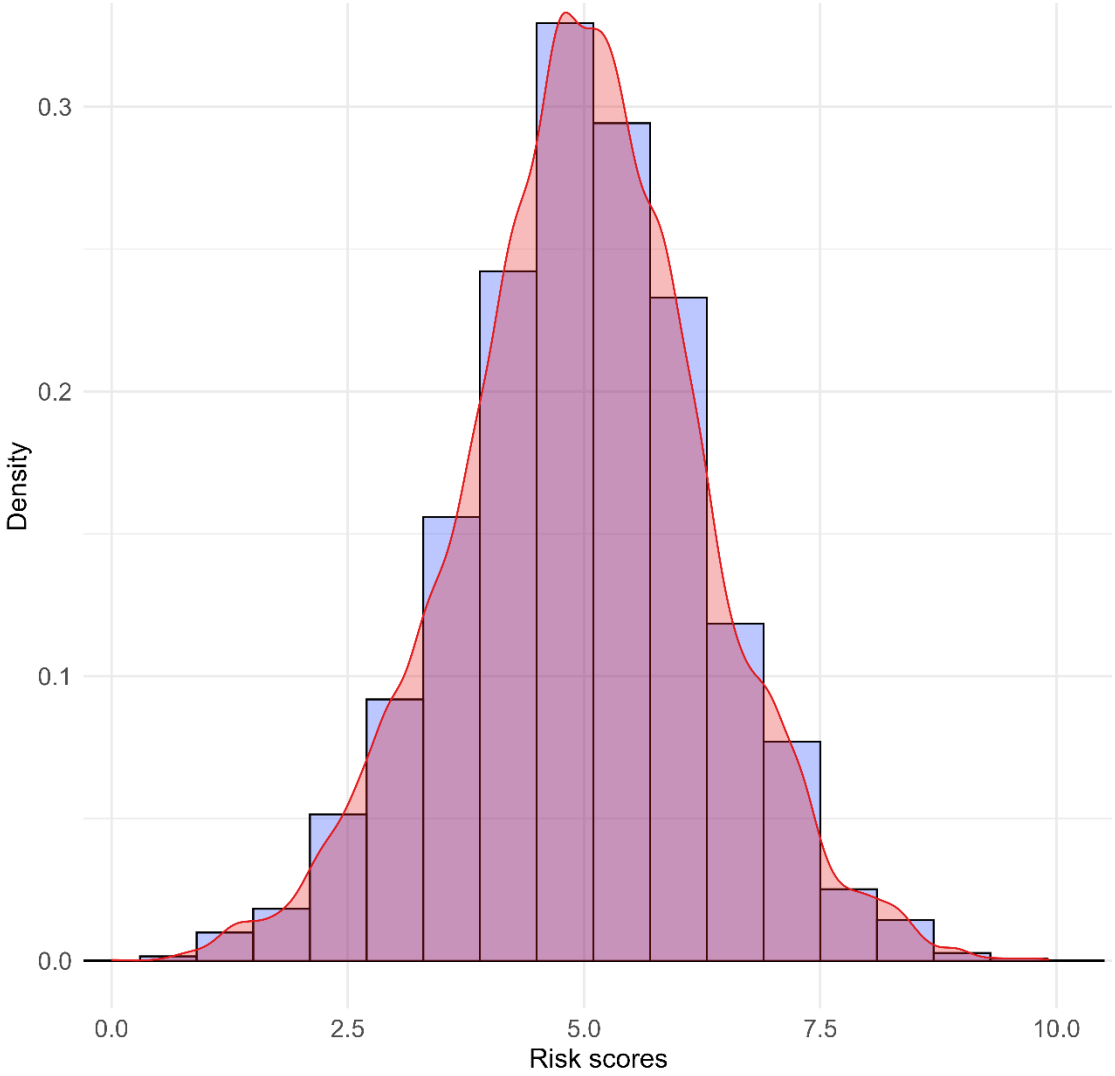


**Fig. S4** Distribution of conditional absolute rate difference for the effect-based approach to analyzing heterogeneous treatment effects.

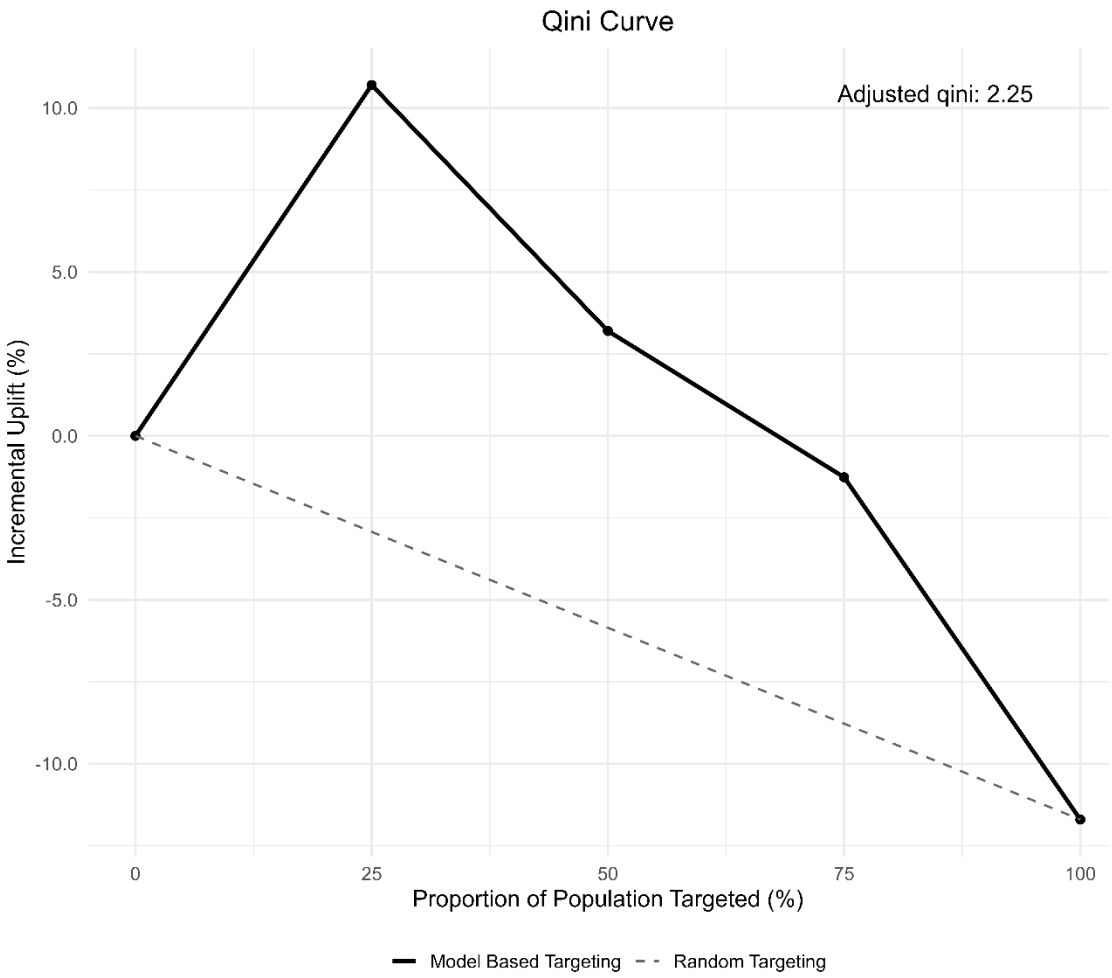


**Fig. S5 Qini curve for the causal forest model.**

Patients in the validation cohort were ranked by predicted individualized benefit and cumulatively included along the x-axis. The solid curve shows the cumulative incremental improvement in 28-day survival achieved by model-based prioritization compared with random allocation (dashed line). The adjusted Qini value was 2.25.

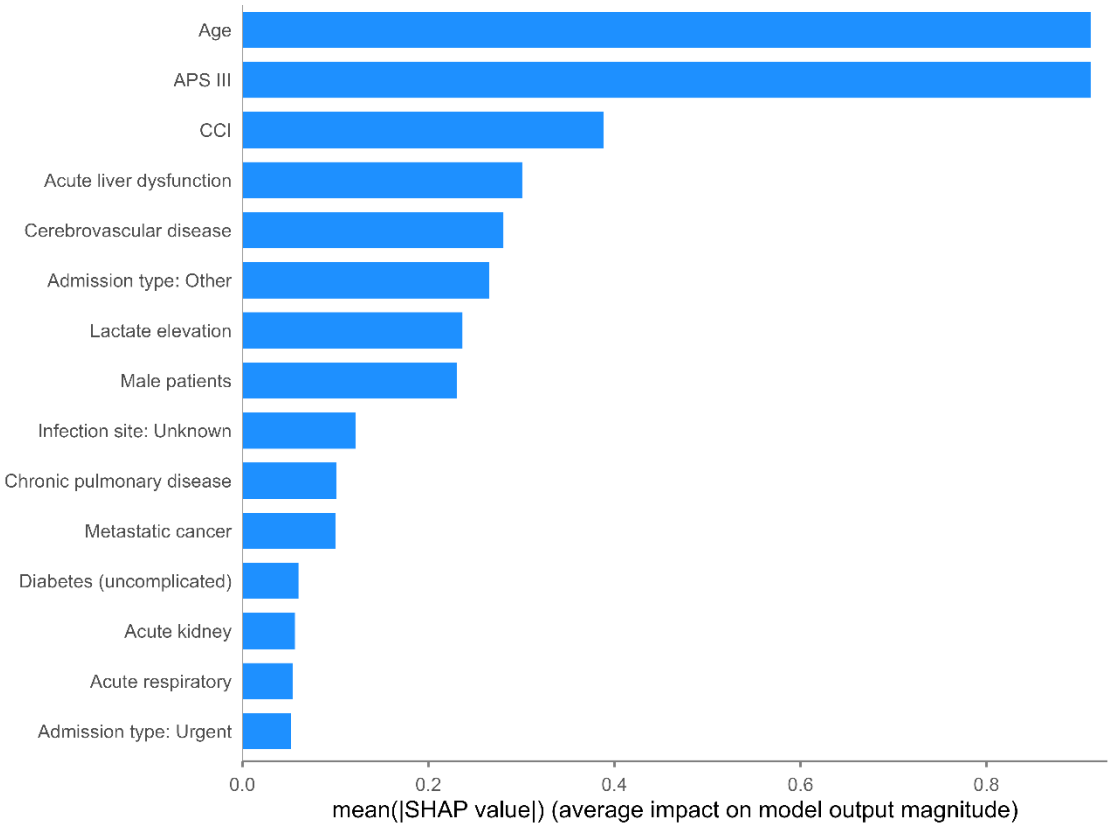


**Fig. S6 Variable importance plot.**

The importance ranking of the top 15 variables according to the mean (|SHAP value|).

APS III: Acute Physiology Score III; CCI: Charlson Comorbidity Index.

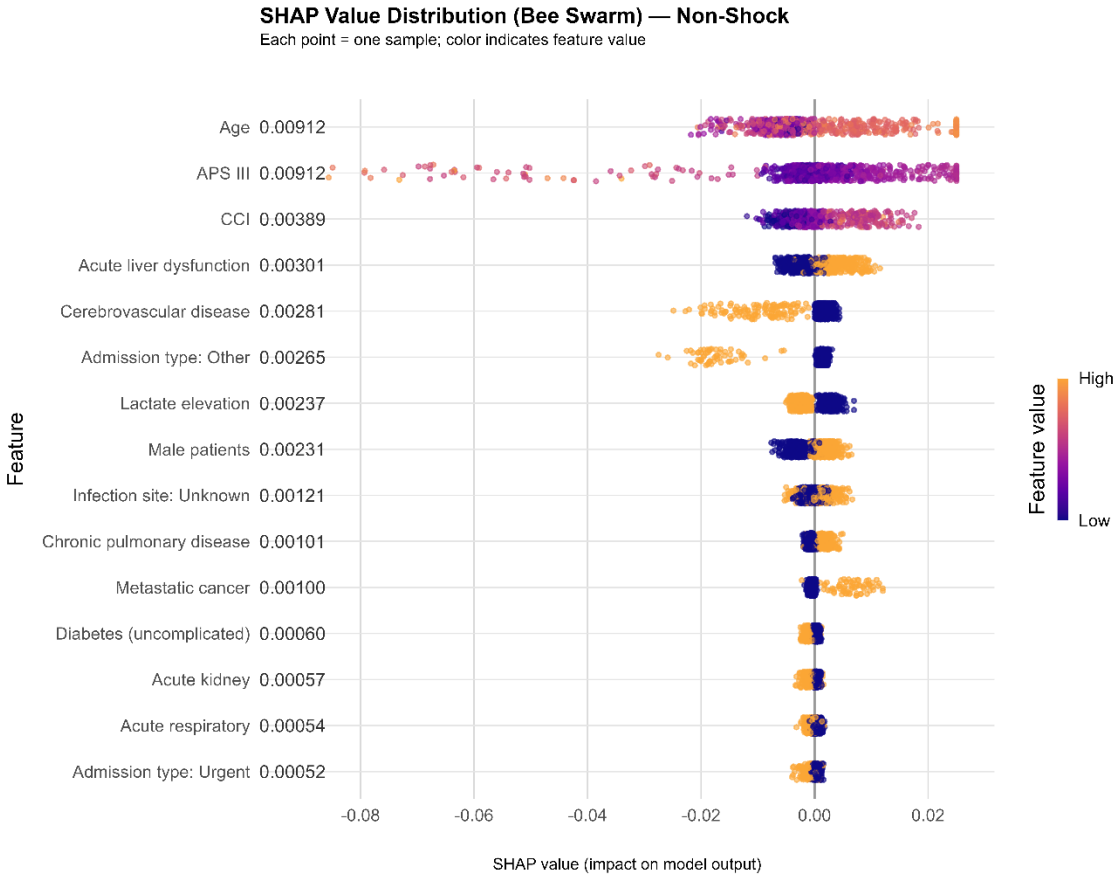


**Fig. S7 Top 15 SHAP features for predicted benefit from shorter time-to-antibiotics.**

The importance ranking of the top 15 risk factors with stability and interpretation using the optimal model. The higher SHAP value of a feature is given, the higher predicted benefit from shorter time-to-antibiotics the patient would have. The yellow part in feature value represents higher value.

APS III: Acute Physiology Score III; CCI: Charlson Comorbidity Index.

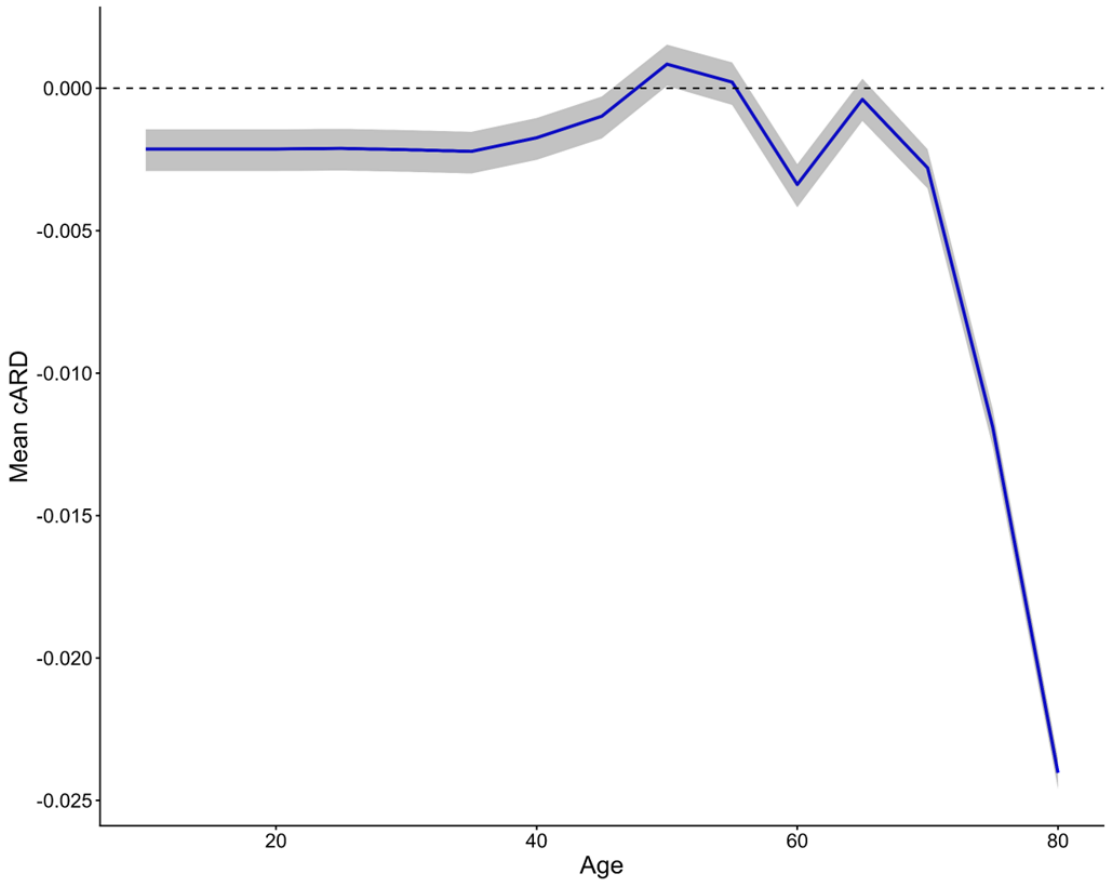


**Fig. S8 Partial dependence of age on predicted benefit.**

Partial dependence plot showing the association between age and the model-predicted conditional absolute rate difference (cARD) for 28-day mortality. The x-axis represents age, and the y-axis represents the average predicted cARD at each age value. More negative cARD values indicate greater predicted benefit from shorter time-to-antibiotics, reflecting a larger reduction in mortality with earlier treatment. The dashed horizontal line denotes no treatment effect. The shaded band represents the 95% confidence interval. Predicted benefit was minimal at younger ages, increased gradually with advancing age, and became most pronounced among older patients.

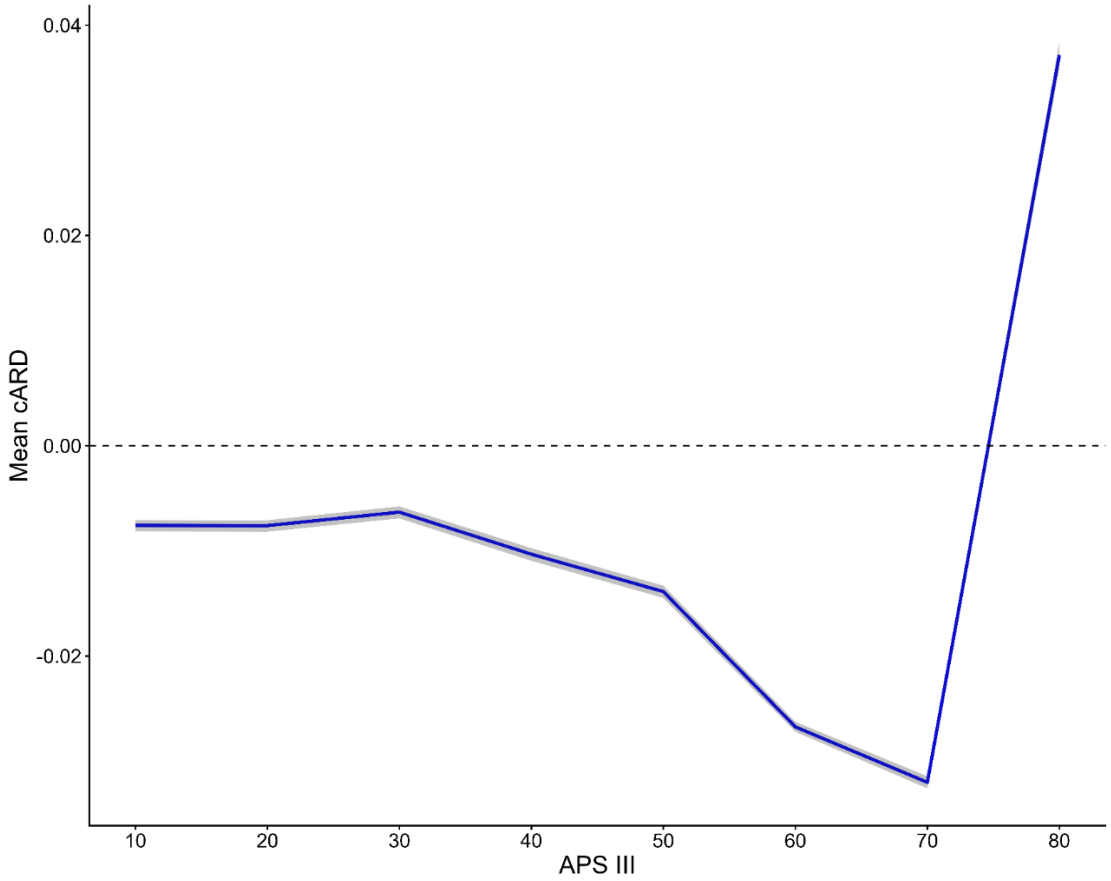


**Fig. S9 Partial dependence of APS III on predicted benefit.**

Partial dependence plot illustrating the association between APS III score and the model-predicted conditional absolute rate difference (cARD) for 28-day mortality. The x-axis represents APS III, and the y-axis represents the average predicted cARD at each score value. More negative cARD values indicate greater predicted benefit from shorter time-to-antibiotics, corresponding to a larger reduction in mortality with earlier treatment. The dashed horizontal line denotes no treatment effect, and the shaded band represents the 95% confidence interval. Predicted benefit was limited at lower APS III scores, increased progressively with rising severity, and was most pronounced among patients with APS III scores approximately between 60 and 70, before attenuating at very high scores.

APSIII: Acute Physiology Score III.

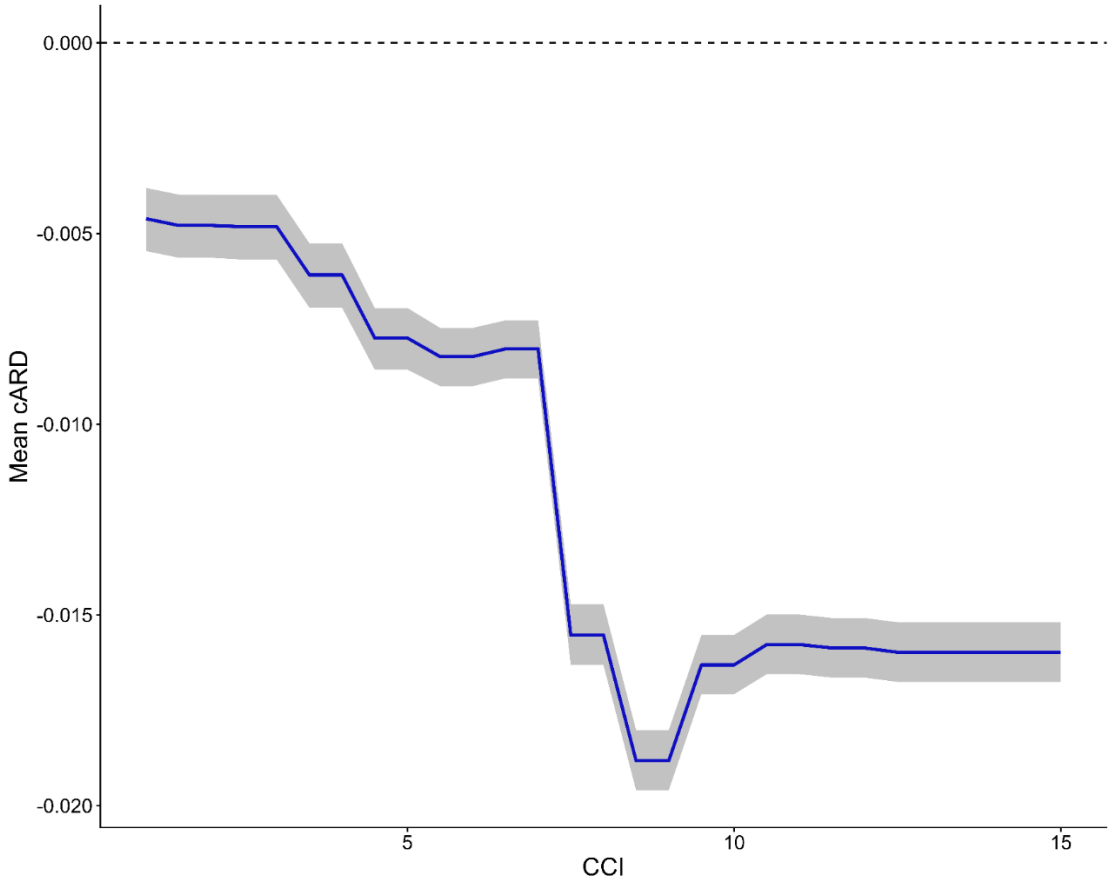


**Fig. S10 Partial dependence of CCI on predicted benefit.**

Partial dependence plot of the model-predicted conditional absolute rate difference (cARD) for 28-day mortality across the Charlson Comorbidity Index (CCI). The x-axis shows CCI, and the y-axis shows the mean predicted cARD; more negative values indicate greater predicted benefit from shorter time-to-antibiotics (larger mortality reduction with earlier treatment). The dashed horizontal line denotes no treatment effect, and the shaded band represents the 95% confidence interval. Predicted benefit increased gradually with rising CCI, with a pronounced increase around CCI 8–9, and then remained relatively stable at higher CCI values.

CCI: Charlson Comorbidity Index.

# Supplementary Checklist. STROBE Statement—Checklist of items that should be included in reports of observational studies

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Pages |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-4 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5-6 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 7-8 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-8 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 7-8 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | 9-10 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 9-13 |
| Study size | 10 | Explain how the study size was arrived at | 7-8 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 9-13 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10-11 |
| | | (*c*) Explain how missing data were addressed | 9-13 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | NA |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 13-14 |
| | | (b) Give reasons for non-participation at each stage | 13 |

| | | | |
|---|---|---|---|
| | | (c) Consider use of a flow diagram | 14 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 13-15 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 13-15 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 13-15 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 13-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 13-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 14-15 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 15-19 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 19 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 23-25 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 19-23 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 23-25 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 26 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.