VICTAS

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1 Overview

The goal of this analysis is to investigate the relationship between the combined therapy of Vitamin C, Thiamine, and Hydrocortisone in the reduction of mortality in patients with septic shock.

1.1 End points

1.1.1 Primary end point

- Ventilator and Vasopressor free days (VVFD) starting on day 30 following mid-night of the randomization day. Endpoint is an ordinal variable computed as a backwards count of consecutive whole days free of both respiratory and vasopressor support between day 30 and the most recent use of either respiratory or vasopressors.

1.1.2 Secondary end point

- Binary variable indicating mortality within 30-days. Endpoint starts from midnight on the day of randomization (i.e. day 0).

1.1.3 Potential exploratory end points

- **SOFA score**: Continuous variable measured between baseline and day 4.
- **Mortality within 180 days**: Binary variable.
- **Mortality between time of randomization and ICU discharge**: Binary variable.
- **Lenght of ICU stay**: Continuous variable measured in days.
- **Lenght of hospital stay**: Continuous variable measured in days.
- **Renal replacement free days at day 30**: Continuous variable measured in days.
- **ICU delirium**: Continuous variable measured in days.
- **Neurocognitive outcomes**: Continuous variables measured at 180 days.
  a) Attention (Wechsler Adult Intelligence Scale IV)
  b) Delirium (telephone confusion assessment method)
  c) Executive Functioning (Hayling test)
  d) Language (controlled oral word association test)
  e) Orientation (telephone interview for cognitive status)
  f) Memory (Wechsler Memory Scale IV)
  g) Reasoning (Wechsler Adult Intelligence Scale IV)
  h) Activities of daily living (Katz)
  i) Employment (employment questionnaire)
  j) Instrumental activities of daily living (functional activities questionnaire)
  k) Depression (Beck Depression Inventory II)
  l) Post-traumatic stress disorder checlist (Diagnostic and Statistical Manual 5th revision)
  m) EuroQol (five dimensions)

1.2 Demographic & Clinical variables

- Age (years)
- Race (African American, Caucasian, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, or not reported)
- Sex (male or female)
- Education (less than high school, high school or general education diploma, some college)

- Body mass index (kg/m^2)
- Medical history (yes, no):
  a) Diabetes
  b) Cardiovascular disease
  c) Neurological disease
  d) Respiratory illness
  e) Current Cancer
- Eligibility criterion (respiratory support, vasopressor support, both)
- Source of admission
- Admission reason
- Baseline vital measurements:
  a) Heart rate (beats per minute)
  b) Systolic blood pressure (mmHg)
  c) Diastolic blood pressure (mmHg)
  d) Mean arterial pressure (mmHg)
  e) Respiration rate
  f) Temperature ($°C$)
- Baseline laboratory values:
  a) White blood cell count (K/mm^3)
  b) Platelets (K/mm^3)
  c) Hemoglobin (g/dL)
  d) Lactate (mmol/L)
  e) Creatinine (mg/dL)
- Baseline severity:
  a) APACHE II score
  b) SOFA score
  c) CAM-ICU
- Infection
  a) Infection source
  b) Gram-positive organism
  c) Gram-negative organism
  d) Fungal infection
  e) Organism not identified
  f) Other infection
  g) Unknown infection

According to the intent-to-treat analysis set, categorical variables will be described using frequencies and proportions. Continuous variables will be described using mean and standard deviation, as well as median and interquartile range (IQR). The sample will be described overall and stratified by group assignment.

1.3 Main analysis

Enpoints wll be described using the median and IQR for the VVFD outcome and frequency and percentages for the mortality outcome. For each outcome, descriptions will be summarized overall and by treatment group. The main analysis will be a comparison between the two treatment groups according to the intent-to-treat principle. For the ordinal VVFD outcome a Wilcoxon rank-sum test or equivalent univariate proportional odds model will be fit, and for the binary mortality outcome a chi-square test or equivalent logistic regression model will be fit along with a cox proportional hazard model. For the PO and Logistic model, results will be displayed with odds ratios and 95% confidence intervals. For the Cox model, results will be displayed with hazard ratios and 95% confidence intervals.

1.3.1 Adjusted analysis

We will use two approaches to estimate treatment effects adjusted for covariates. Generalized linear mixed models will be used to estimate the conditional effect of treatment with site as a random effect. Generalized estimating equations will be used to estimate the marginal effect of study treatment. Mortality will be modeled assuming a logit link function. A proportional odds model will be specified for VVFDs. Models will consider baseline variables as listed in the descriptive analysis. Multiple imputation based on predictive mean matching will be used to overcome any missingness in covariates. Restricted cubic splines will be used for addressing potential nonlinearities in the association between continuous variables and outcomes.

1.3.2 Subgroup analysis

Using the fitted models from the principal adjusted analysis, we will evaluate the interaction between treatment group assignment and each of the following variables: sex, race, ethnicity, age, admission reason, source of admission, infection, baseline illness severity, baseline lactic acid, and eligibility criteria. If any interaction achieves a P value ≤ 0.2, we will report treatment effects within each subgroup defined by that interaction variable.

1.3.3 Exploratory end points analysis

Exploratory end points will analyzed in a similar manner as for the primary and secondary endpoints. All analyses will based on the intent-to-treat analysis set, in the presence of missing outcomes a complete case analysis will be implemented. As follow up, a sensitivity analysis using multiple imputation will be conducted.

2 Summary Analyses (Intent-to-treat analysis set)

2.1 Descriptives

```
latex(summaryM(age.yrs+race.cat+ethnicity.cat+male.cat.2+yrs.educat+weight+bmi+system.3.cat
            system.4.cat.2+system.1.cat.2+system.7.cat.2+malignancy.cat.2+ventilator+
            ventilator.vent.2+ventilator.supporttype+ventilator.vaso.2+
            ics.admit.source.cat+admit.reason.cat+vitals_5+systolic_blood_pressure+
            diastolic_blood_pressure+vitals_1+vitals_7+vitals.9.celcius+wbc_value+
            platelets_value+hem_value_3+lactic_acid+creat_value+ap2_total_score+sofa_seib+
            first.studydrugdose.hrs+infect.source.cat+organism0.cat.2+organism1.cat.2+
            organism2.cat.2+organism4.cat.2+organism5.cat.2+organism6.cat.2+vvfd.zero.2+
            vitc.less4doses.reason+thiamine.less4doses.reason~treatment,
            data=addMarginal(dat.victas,treatment,label='Total', margloc='last')),
            file="",where="!h",caption="Demographic \\& Clinical variables by
            Treatment Assignment", exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE,
            npct="both",digits=2, landscape=FALSE, longtable=TRUE,
            lines.page=82,what = '%',  legend.bottom = TRUE,size="small")
```

Table 1: Demographic & Clinical variables by Treatment Assignment

	N	Control $N = 249$	Treatment $N = 252$	Total $N = 501$
Age (years)	501	50 61 72 (60 ±17)	51 62 69 (60 ±15)	50 62 70 (60 ±16)
Race	501			
Black		32% $\frac{80}{249}$	28% $\frac{70}{252}$	30% $\frac{150}{501}$
Caucasian		54% $\frac{135}{249}$	59% $\frac{149}{252}$	57% $\frac{284}{501}$
Other		14% $\frac{34}{249}$	13% $\frac{33}{252}$	13% $\frac{67}{501}$
Ethnicity	501			
Hispanic or Latino		10% $\frac{24}{249}$	13% $\frac{32}{252}$	11% $\frac{56}{501}$
Not Hispanic or Latino		86% $\frac{215}{249}$	84% $\frac{211}{252}$	85% $\frac{426}{501}$
Not Reported		4% $\frac{10}{249}$	4% $\frac{9}{252}$	4% $\frac{19}{501}$
Male	501	54% $\frac{134}{249}$	55% $\frac{139}{252}$	54% $\frac{273}{501}$
Education	501			
Less than High School		10% $\frac{24}{249}$	9% $\frac{22}{252}$	9% $\frac{46}{501}$
High School or GED		16% $\frac{39}{249}$	13% $\frac{34}{252}$	15% $\frac{73}{501}$
Some College		22% $\frac{56}{249}$	25% $\frac{62}{252}$	24% $\frac{118}{501}$
Unknown		52% $\frac{130}{249}$	53% $\frac{134}{252}$	53% $\frac{264}{501}$
Weight (kg)	501	67 80 97 (84 ±26)	68 80 96 (85 ±28)	68 80 97 (85 ±27)
BMI	491	22.7 26.8 33.4 (28.9 ± 9.0)	23.9 27.3 32.8 (29.3 ± 9.2)	23.2 27.1 33.1 (29.1 ± 9.1)
Diabetes	501	31% $\frac{77}{249}$	34% $\frac{85}{252}$	32% $\frac{162}{501}$
Cardiovascular disease	501	51% $\frac{126}{249}$	51% $\frac{129}{252}$	51% $\frac{255}{501}$
Neurological disease	501	19% $\frac{48}{249}$	18% $\frac{46}{252}$	19% $\frac{94}{501}$
Respiratory illness	501	22% $\frac{56}{249}$	22% $\frac{55}{252}$	22% $\frac{111}{501}$
Current Cancer	501	22% $\frac{55}{249}$	16% $\frac{41}{252}$	19% $\frac{96}{501}$
Respiratory Support	500			
Ventilator		22% $\frac{54}{248}$	19% $\frac{49}{252}$	21% $\frac{103}{500}$
Vasopressor		39% $\frac{97}{248}$	37% $\frac{93}{252}$	38% $\frac{190}{500}$
Both		39% $\frac{97}{248}$	44% $\frac{110}{252}$	41% $\frac{207}{500}$
On Ventilator	501	61% $\frac{151}{249}$	63% $\frac{159}{252}$	62% $\frac{310}{501}$
Type of Ventilator Support	309			
Intubation		64% $\frac{96}{151}$	68% $\frac{108}{158}$	66% $\frac{204}{309}$
CPAP or BIPAP		17% $\frac{26}{151}$	18% $\frac{29}{158}$	18% $\frac{55}{309}$
Nasal Flow		19% $\frac{29}{151}$	12% $\frac{19}{158}$	16% $\frac{48}{309}$
Intubation/CPAP/BIPAP/Nasal		0% $\frac{0}{151}$	1% $\frac{2}{158}$	1% $\frac{2}{309}$
On Vasopressors	500	78% $\frac{194}{248}$	81% $\frac{203}{252}$	79% $\frac{397}{500}$
ICU Admission Source	501			
ED		74% $\frac{184}{249}$	67% $\frac{169}{252}$	70% $\frac{353}{501}$
Intermediate Care		0% $\frac{1}{249}$	1% $\frac{3}{252}$	1% $\frac{4}{501}$
Step Down Unit		3% $\frac{8}{249}$	4% $\frac{9}{252}$	3% $\frac{17}{501}$
Hospital Floor		16% $\frac{40}{249}$	19% $\frac{47}{252}$	17% $\frac{87}{501}$
Other		6% $\frac{16}{249}$	10% $\frac{24}{252}$	8% $\frac{40}{501}$

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

Table 1: *(continued)*

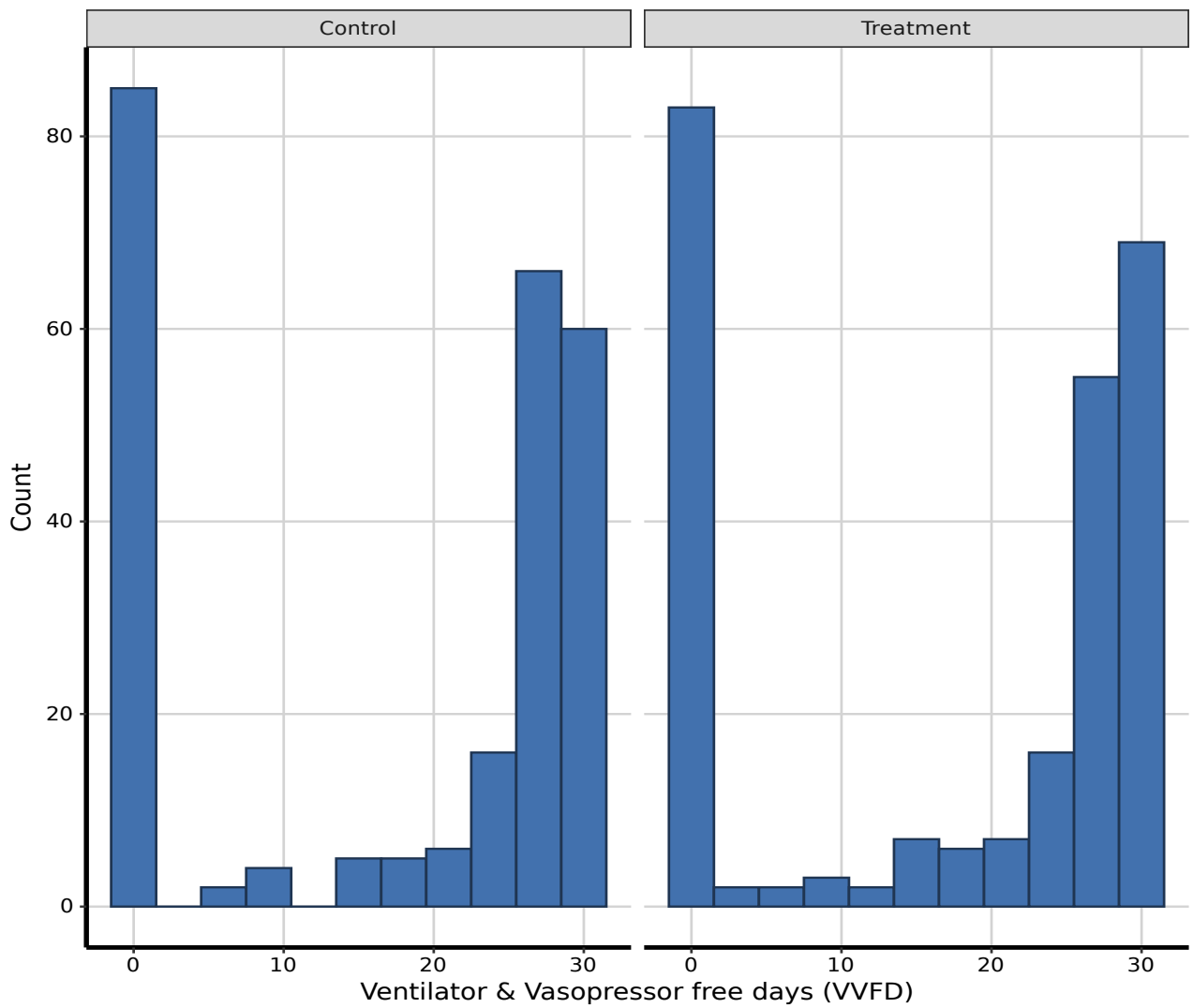
	N	Control $N = 249$	Treatment $N = 252$	Total $N = 501$
Admission Reason	501			
Sepsis		71% $\frac{176}{249}$	71% $\frac{180}{252}$	71% $\frac{356}{501}$
Other Medical		27% $\frac{67}{249}$	25% $\frac{63}{252}$	26% $\frac{130}{501}$
Other Surgical		2% $\frac{6}{249}$	4% $\frac{9}{252}$	3% $\frac{15}{501}$
Heart Rate	501	78 94 110 (95 ± 23)	84 100 115 (99 ± 23)	80 96 113 (97 ± 23)
Systolic Blood Pressure	501	91 103 118 (106 ± 23)	90 103 120 (105 ± 25)	91 103 119 (106 ± 24)
Diastolic Blood Pressure	501	51 56 66 (59 ±15)	49 58 68 (60 ±15)	50 57 67 (59 ±15)
Mean Arterial Pressure (MAP)	500	65 71 79 (73 ±16)	64 72 82 (74 ±15)	64 72 81 (74 ±15)
Respiratory Rate	499	18.0 22.0 27.0 (23.4 ± 7.6)	18.0 22.0 28.0 (22.8 ± 6.9)	18.0 22.0 28.0 (23.1 ± 7.3)
Temperature (celsius)	495	36.6 36.9 37.8 (37.0 ± 1.4)	36.4 36.9 37.8 (37.1 ± 1.3)	36.5 36.9 37.8 (37.1 ± 1.4)
White Blood Cell Count	496	6.2 12.0 18.8 (14.4 ± 12.2)	7.0 14.5 22.3 (103.2 ±1063.5)	6.6 13.4 19.9 (59.0 ± 754.1)
Platelets Count	492	89 172 256 (192 ±142)	111 182 264 (194 ±112)	100 178 258 (193 ±128)
Hemoglobin	498	8.6 10.1 12.0 (10.3 ± 2.5)	8.4 10.2 12.3 (10.5 ± 2.8)	8.5 10.1 12.1 (10.4 ± 2.7)
Lactic Acid	393	1.8 3.0 4.8 (5.2 ±13.8)	1.8 2.6 5.3 (4.1 ± 3.8)	1.8 2.8 5.1 (4.7 ±10.0)
Creatinine Value	498	1.0 1.7 2.6 (2.2 ±2.0)	1.1 1.8 3.1 (2.4 ±2.0)	1.1 1.7 2.8 (2.3 ±2.0)
APACHE II Score	472	19.0 27.0 33.0 (26.7 ± 9.3)	22.0 27.0 33.0 (27.5 ± 8.6)	20.8 27.0 33.0 (27.1 ± 9.0)
SOFA Score	501	6.0 9.0 11.0 (8.9 ± 3.5)	7.0 9.0 12.0 (9.4 ± 3.6)	7.0 9.0 12.0 (9.1 ± 3.5)
Time to Tx (Hrs)	490	7.8 13.6 19.9 (14.4 ± 7.9)	8.4 15.4 21.5 (15.9 ±10.4)	7.9 14.7 20.9 (15.1 ± 9.2)
Infection Source	498			
Lung		37% $\frac{91}{247}$	35% $\frac{88}{251}$	36% $\frac{179}{498}$
Blood/Vascular access		11% $\frac{26}{247}$	15% $\frac{38}{251}$	13% $\frac{64}{498}$
Urinary Tract		19% $\frac{48}{247}$	12% $\frac{29}{251}$	15% $\frac{77}{498}$
Intra-abdominal		12% $\frac{30}{247}$	18% $\frac{45}{251}$	15% $\frac{75}{498}$
Skin or Soft Tissues		7% $\frac{18}{247}$	6% $\frac{14}{251}$	6% $\frac{32}{498}$
Central Nervous System (CNS)		0% $\frac{1}{247}$	2% $\frac{5}{251}$	1% $\frac{6}{498}$
Bone/Joint		1% $\frac{2}{247}$	1% $\frac{3}{251}$	1% $\frac{5}{498}$
Other		6% $\frac{15}{247}$	4% $\frac{11}{251}$	5% $\frac{26}{498}$
Unknown		6% $\frac{16}{247}$	7% $\frac{18}{251}$	7% $\frac{34}{498}$
Organism: Gram Positive	501	31% $\frac{76}{249}$	31% $\frac{78}{252}$	31% $\frac{154}{501}$
Organism: Gram Negative	501	32% $\frac{79}{249}$	29% $\frac{73}{252}$	30% $\frac{152}{501}$
Organism: Fungal	501	7% $\frac{17}{249}$	5% $\frac{12}{252}$	6% $\frac{29}{501}$
Organism: Not Identified	501	14% $\frac{36}{249}$	13% $\frac{34}{252}$	14% $\frac{70}{501}$
Organism: Other	501	14% $\frac{36}{249}$	15% $\frac{38}{252}$	15% $\frac{74}{501}$
Organism: Unknown	501	15% $\frac{38}{249}$	15% $\frac{37}{252}$	15% $\frac{75}{501}$
Zero VVFD due to death	168	71% $\frac{60}{85}$	67% $\frac{56}{83}$	69% $\frac{116}{168}$
Vitamin C: reasons for doses<4	45			
ICU Discharge		38% $\frac{8}{21}$	33% $\frac{8}{24}$	36% $\frac{16}{45}$
Death		52% $\frac{11}{21}$	62% $\frac{15}{24}$	58% $\frac{26}{45}$
Other		10% $\frac{2}{21}$	4% $\frac{1}{24}$	7% $\frac{3}{45}$
Thiamine: reasons for doses<4	44			
ICU Discharge		35% $\frac{7}{20}$	33% $\frac{8}{24}$	34% $\frac{15}{44}$
Death		55% $\frac{11}{20}$	62% $\frac{15}{24}$	59% $\frac{26}{44}$
Other		10% $\frac{2}{20}$	4% $\frac{1}{24}$	7% $\frac{3}{44}$

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

2.2 Primary end point: VVFD

2.2.1 Histogram

```
p1 ← ggplot(dat.victas, aes(x = days.vvfd)) +
        geom_histogram(aes(y = ..count..), binwidth = 3,
                       colour = barlines, fill = barfill) +
        scale_x_continuous(name = "Ventilator & Vasopressor free days (VVFD)") +
        scale_y_continuous(name = "Count") +
        ggtitle("") +
        theme_bw() +
        theme(axis.line = element_line(size=1, colour = "black"),
              panel.grid.major = element_line(colour = "#d3d3d3"),
              panel.grid.minor = element_blank(),
              panel.border = element_blank(), panel.background = element_blank(),
              plot.title = element_text(size = 14, family = "Tahoma", face = "bold"),
              text=element_text(family="Tahoma"),
              axis.text.x=element_text(colour="black", size = 9),
              axis.text.y=element_text(colour="black", size = 9)) +
        facet_grid(. ~ treatment, scales = "free")
```



2.2.2 Descriptives

```
latex(summaryM(days.vvfd~treatment, data=addMarginal(dat.victas,treatment,
                label='Total', margloc='last')),file="",where="!h",
                caption="Ventilator and Vasopressor free days (VVFD) by
                Treatment Assignment",
                exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
                digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 2: Ventilator and Vasopressor free days (VVFD) by Treatment Assignment

	N	Control	Treatment	Total
		$N = 249$	$N = 252$	$N = 501$
VVFD	501	$_0$ 26 $_{28}$ (17 ±13)	$_0$ 25 $_{29}$ (17 ±13)	$_0$ 25 $_{29}$ (17 ±13)

$_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

2.2.3 Wilcoxon Rank-Sum Test

```
control.vvfd←subset(dat.victas,treatment=="Control")$days.vvfd
treatment.vvfd←subset(dat.victas,treatment=="Treatment")$days.vvfd
primary.test←wilcox.test(control.vvfd,treatment.vvfd,paired=FALSE,conf.int=TRUE)
set.seed(10)
MedDiff←Median.diff(control.vvfd, treatment.vvfd, conf.level=0.95,R=10000)
```

```
Tablemodel1←data.frame(variable=c("{\\bf VVFD}"),
                    test.stat=c(format(0.030,nsmall=3)),
                    p.val=c(round(primary.test$p.val,3)),
                    diff.med=c(format(round((MedDiff)$estimate,3),nsmall=3)),
                    c.i=c(paste(format(round(MedDiff$conf.int[1],3),nsmall=3),
                          format(round(MedDiff$conf.int[2],3),nsmall=3),sep=" - ")))
```

```
latex(Tablemodel1,file="", where="!h",caption = "Wilcoxon Rank-Sum Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Difference in Median',
      '{\\bf 95\\% C.I.}'), insert.bottom = "",col.just=c("l","c","c","c","c"),
      rowname=NULL)
```

Table 3: Wilcoxon Rank-Sum Test

	Test Statistic	**P-value**	**Difference in Median**	**95% C.I.**
VVFD	0.030	0.852	1.000	-2.000 - 4.000

Results indicate no statistically significant difference in number of ventilator-and-vasopressor free days between the treatment group assignments.

2.2.4 Proportional Odds Model

```
dat.model1←subset(dat.victas,select=c(record_id,days.vvfd,treatment,age.yrs))
dat.model1←upData(dat.model1,treatment=factor(treatment,
                                              levels=c("Treatment","Control")),
                                 treatment=relevel(treatment,ref="Control"))
ddist1 ← datadist(dat.model1)
options(datadist = "ddist1")
po.model1←lrm(days.vvfd~treatment,data=dat.model1)
```

To compare the ventilator-and-vasopressor free days between treatment groups, a univariate proportional odds model was fit due to the ordered nature of the outcome (i.e. VVFD). In the proportional odds model we assume that the relationship between each level in the outcome variable is proportional, so the coefficients that describe the relationship between the lowest category versus all higher categories of the outcome variable is the same as the relationship that describes the next lowest category and all higher categories and continues for each addtional category. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of having an increased number of VVFDs when compared to the reference control group.

	Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs 501	LR χ^2	0.04	R^2	0.000	C	0.503
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$ 1×10^{-11}	d.f.	1	g	0.015	D_{xy}	0.006
	Pr($>\chi^2$)	0.8515	g_r	1.015	γ	0.011
			g_p	0.004	τ_a	0.005
			Brier	0.238		

Table 4: Proportional Odds Model

	OR	**95% C.I.**	**P-value**
Treatment vs. Control	1.030	0.755 - 1.405	0.851

In the univariate model, although results indicate that treatment group is not statistically associated with ventilator and vasopressor free days. When comparing treatment group to the control group the odds of having an increased number of ventilator and vasopressor free days increases by approximately 3% (OR=1.030 and p-value=0.851)

2.3 Secondary end point: 30-Day Mortality

2.3.1 Descriptives

```
latex(summaryM(death_30d.cat.2~treatment, data=addMarginal(dat.victas,treatment,
               label='Total', margloc='last')),file="",where="!h",
               caption="30-Day Mortality by Treatment Assignment",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
               digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 5: 30-Day Mortality by Treatment Assignment

	N	Control	Treatment	Total
		$N = 249$	$N = 252$	$N = 501$
30-Day Mortality	501	24% $\frac{60}{249}$	22% $\frac{56}{252}$	23% $\frac{116}{501}$

N is the number of non-missing values.

2.3.2 Pearson Chi-Square Test

```
tbl1 <- table(dat.victas$treatment,dat.victas$death_30d.cat)
secondary.test1 <- chisq.test(tbl1,correct=FALSE)
secondary.test2 <- prop.test(table(dat.victas$treatment,dat.victas$death_30d.cat),
                             correct=FALSE)
```

```
latex(Tablemodel3,file="", where="!h",caption = "Pearson Chi-Square Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Control Prop',
      '\\bf Treatment Prop','{\\bf 95\\% C.I.}'),
      insert.bottom = "",col.just=c("l","c","c","c","c","c"),rowname=NULL)
```

Table 6: Pearson Chi-Square Test

	Test Statistic	**P-value**	**Control Prop**	**Treatment Prop**	**95% C.I.**
30-Day Mortality	0.247	0.619	0.241	0.222	-0.055 - 0.093

Results indicate no statistically significant difference in proportions between treatment group on 30-day mortality.

2.3.3 Logistic Regression Model

```
dat.model2←subset(dat.victas,select=c(record_id,treatment,death_30d,
                                      death_30d.cat,death_30days))
dat.model2←upData(dat.model2,treatment=factor(treatment,
                                              levels=c("Treatment","Control")),
                                 treatment=relevel(treatment,ref="Control"),
                                 Srv_mortality=Surv(death_30days,death_30d))
ddist2 ← datadist(dat.model2)
options(datadist = "ddist2")
lrm.model1←lrm(death_30d.cat=="Yes"~treatment,data=dat.model2)
```

To compare 30-day mortality between treatment groups, a univariate logistic regression model was fit due to the binary nature of the outcome (i.e. 30-day mortality). The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	0.25	R^2	0.001	C	0.513
FALSE	385	d.f.	1	g	0.053	D_{xy}	0.026
TRUE	116	Pr($>\chi^2$)	0.6190	g_r	1.054	γ	0.053
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	6×10^{-13}			g_p	0.009	τ_a	0.009
				Brier	0.178		

Table 7: Logistic Regresion Model

	OR	**95% C.I.**	**P-value**
Treatment vs. Control	0.900	0.594 - 1.363	0.619

In the univariate model, although results indicate that treatment group is not statistically associated with 30-day mortality. When comparing treatment group to the control group the odds of an 30-day mortality decreases by approximately 10% (OR=0.900 and p-value=0.619).

2.3.4 Cox Proportional Hazard Model

```
cph.model1 ← cph(Surv(death_30days,death_30d)~treatment,data=dat.model2)
```

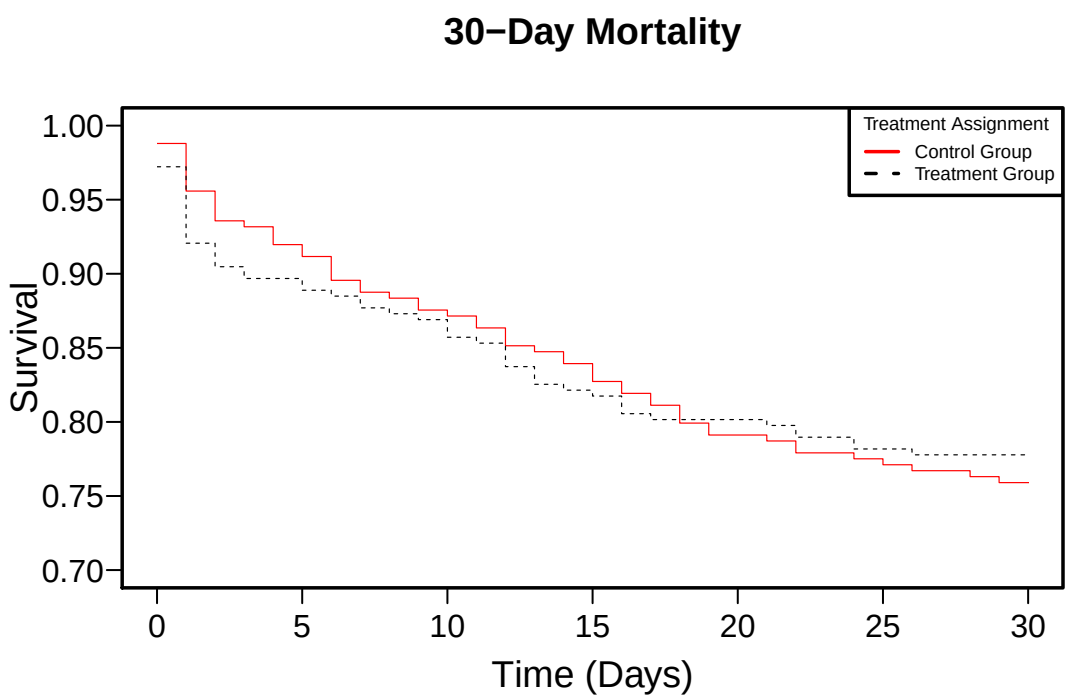
To investigate the time to 30-day mortality between treatment groups, a univariate cox regression model was fit to the data. The point estimates from the model are summarized with Hazard Ratios (HR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the hazard ratio (HR) is the risk of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Tests		Discrimination Indexes	
Obs	501	LR χ^2	0.12	R^2	0.000
Events	116	d.f.	1	D_{xy}	0.010
Center	-0.0329	Pr($>\chi^2$)	0.7249	g	0.033
		Score χ^2	0.12	g_r	1.033
		Pr($>\chi^2$)	0.7249		

Table 8: Cox Regresion Model

	HR	**95% C.I.**	**P-value**
Treatment vs. Control	0.937	0.651 - 1.348	0.725

In the univariate model, although results indicate that treatment group is not statistically associated with time to death within 30-days. When comparing treatment group to the control group the risk of an death decreases by approximately 6% (HR=0.937 and p-value=0.725).



2.4 Secondary end point: 180-Day Mortality

2.4.1 Descriptives

```
latex(summaryM(death_180d.cat.2~treatment, data=addMarginal(dat.victas,treatment,
               label='Total', margloc='last')),file="",where="!h",
               caption="180-Day Mortality by Treatment Assignment",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
               digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 9: 180-Day Mortality by Treatment Assignment

	N	Control	Treatment	Total
		$N = 249$	$N = 252$	$N = 501$
180-Day Mortality	501	38% $\frac{94}{249}$	40% $\frac{102}{252}$	39% $\frac{196}{501}$

N is the number of non-missing values.

2.4.2 Pearson Chi-Square Test

```
tbl1.180 <- table(dat.victas$treatment,dat.victas$death_180d.cat)
secondary.test1.180 <- chisq.test(tbl1.180,correct=FALSE)
secondary.test2.180 <- prop.test(table(dat.victas$treatment,dat.victas$death_180d.cat),
                                 correct=FALSE)
```

```
latex(Tablemodel3.180,file="", where="!h",caption = "Pearson Chi-Square Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Control Prop',
      '\\bf Treatment Prop','{\\bf 95\\% C.I.}'),
      insert.bottom = "",col.just=c("l","c","c","c","c","c"),rowname=NULL)
```

Table 10: Pearson Chi-Square Test

	Test Statistic	**P-value**	**Control Prop**	**Treatment Prop**	**95% C.I.**
180-Day Mortality	0.391	0.532	0.378	0.405	-0.113 - 0.058

Results indicate no statistically significant difference in proportions between treatment group on 180-day mortality.

2.4.3 Logistic Regression Model

```
dat.model2.180 ← subset(dat.victas,select=c(record_id,treatment,death_180d,
                                        death_180d.cat,death_180days))
dat.model2.180 ← upData(dat.model2.180,treatment=factor(treatment,
                                          levels=c("Treatment","Control")),
                              treatment=relevel(treatment,ref="Control"),
                              Srv_mortality=Surv(death_180days,death_180d))
ddist180 ← datadist(dat.model2.180)
options(datadist = "ddist180")
lrm.model1.180 ← lrm(death_180d.cat=="Yes"~treatment,data=dat.model2.180)
```

To compare 180-day mortality between treatment groups, a univariate logistic regression model was fit due to the binary nature of the outcome (i.e. 180-day mortality). The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	0.39	R^2	0.001	C	0.514
FALSE	305	d.f.	1	g	0.057	D_{xy}	0.029
TRUE	196	Pr($>\chi^2$)	0.5320	g_r	1.059	γ	0.057
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	6×10^{-14}			g_p	0.014	τ_a	0.014
				Brier	0.238		

Table 11: Logistic Regresion Model

	OR	**95% C.I.**	**P-value**
Treatment vs. Control	1.121	0.783 - 1.606	0.532

In the univariate model results indicate that treatment group is not statistically associated with 180-day mortality.

2.4.4 Cox Proportional Hazard Model

```
cph.model1.180 <- cph(Surv(death_180days,death_180d)~treatment,data=dat.model2.180)
```

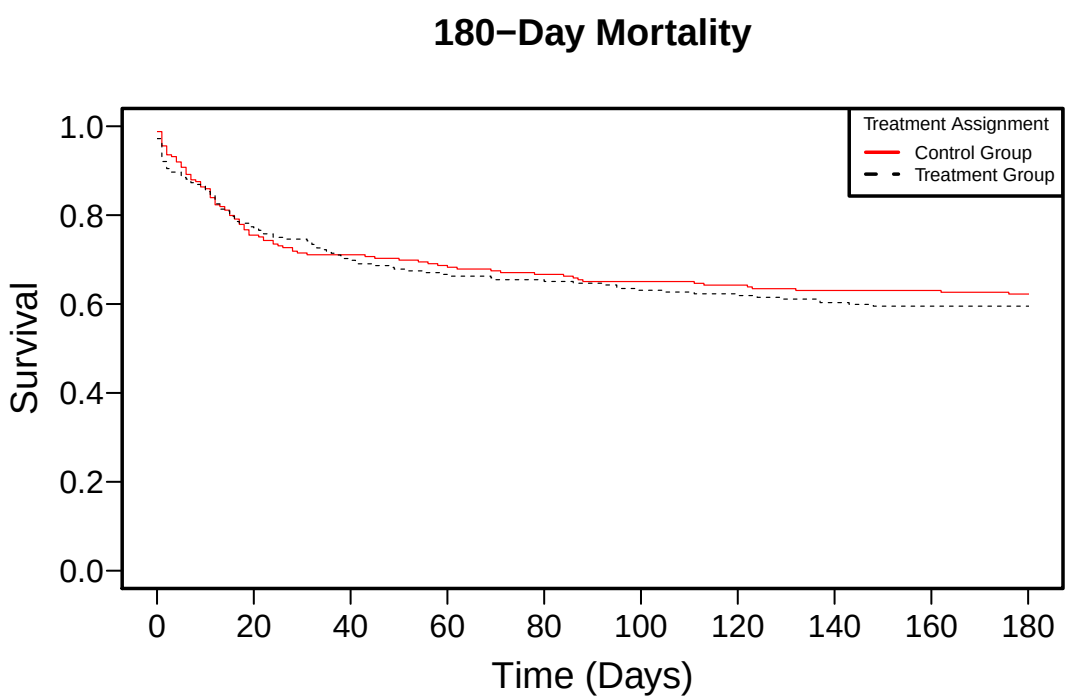
To investigate the time to 180-day mortality between treatment groups, a univariate cox regression model was fit to the data. The point estimates from the model are summarized with Hazard Ratios (HR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the hazard ratio (HR) is the risk of incurring an death within 180 days from randomization when compared to the reference control group.

		Model Tests		Discrimination Indexes	
Obs	501	LR χ^2	0.32	R^2	0.001
Events	196	d.f.	1	D_{xy}	0.019
Center	0.0405	Pr($>\chi^2$)	0.5732	g	0.040
		Score χ^2	0.32	g_r	1.041
		Pr($>\chi^2$)	0.5733		

Table 12: Cox Regresion Model

	HR	**95% C.I.**	**P-value**
Treatment vs. Control	1.084	0.819 - 1.434	0.573

In the univariate model results indicate that treatment group is not statistically associated with time to death within 180-days.



2.5 Adjusted Analyses

2.5.1 Primary endpoint: VVFD (Proportional Odds Model)

```
po.model2←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                          ventilator.vent+ventilator.vaso+admit.reason.cat2+
                          ics.admit.source.cat2+rcs(ap2_total_score,3)+
                          infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                          x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(21)
po.model.bootstrap←bootcov(po.model2, dat.model3.impute1$site)
```

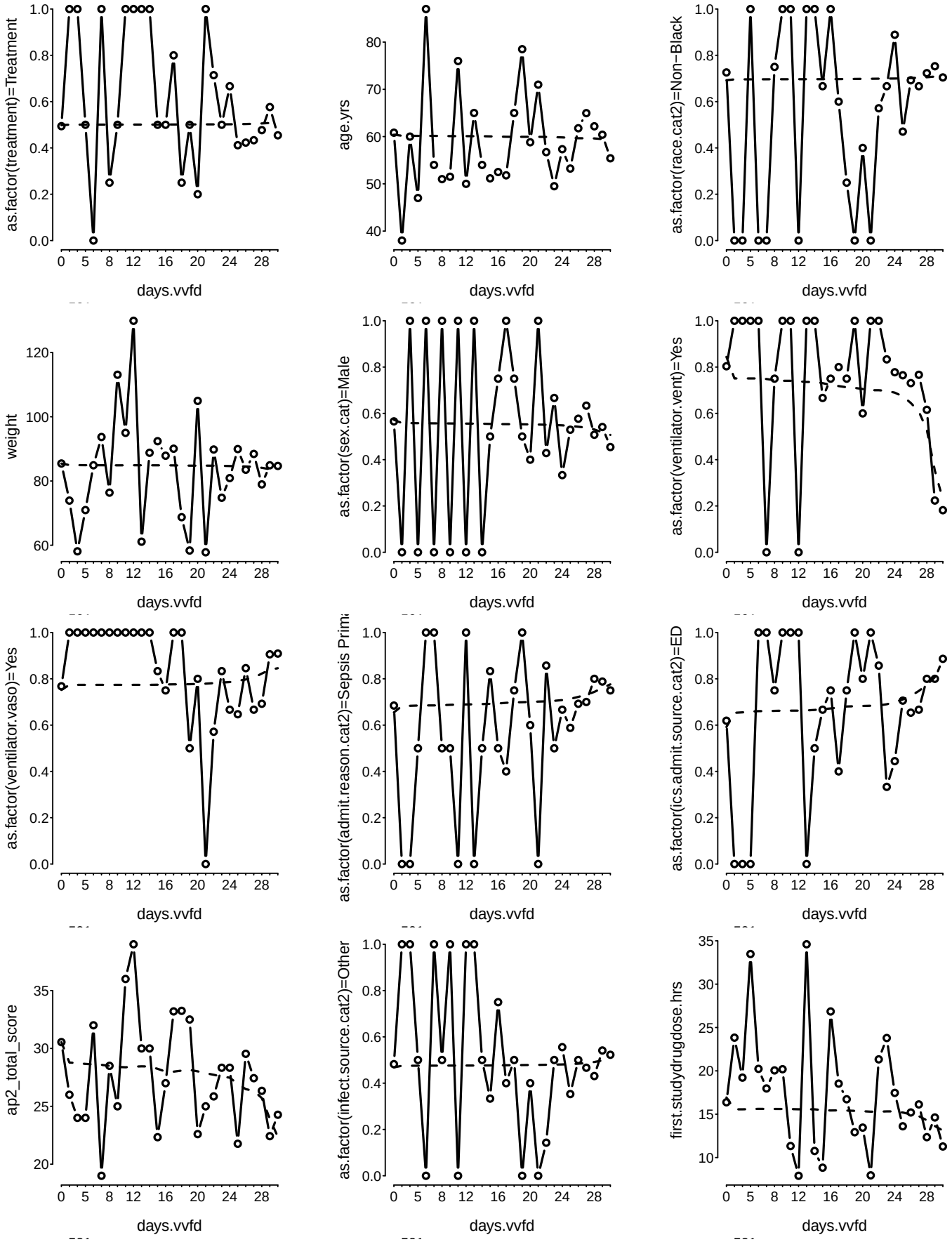
To compare the ventilator-and-vasopressor free days between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable proportional odds model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	186.67	R^2	0.315	C	0.726
Cluster on `dat.model3.impute1$site`		d.f.	17	g	1.374	D_{xy}	0.453
Clusters	41	Pr($> \chi^2$)	<0.0001	g_r	3.951	γ	0.453
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	1×10^{-11}			g_p	0.258	τ_a	0.374
				Brier	0.197		

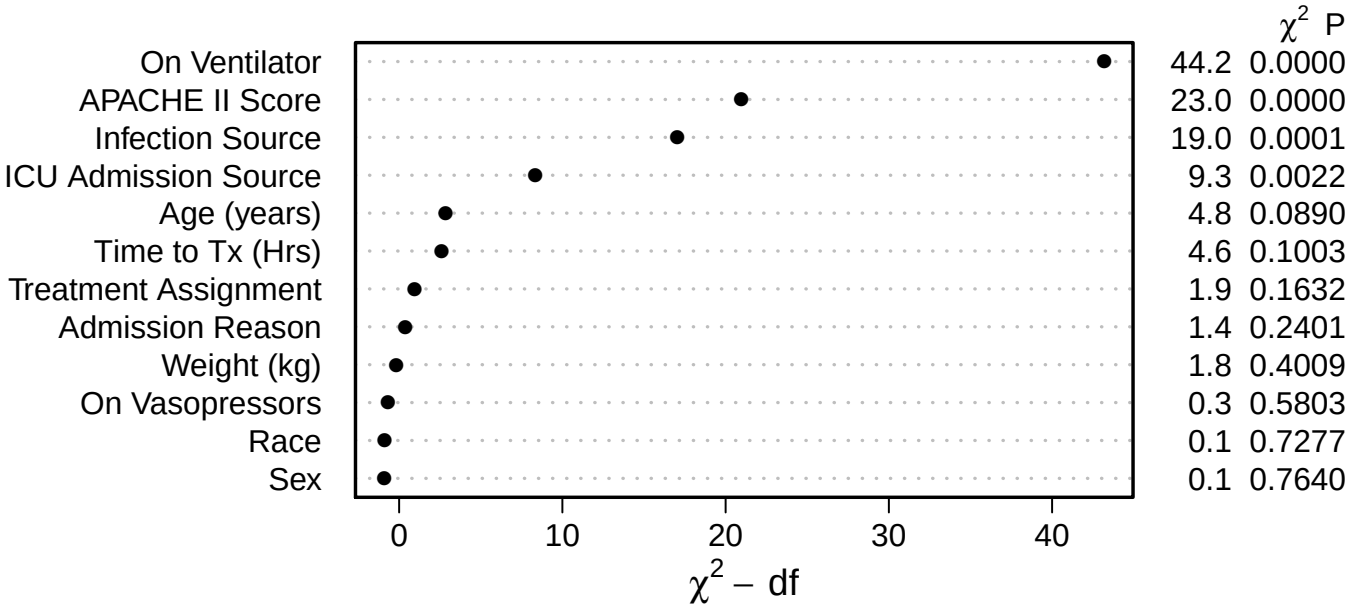
Table 13: Primary Endpoint: Proportional Odds Model

	OR	**95% C.I.**	**P-value**
Age (per IQR)	0.899	0.74 - 1.093	0.089
Weight(kg) (per IQR)	1.039	0.855 - 1.234	0.401
APACHE II (per IQR)	0.533	0.395 - 0.678	<0.0001
Time to Tx (Hrs) (per IQR)	0.700	0.516 - 0.962	0.100
Treatment vs. Control	1.265	0.896 - 1.668	0.163
Black vs. Non-Black	0.949	0.701 - 1.238	0.728
Male vs. Female	1.058	0.733 - 1.562	0.764
Ventilator vs. No Ventilator	0.178	0.105 - 0.281	<0.0001
Vasopressor vs. No Vasopressor	0.896	0.611 - 1.35	0.580
Sepsis Primary vs. Sepsis Secondary	0.756	0.462 - 1.172	0.240
ED Admission vs. Other Admission	1.842	1.331 - 3.031	0.002
Lung Infection vs. Other Type of Infection	1.202	0.870 - 1.643	0.257
Urinary Tract Infection vs. Other Type of Infection	2.635	1.713 - 4.048	<0.0001

2.5.2 PO Plots


as.factor(treatment)=Treatment
age.yrs
as.factor(race.cat2)=Non−Black
weight
as.factor(sex.cat)=Male
as.factor(ventilator.vent)=Yes
as.factor(ventilator.vaso)=Yes
as.factor(admit.reason.cat2)=Sepsis Prim
as.factor(ics.admit.source.cat2)=ED
ap2_total_score
as.factor(infect.source.cat2)=Other
first.studydrugdose.hrs
days.vvfd

2.5.3 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

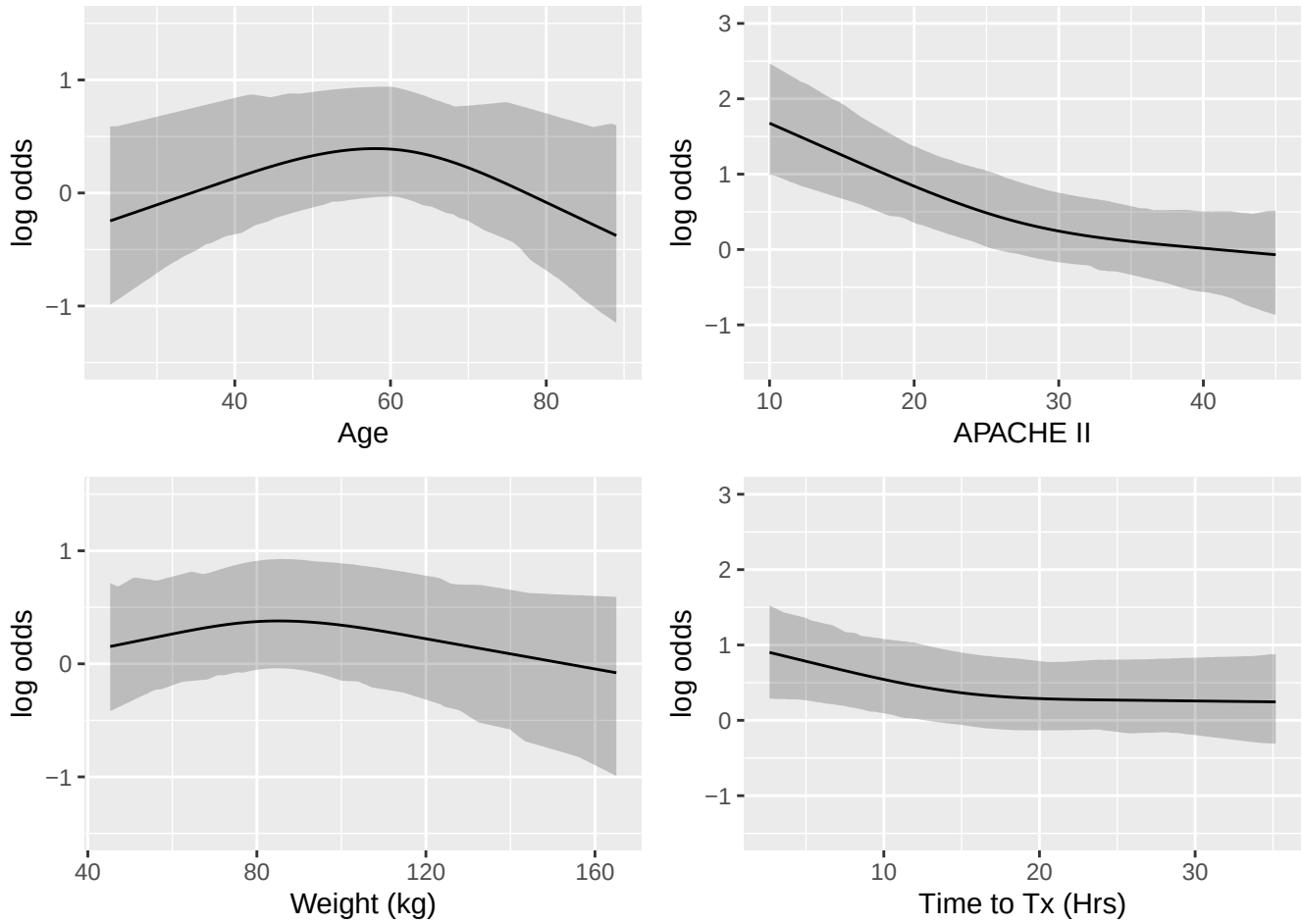
2.5.4 Partial Effect Plots

```
po2.1 <- ggplot(Predict(po.model.bootstrap,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Age")
```

```
po2.2 <- ggplot(Predict(po.model.bootstrap,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Weight (kg)")
```

```
po2.3 <- ggplot(Predict(po.model.bootstrap,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "APACHE II")
```

```
po2.4 <- ggplot(Predict(po.model.bootstrap,first.studydrugdose.hrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



2.5.5 Primary endpoint: VVFD (Interaction Table)

```
po.model2.interact←lrm((days.vvfd)~treatment*(rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                    sex.cat+ventilator.vent+ventilator.vaso+
                                    admit.reason.cat2+ics.admit.source.cat2+
                                    rcs(ap2_total_score,3)+infect.source.cat2+
                                    rcs(first.studydrugdose.hrs,3)),
                                    x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(721)
po.model2.interact.bootstrap←bootcov(po.model2.interact, dat.model3.impute1$site)
```

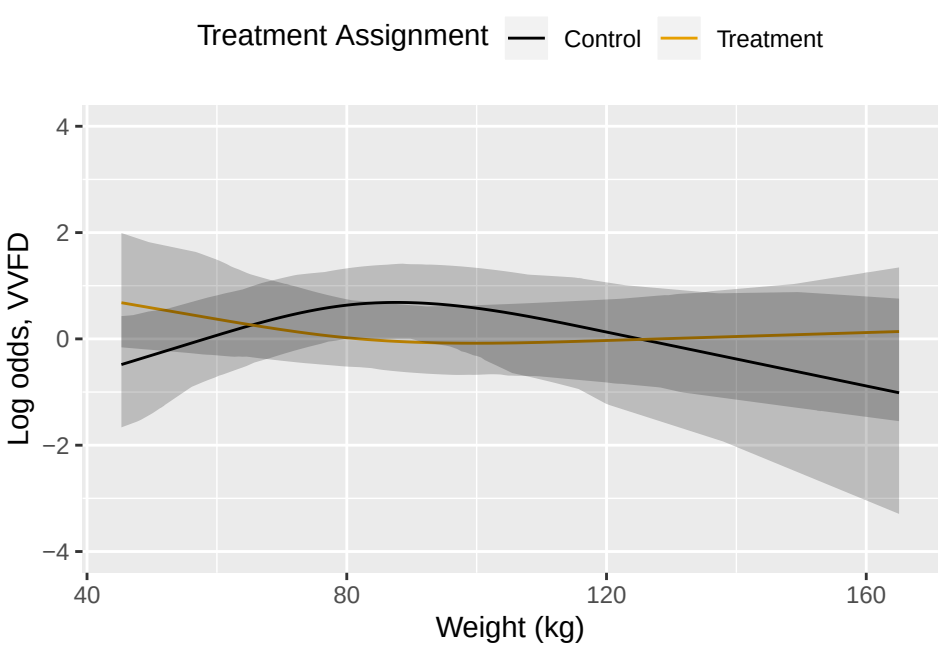
Table 14: Primary Endpoint: Proportional Odds Model (Interaction Table)

po.model2.anova	Chi-Square	d.f.	P
treatment * Age	0.530	2	0.767
treatment * Race	0.002	1	0.964
treatment * Weight	8.187	2	0.017
treatment * Sex	0.342	1	0.559
treatment * On Ventilator	0.745	1	0.388
treatment * On Vasopressor	0.285	1	0.594
treatment * Admission Reason	1.146	1	0.284
treatment * ICU Admission Source	0.076	1	0.783
treatment * APACHE II Score	0.707	2	0.702
treatment * Infection Source	0.083	2	0.960
treatment * Time to Tx	2.654	2	0.265
TOTAL INTERACTION	32.065	16	0.010

Per SAP, results indicate the interaction terms with p-value≤0.2 are Treatment Assignment by Weight.

2.5.6 Partial Effect Plots

```
po2.2.interact←ggplot(Predict(po.model2.interact.bootstrap,weight,treatment),
adj.subtitle=FALSE, legend.position='top')+coord_cartesian(ylim = c(-4.0, 4.0))+
scale_x_continuous(name = "Weight (kg)")+ylab("Log odds, VVFD")
```



2.5.7 Primary endpoint: VVFD (Proportional Odds Model) Sub-Analysis

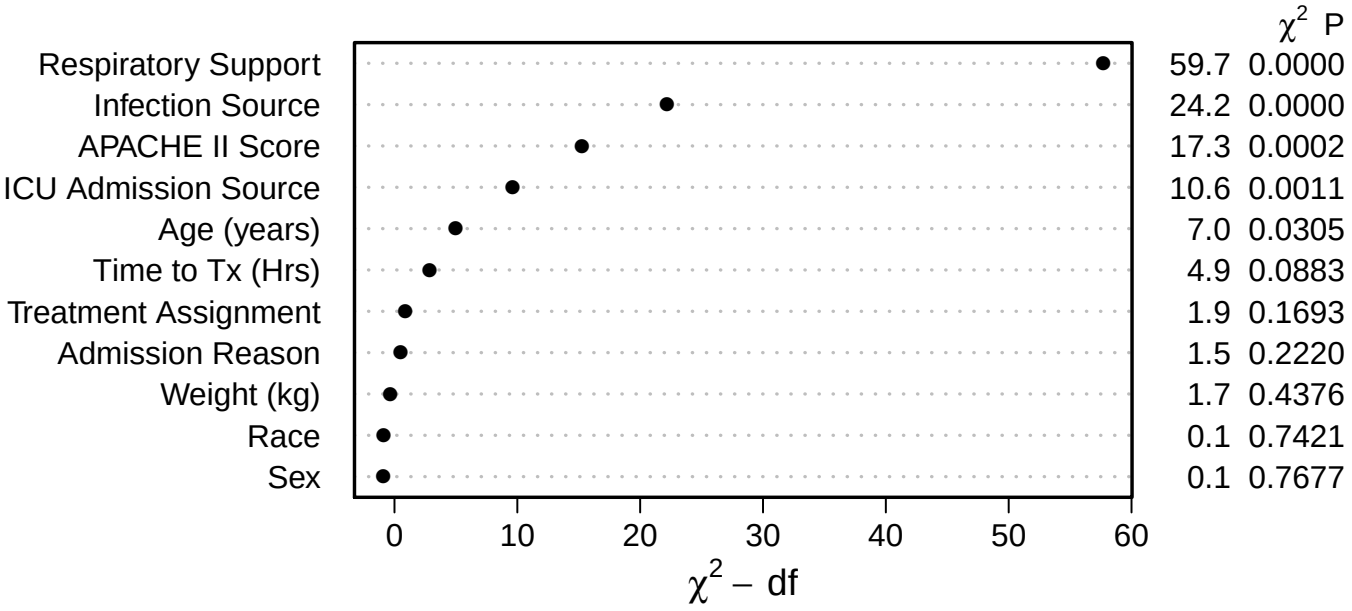
```
po.model2sub←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                          ventilator.3grp+admit.reason.cat2+
                          ics.admit.source.cat2+rcs(ap2_total_score,3)+
                          infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                          x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(31)
po.model.bootstrapsub←bootcov(po.model2sub, dat.model3.impute1$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	183.86	R^2	0.311	C	0.725
Cluster on `dat.model3.impute1$site`		d.f.	17	g	1.358	D_{xy}	0.451
Clusters	41	Pr($>\chi^2$)	<0.0001	g_r	3.889	γ	0.451
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	9×10^{-12}			g_p	0.256	τ_a	0.373
				Brier	0.197		

Table 15: Primary Endpoint: Proportional Odds Model

	OR	**95% C.I.**	**P-value**
Age (per IQR)	0.897	0.722 - 1.098	0.030
Weight(kg) (per IQR)	1.039	0.835 - 1.220	0.438
APACHE II (per IQR)	0.533	0.387 - 0.702	0.0002
Time to Tx (Hrs) (per IQR)	0.698	0.498 - 0.944	0.088
Treatment vs. Control	1.261	0.930 - 1.770	0.169
Black vs. Non-Black	0.947	0.680 - 1.282	0.742
Male vs. Female	1.061	0.680 - 1.559	0.768
Ventilator vs. Both	1.114	0.779 - 1.861	0.652
Vasopressor vs. Both	5.410	3.330 - 8.949	<0.0001
Sepsis Primary vs. Sepsis Secondary	0.754	0.490 - 1.165	0.222
ED Admission vs. Other Admission	1.846	1.330 - 2.655	0.001
Lung Infection vs. Other Type of Infection	1.188	0.889 - 1.540	0.235
Urinary Tract Infection vs. Other Type of Infection	2.656	1.754 - 3.827	<0.00

2.5.8 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

2.5.9 Primary endpoint: VVFD (GEE Model)

```
primary.gee1←geeglm(log(days.vvfd+1)~treatment+age.yrs+race.cat2+weight+sex.cat+
                                      ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                      ics.admit.source.cat2+ap2_total_score+
                                      infect.source.cat2+first.studydrugdose.hrs,
                                      family=(link="gaussian"),
                                      data=dat.model3.impute1, id=site,
                                      corstr = "exchangeable", std.err="san.se")
```

To estimate the marginal treatment effect on ventilator-and-vasopressor free days while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. To improve the distribution of the outcome variable a log transformation was implemented. The resulting point estimates from the model are summarized with the Geometric Mean (GM), 95% confidence intervals, and p-value. For the continuous variables the GM is based on the expected mean number of VVFD's per one unit increase. For the categorical variables the GM is based in comparison to their reference group (vs.).

Table 16: Primary Endpoint: GEE Model

PTable1	**GM**	**95% C.I.**	**P-value**
Age (per 1 year)	1.001	0.995 - 1.008	0.705
Weight(kg) (per kg)	1.001	0.998 - 1.004	0.483
APACHE II (per 1 point)	0.962	0.944 - 0.979	<0.0001
Time to Tx (Hrs) (per Hr)	0.987	0.973 - 1.001	0.076
Treatment vs. Control	1.180	0.936 - 1.487	0.161
Black vs. Non-Black	0.814	0.601 - 1.101	0.182
Male vs. Female	1.060	0.832 - 1.350	0.638
Ventilator vs. No Ventilator	0.420	0.296 - 0.597	<0.0001
Vasopressor vs. No Vasopressor	0.930	0.715 - 1.209	0.588
Sepsis Primary vs. Sepsis Secondary	0.883	0.623 - 1.254	0.487
ED Admission vs. Other Admission	1.437	1.046 - 1.975	0.025
Lung Infection vs. Other Type of Infection	1.155	0.897 - 1.487	0.263
Urinary Tract Infection vs. Other Type of Infection	1.874	1.441 - 2.437	<0.0001

2.5.10 Secondary endpoint: 30-Day Mortality (Logistic Regression Model)

```
lrm.model2←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                                ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(19)
lrm.model.bootstrap←bootcov(lrm.model2, dat.model3.impute1$site)
```

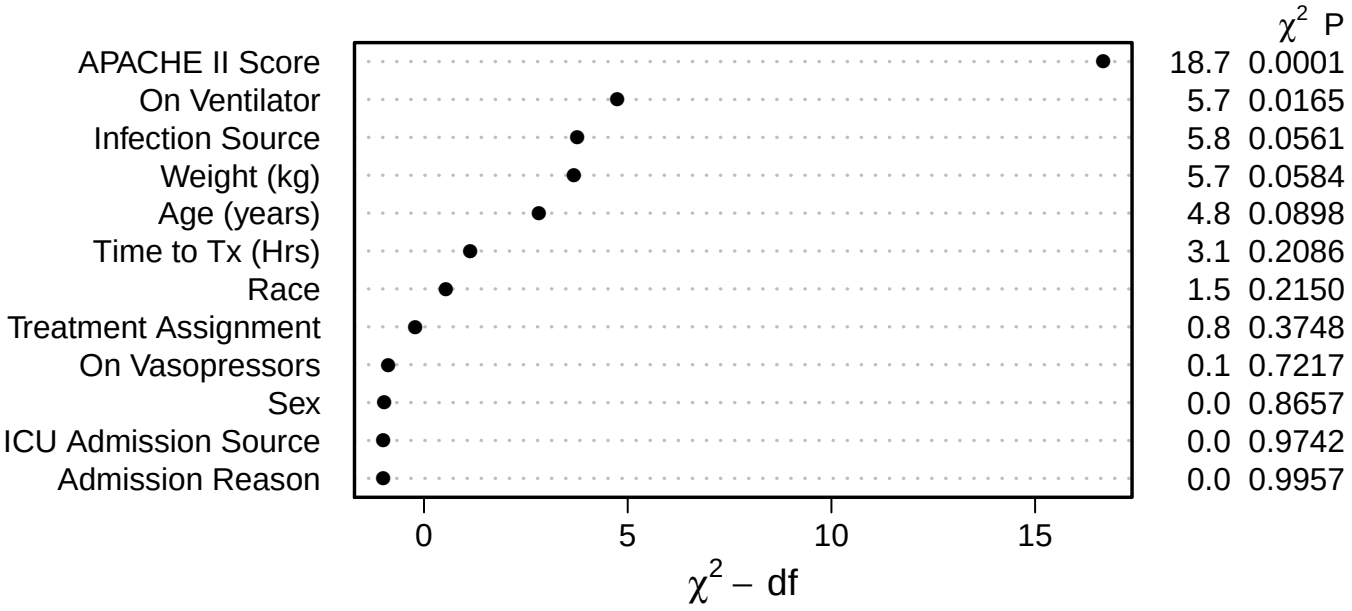
To compare 30-day mortality between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable logistic regression model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	80.22	R^2	0.224	C	0.763
FALSE	385	d.f.	17	g	1.356	D_{xy}	0.525
TRUE	116	Pr($>\chi^2$)	<0.0001	g_r	3.879	γ	0.525
Cluster on `dat.model3.impute1$site`				g_p	0.186	τ_a	0.187
Clusters	41			Brier	0.150		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	3×10^{-6}						

Table 17: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.401	1.000 - 2.119	0.090
Weight(kg) (per IQR)	0.690	0.536 - 1.026	0.058
APACHE II (per IQR)	2.996	1.923 - 6.081	0.0001
Time to Tx (Hrs) (per IQR)	1.346	0.853 - 2.173	0.209
Treatment vs. Control	0.780	0.417 - 1.176	0.375
Black vs. Non-Black	0.703	0.377 - 1.144	0.215
Male vs. Female	0.944	0.471 - 1.805	0.866
Ventilator vs. No Ventilator	2.544	1.332 - 5.378	0.016
Vasopressor vs. No Vasopressor	0.909	0.539 - 1.395	0.722
Sepsis Primary vs. Sepsis Secondary	1.002	0.588 - 1.908	0.995
ED Admission vs. Other Admission	0.991	0.583 - 1.561	0.974
Lung Infection vs. Other Type of Infection	0.789	0.544 - 1.174	0.272
Urinary Tract Infection vs. Other Type of Infection	0.305	0.115 - 0.811	0.017

2.5.11 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

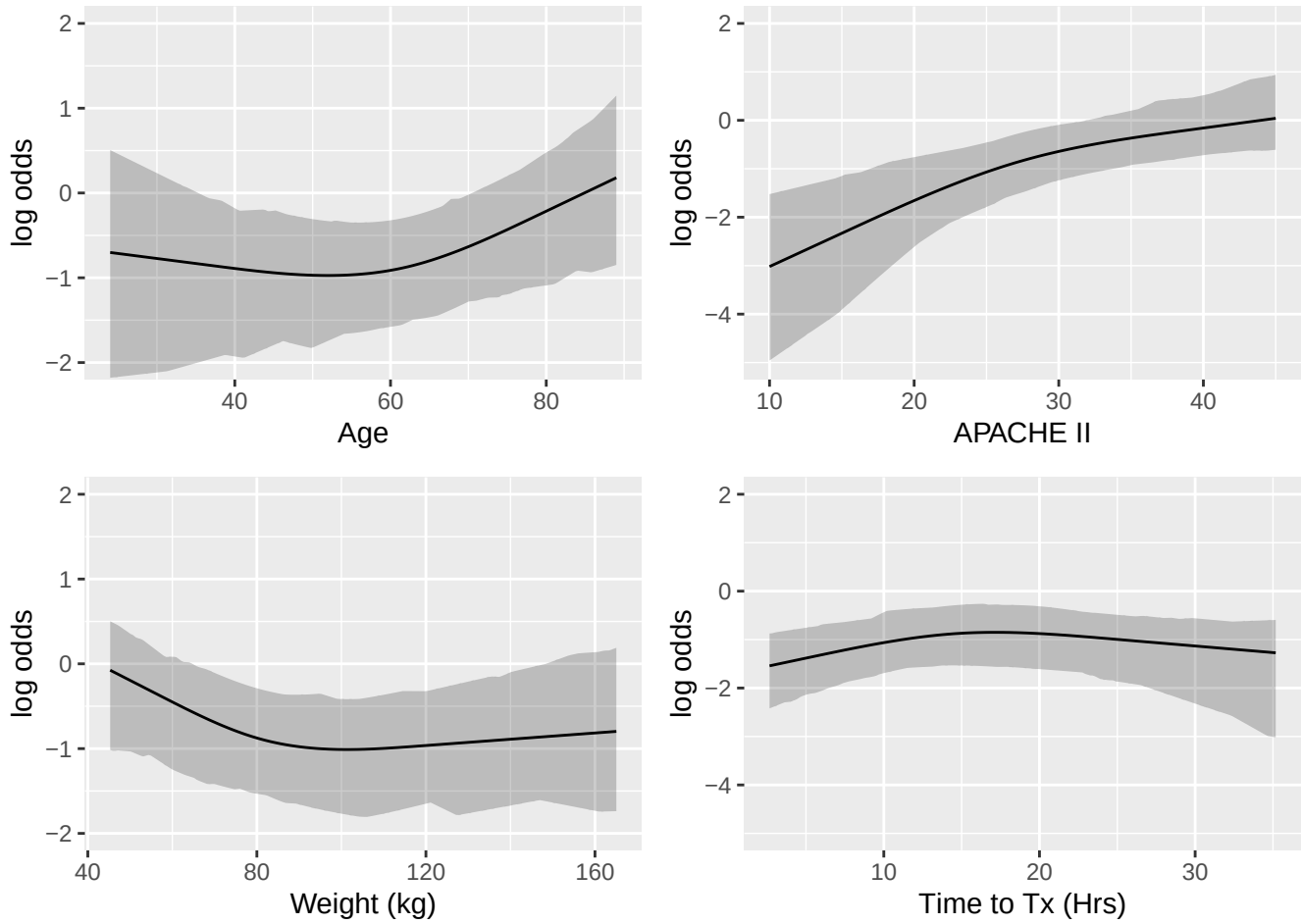
2.5.12 Partial Effect Plots

```
lrm2.1 <- ggplot(Predict(lrm.model.bootstrap,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-2, 2))+
             scale_x_continuous(name = "Age")
```

```
lrm2.2 <- ggplot(Predict(lrm.model.bootstrap,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-2, 2))+
             scale_x_continuous(name = "Weight (kg)")
```

```
lrm2.3 <- ggplot(Predict(lrm.model.bootstrap,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
             scale_x_continuous(name = "APACHE II")
```

```
lrm2.4 <- ggplot(Predict(lrm.model.bootstrap,first.studydrugdose.hrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



2.5.13 Secondary endpoint: 30-Day Mortality (Interaction Table)

```
lrm.model2.interact←lrm(death_30d=="1"~treatment*(rcs(age.yrs,3)+race.cat2+
                                    rcs(weight,3)+
                                    sex.cat+ventilator.vent+ventilator.vaso+
                                    admit.reason.cat2+ics.admit.source.cat2+
                                    rcs(ap2_total_score,3)+infect.source.cat2+
                                    rcs(first.studydrugdose.hrs,3)),
                                    x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(727)
lrm.model2.interact.bootstrap←bootcov(lrm.model2.interact, dat.model3.impute1$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	98.36	R^2	0.270	C	0.788
FALSE	385	d.f.	33	g	1.573	D_{xy}	0.577
TRUE	116	Pr($>\chi^2$)	<0.0001	g_r	4.823	γ	0.577
Cluster on `dat.model3.impute1$site`				g_p	0.203	τ_a	0.206
Clusters	41			Brier	0.143		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	0.0002						

Table 18: Secondary Endpoint: Logistic Regression Model (Interaction Table)

lrm.model2.anova	Chi-Square	d.f.	P
treatment * Age	0.238	2	0.888
treatment * Race	3.052	1	0.081
treatment * Weight	4.306	2	0.116
treatment * Sex	1.029	1	0.310
treatment * On Ventilator	1.280	1	0.258
treatment * On Vasopressor	0.334	1	0.563
treatment * Admission Reason	2.211	1	0.137
treatment * ICU Admission Source	0.002	1	0.967
treatment * APACHE II Score	0.774	2	0.679
treatment * Infection Source	0.611	2	0.737
treatment * Time to Tx	0.281	2	0.869
TOTAL INTERACTION	17.936	16	0.328

Per SAP, results indicate the interaction terms with p-value≤0.2 are Treatment Assignment by Race, Treatment Assignment by Weight, and Treatment Assignment by Admission Reason.

Table 19: Secondary Endpoint: Logistic Regression Model

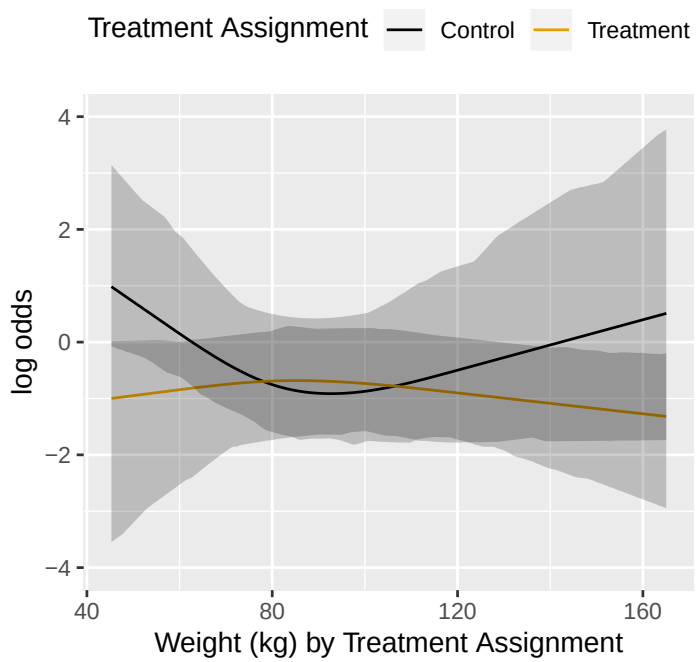
	OR	**95% C.I.**
Control: Sepsis Primary vs. Sepsis Secondary	0.678	0.328 - 1.911
Treatment: Sepsis Primary vs. Sepsis Secondary	1.706	0.556 - 5.993

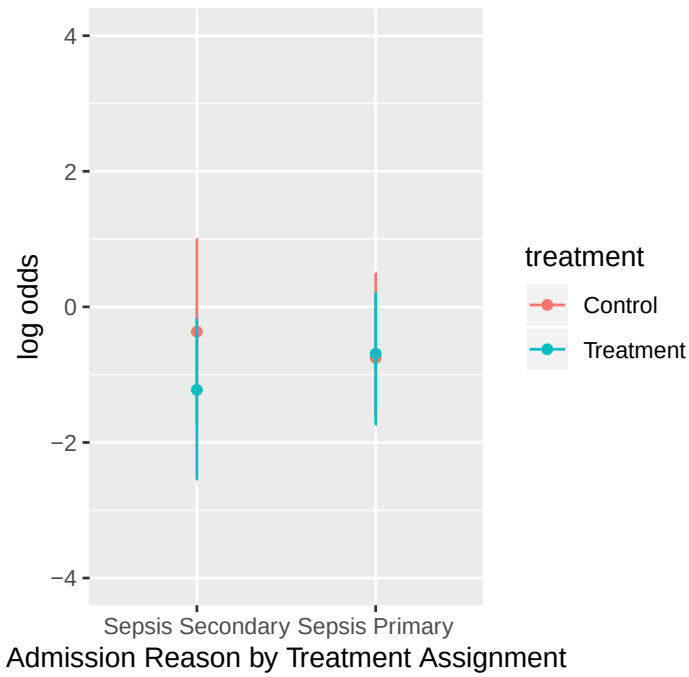
2.5.14 Partial Effect Plots

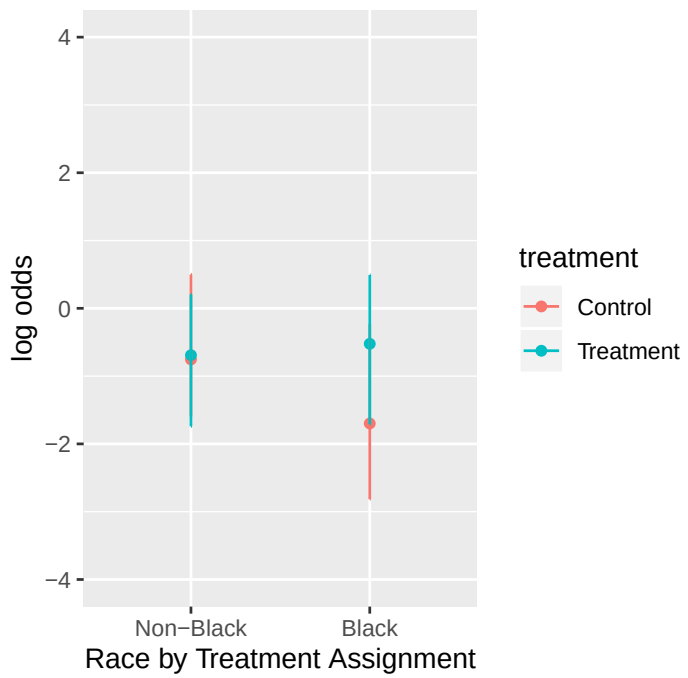
```
lrm2.2.interact←ggplot(Predict(lrm.model2.interact.bootstrap,weight,treatment),
adj.subtitle=FALSE,legend.position='top')+coord_cartesian(ylim = c(-4.0, 4.0))+
scale_x_continuous(name = "Weight (kg) by Treatment Assignment")
```

```
lrm2.2.1.interact←ggplot(Predict(lrm.model2.interact.bootstrap,race.cat2,treatment),
adj.subtitle=FALSE,legend.position='top',xlab=xl1)+coord_cartesian(ylim = c(-4.0, 4.0))
```

```
lrm2.5.interact←ggplot(Predict(lrm.model2.interact.bootstrap,admit.reason.cat2,treatment),
adj.subtitle=FALSE,legend.position='top',xlab=xl2)+coord_cartesian(ylim = c(-4.0, 4.0))
```







2.5.15 Secondary endpoint: 30-Day Mortality (Logistic Regression Model) Sub-Analysis

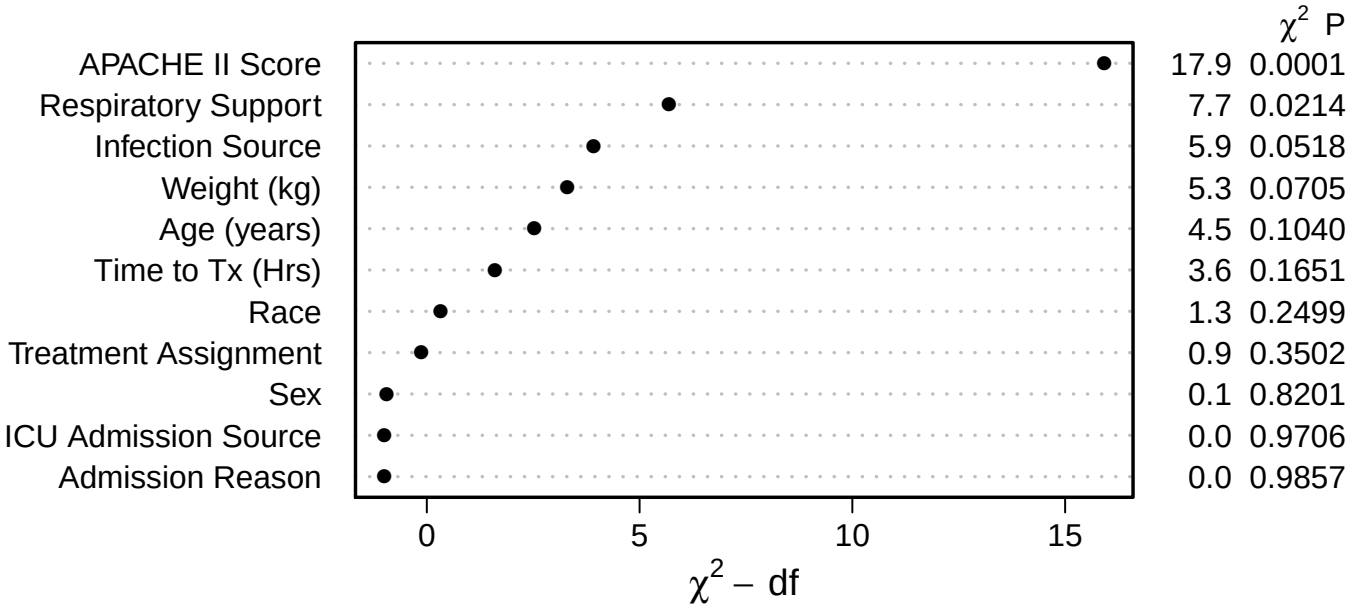
```
lrm.model2sub←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                sex.cat+ventilator.3grp+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3.impute1)
set.seed(30)
lrm.model.bootstrapsub←bootcov(lrm.model2sub, dat.model3.impute1$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	501	LR χ^2	79.98	R^2	0.223	C	0.762
FALSE	385	d.f.	17	g	1.354	D_{xy}	0.524
TRUE	116	Pr($>\chi^2$)	<0.0001	g_r	3.871	γ	0.525
Cluster on `dat.model3.impute1$site`				g_p	0.185	τ_a	0.187
Clusters	41			Brier	0.150		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	3×10^{-6}						

Table 20: Secondary Endpoint: Logistic Regression Model

	OR	**95% C.I.**	**P-value**
Age (per IQR)	1.403	1.057 - 2.027	0.104
Weight(kg) (per IQR)	0.691	0.529 - 1.001	0.070
APACHE II (per IQR)	2.994	1.824 - 5.822	0.0001
Time to Tx (Hrs) (per IQR)	1.348	0.873 - 2.045	0.1651
Treatment vs. Control	0.781	0.454 - 1.328	0.350
Black vs. Non-Black	0.704	0.373 - 1.141	0.250
Male vs. Female	0.941	0.565 - 1.619	0.820
Ventilator vs. Both	1.092	0.548 - 1.801	0.781
Vasopressor vs. Both	0.396	0.176 - 0.781	0.017
Sepsis Primary vs. Sepsis Secondary	1.006	0.588 - 2.031	0.986
ED Admission vs. Other Admission	0.988	0.486 - 1.780	0.971
Lung Infection vs. Other Type of Infection	0.792	0.515 - 1.238	0.344
Urinary Tract Infection vs. Other Type of Infection	0.301	0.089 - 0.616	0.016

2.5.16 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

2.5.17 Secondary endpoint: 30-day Mortality (GEE Model)

```
secondary.gee2←geeglm(death_30d=="1"~treatment+age.yrs+race.cat2+weight+sex.cat+
                                      ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                      ics.admit.source.cat2+ap2_total_score+
                                      infect.source.cat2+first.studydrugdose.hrs,
                                      family=binomial(link="logit"),
                                      data=dat.model3.impute1, id=site,
                                      corstr = "exchangeable", std.err="san.se")
```

To estimate the marginal treatment effect on 30-day mortality while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. The point estimates from the model are summarized with the Odds Ratios (OR), 95% confidence intervals, and p-value. For the continuous variables the OR is based on the odds of 30-day mortality per one unit increase. For the categorical variables the OR is based in comparison to their reference group (vs.).

Table 21: Secondary Endpoint: GEE Model

STable1	**OR**	**95% C.I.**	**P-value**
Age (per 1 year)	1.017	0.997 - 1.036	0.090
Weight(kg) (per kg)	0.994	0.984 - 1.004	0.208
APACHE II (per 1 point)	1.074	1.044 - 1.105	<0.0001
Time to Tx (Hrs) (per Hr)	1.005	0.985 - 1.026	0.634
Treatment vs. Control	0.756	0.462 - 1.237	0.266
Black vs. Non-Black	0.712	0.444 - 1.143	0.160
Male vs. Female	0.892	0.543 - 1.466	0.653
Ventilator vs. No Ventilator	2.668	1.322 - 5.383	0.006
Vasopressors vs. No Vasopressors	1.014	0.615 - 1.670	0.958
Sepsis Primary vs. Sepsis Secondary	1.069	0.615 - 1.858	0.814
ED Admission vs. Other Admission	0.952	0.603 - 1.504	0.833
Lung Infection vs. Other Type of Infection	0.841	0.560 - 1.261	0.401
Urinary Tract Infection vs. Other Type of Infection	0.340	0.140 - 0.825	0.017

2.6 Adjusted Analyses (Complete Case)

2.6.1 Descriptives

```
latex(summaryM(age.yrs+race.cat+ethnicity.cat+male.cat.2+yrs.educat+weight+bmi+system.3.cat
            system.4.cat.2+system.1.cat.2+system.7.cat.2+malignancy.cat.2+ventilator+
            ventilator.vent.2+ventilator.supporttype+ventilator.vaso.2+
            ics.admit.source.cat+admit.reason.cat+vitals_5+systolic_blood_pressure+
            diastolic_blood_pressure+vitals_1+vitals_7+vitals.9.celcius+wbc_value+
            platelets_value+hem_value_3+lactic_acid+creat_value+ap2_total_score+sofa_seib+
            first.studydrugdose.hrs+infect.source.cat+organism0.cat.2+organism1.cat.2+
            organism2.cat.2+organism4.cat.2+organism5.cat.2+organism6.cat.2+vvfd.zero.2+
            vitc.less4doses.reason+thiamine.less4doses.reason~incl.excl,
            data=addMarginal(dat.victas.cc,incl.excl,label='Total', margloc='last')),
            file="",where="!h",caption="Demographic \\& Clinical variables by
            Inclusion/Exclusion", exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE,
            npct="both",digits=2, landscape=FALSE, longtable=TRUE,
            lines.page=82,what = '%',  legend.bottom = TRUE,size="")
```

Table 22: Demographic & Clinical variables by Inclusion/Exclusion

	N	Inclusion Group $N = 458$	Exclusion Group $N = 43$	Total $N = 501$
Age (years)	501	50 62 71 (60 ±16)	50 58 66 (59 ±17)	50 62 70 (60 ±16)
Race	501			
Black		30% $\frac{137}{458}$	30% $\frac{13}{43}$	30% $\frac{150}{501}$
Caucasian		57% $\frac{259}{458}$	58% $\frac{25}{43}$	57% $\frac{284}{501}$
Other		14% $\frac{62}{458}$	12% $\frac{5}{43}$	13% $\frac{67}{501}$
Ethnicity	501			
Hispanic or Latino		11% $\frac{51}{458}$	12% $\frac{5}{43}$	11% $\frac{56}{501}$
Not Hispanic or Latino		85% $\frac{391}{458}$	81% $\frac{35}{43}$	85% $\frac{426}{501}$
Not Reported		3% $\frac{16}{458}$	7% $\frac{3}{43}$	4% $\frac{19}{501}$
Male	501	54% $\frac{248}{458}$	58% $\frac{25}{43}$	54% $\frac{273}{501}$
Education	501			
Less than High School		9% $\frac{42}{458}$	9% $\frac{4}{43}$	9% $\frac{46}{501}$
High School or GED		14% $\frac{66}{458}$	16% $\frac{7}{43}$	15% $\frac{73}{501}$
Some College		24% $\frac{110}{458}$	19% $\frac{8}{43}$	24% $\frac{118}{501}$
Unknown		52% $\frac{240}{458}$	56% $\frac{24}{43}$	53% $\frac{264}{501}$
Weight (kg)	501	68 80 97 (85 ±27)	64 78 86 (81 ±27)	68 80 97 (85 ±27)
BMI	491	23.5 27.4 33.2 (29.2 ± 9.1)	22.6 25.4 30.7 (27.9 ± 8.9)	23.2 27.1 33.1 (29.1 ± 9.1)
Diabetes	501	33% $\frac{150}{458}$	28% $\frac{12}{43}$	32% $\frac{162}{501}$
Cardiovascular disease	501	52% $\frac{237}{458}$	42% $\frac{18}{43}$	51% $\frac{255}{501}$
Neurological disease	501	19% $\frac{85}{458}$	21% $\frac{9}{43}$	19% $\frac{94}{501}$
Respiratory illness	501	22% $\frac{102}{458}$	21% $\frac{9}{43}$	22% $\frac{111}{501}$
Current Cancer	501	19% $\frac{89}{458}$	16% $\frac{7}{43}$	19% $\frac{96}{501}$
Respiratory Support	500			
Ventilator		20% $\frac{93}{458}$	24% $\frac{10}{42}$	21% $\frac{103}{500}$
Vasopressor		38% $\frac{174}{458}$	38% $\frac{16}{42}$	38% $\frac{190}{500}$
Both		42% $\frac{191}{458}$	38% $\frac{16}{42}$	41% $\frac{207}{500}$
On Ventilator	501	62% $\frac{284}{458}$	60% $\frac{26}{43}$	62% $\frac{310}{501}$
Type of Ventilator Support	309			
Intubation		66% $\frac{186}{283}$	69% $\frac{18}{26}$	66% $\frac{204}{309}$
CPAP or BIPAP		18% $\frac{50}{283}$	19% $\frac{5}{26}$	18% $\frac{55}{309}$
Nasal Flow		16% $\frac{45}{283}$	12% $\frac{3}{26}$	16% $\frac{48}{309}$
Intubation/CPAP/BIPAP/Nasal		1% $\frac{2}{283}$	0% $\frac{0}{26}$	1% $\frac{2}{309}$
On Vasopressors	500	80% $\frac{365}{458}$	76% $\frac{32}{42}$	79% $\frac{397}{500}$
ICU Admission Source	501			
ED		70% $\frac{321}{458}$	74% $\frac{32}{43}$	70% $\frac{353}{501}$
Intermediate Care		1% $\frac{3}{458}$	2% $\frac{1}{43}$	1% $\frac{4}{501}$
Step Down Unit		3% $\frac{16}{458}$	2% $\frac{1}{43}$	3% $\frac{17}{501}$
Hospital Floor		18% $\frac{82}{458}$	12% $\frac{5}{43}$	17% $\frac{87}{501}$
Other		8% $\frac{36}{458}$	9% $\frac{4}{43}$	8% $\frac{40}{501}$
Admission Reason	501			
Sepsis		71% $\frac{326}{458}$	70% $\frac{30}{43}$	71% $\frac{356}{501}$
Other Medical		26% $\frac{117}{458}$	30% $\frac{13}{43}$	26% $\frac{130}{501}$
Other Surgical		3% $\frac{15}{458}$	0% $\frac{0}{43}$	3% $\frac{15}{501}$
Heart Rate	501	80 96 113 (97 ± 23)	81 102 117 (100 ± 25)	80 96 113 (97 ± 23)
Systolic Blood Pressure	501	91 103 118 (105 ± 24)	92 106 122 (107 ± 26)	91 103 119 (106 ± 24)
Diastolic Blood Pressure	501	50 58 67 (59 ±14)	50 55 65 (59 ±20)	50 57 67 (59 ±15)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values.

Table 22: *(continued)*

	N	Inclusion Group $N = 458$	Exclusion Group $N = 43$	Total $N = 501$
Mean Arterial Pressure (MAP)	500	64 72 81 (74 ±15)	65 69 82 (74 ±20)	64 72 81 (74 ±15)
Respiratory Rate	499	18.0 22.0 28.0 (23.1 ± 7.4)	18.0 22.0 27.0 (23.0 ± 6.1)	18.0 22.0 28.0 (23.1 ± 7.3)
Temperature (celsius)	495	36.5 36.9 37.8 (37.1 ± 1.4)	36.6 36.9 38.0 (37.1 ± 1.3)	36.5 36.9 37.8 (37.1 ± 1.4)
White Blood Cell Count	496	6.6 13.4 20.7 (62.9 ±786.4)	7.3 13.2 18.1 (14.1 ± 11.0)	6.6 13.4 19.9 (59.0 ±754.1)
Platelets Count	492	99 178 259 (193 ±128)	120 176 243 (193 ±132)	100 178 258 (193 ±128)
Hemoglobin	498	8.5 10.1 12.0 (10.4 ± 2.6)	8.1 11.3 13.3 (11.0 ± 3.1)	8.5 10.1 12.1 (10.4 ± 2.7)
Lactic Acid	393	1.8 2.8 5.0 (4.7 ±10.3)	1.5 3.1 5.9 (4.8 ± 5.2)	1.8 2.8 5.1 (4.7 ±10.0)
Creatinine Value	498	1.1 1.7 2.8 (2.3 ±2.0)	1.3 1.9 3.5 (2.7 ±1.9)	1.1 1.7 2.8 (2.3 ±2.0)
APACHE II Score	472	20.0 27.0 33.0 (27.0 ± 8.8)	26.5 30.0 38.8 (32.9 ±12.7)	20.8 27.0 33.0 (27.1 ± 9.0)
SOFA Score	501	7.0 9.0 12.0 (9.2 ± 3.5)	7.0 9.0 11.5 (9.1 ± 4.1)	7.0 9.0 12.0 (9.1 ± 3.5)
Time to Tx (Hrs)	490	8.6 15.0 21.3 (15.6 ± 9.2)	4.0 7.3 11.8 (8.8 ± 6.2)	7.9 14.7 20.9 (15.1 ± 9.2)
Infection Source	498			
Lung		35% $\frac{162}{458}$	42% $\frac{17}{40}$	36% $\frac{179}{498}$
Blood/Vascular access		14% $\frac{63}{458}$	2% $\frac{1}{40}$	13% $\frac{64}{498}$
Urinary Tract		16% $\frac{73}{458}$	10% $\frac{4}{40}$	15% $\frac{77}{498}$
Intra-abdominal		15% $\frac{69}{458}$	15% $\frac{6}{40}$	15% $\frac{75}{498}$
Skin or Soft Tissues		6% $\frac{29}{458}$	8% $\frac{3}{40}$	6% $\frac{32}{498}$
Central Nervous System (CNS)		1% $\frac{6}{458}$	0% $\frac{0}{40}$	1% $\frac{6}{498}$
Bone/Joint		1% $\frac{5}{458}$	0% $\frac{0}{40}$	1% $\frac{5}{498}$
Other		5% $\frac{22}{458}$	10% $\frac{4}{40}$	5% $\frac{26}{498}$
Unknown		6% $\frac{29}{458}$	12% $\frac{5}{40}$	7% $\frac{34}{498}$
Organism: Gram Positive	501	32% $\frac{145}{458}$	21% $\frac{9}{43}$	31% $\frac{154}{501}$
Organism: Gram Negative	501	31% $\frac{142}{458}$	23% $\frac{10}{43}$	30% $\frac{152}{501}$
Organism: Fungal	501	6% $\frac{29}{458}$	0% $\frac{0}{43}$	6% $\frac{29}{501}$
Organism: Not Identified	501	13% $\frac{61}{458}$	21% $\frac{9}{43}$	14% $\frac{70}{501}$
Organism: Other	501	15% $\frac{67}{458}$	16% $\frac{7}{43}$	15% $\frac{74}{501}$
Organism: Unknown	501	14% $\frac{65}{458}$	23% $\frac{10}{43}$	15% $\frac{75}{501}$
Zero VVFD due to death	168	68% $\frac{104}{152}$	75% $\frac{12}{16}$	69% $\frac{116}{168}$
Vitamin C: reasons for doses<4	45			
ICU Discharge		38% $\frac{12}{32}$	31% $\frac{4}{13}$	36% $\frac{16}{45}$
Death		59% $\frac{19}{32}$	54% $\frac{7}{13}$	58% $\frac{26}{45}$
Other		3% $\frac{1}{32}$	15% $\frac{2}{13}$	7% $\frac{3}{45}$
Thiamine: reasons for doses<4	44			
ICU Discharge		35% $\frac{11}{31}$	31% $\frac{4}{13}$	34% $\frac{15}{44}$
Death		61% $\frac{19}{31}$	54% $\frac{7}{13}$	59% $\frac{26}{44}$
Other		3% $\frac{1}{31}$	15% $\frac{2}{13}$	7% $\frac{3}{44}$

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values.

2.6.2 Primary endpoint: VVFD (Proportional Odds Model)

```
po.model2cc←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                            ventilator.vent+ventilator.vaso+admit.reason.cat2+
                            ics.admit.source.cat2+rcs(ap2_total_score,3)+
                            infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                            x=TRUE,y=TRUE,data=dat.model3cc)
set.seed(212)
po.model.bootstrapcc←bootcov(po.model2cc, dat.model3cc$site)
```

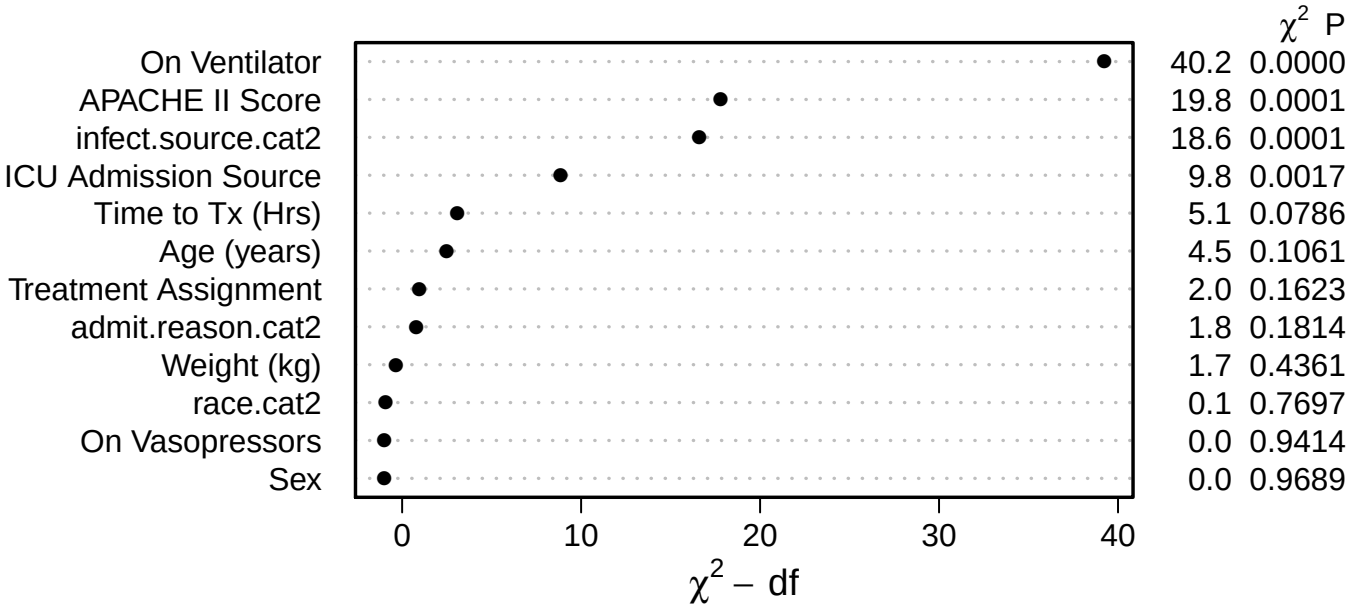
To compare the ventilator-and-vasopressor free days between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable proportional odds model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	458	LR χ^2	180.49	R^2	0.330	C	0.732
Cluster on `dat.model3cc$site`		d.f.	17	g	1.429	D_{xy}	0.464
Clusters	41	Pr($>\chi^2$)	<0.0001	g_r	4.176	γ	0.464
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	7×10^{-12}			g_p	0.263	τ_a	0.384
				Brier	0.196		

Table 23: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.913	0.753 - 1.120	0.106
Weight(kg) (per IQR)	1.042	0.784 - 1.294	0.436
APACHE II (per IQR)	0.495	0.365 - 0.675	0.0001
Time to Tx (Hrs) (per IQR)	0.682	0.466 - 0.948	0.079
Treatment vs. Control	1.316	0.881 - 1.876	0.162
Black vs. Non-Black	0.950	0.694 - 1.323	0.770
Male vs. Female	1.009	0.692 - 1.559	0.969
Ventilator vs. No Ventilator	0.179	0.101 - 0.259	<0.0001
Vasopressor vs. No Vasopressor	1.015	0.698 - 1.516	0.941
Sepsis Primary vs. Sepsis Secondary	0.754	0.487 - 1.111	0.181
ED Admission vs. Other Admission	1.895	1.337 - 2.814	0.002
Lung Infection vs. Other Type of Infection	1.124	0.829 - 1.532	0.442
Urinary Tract Infection vs. Other Type of Infection	2.479	1.693 - 3.826	<0.0001

2.6.3 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

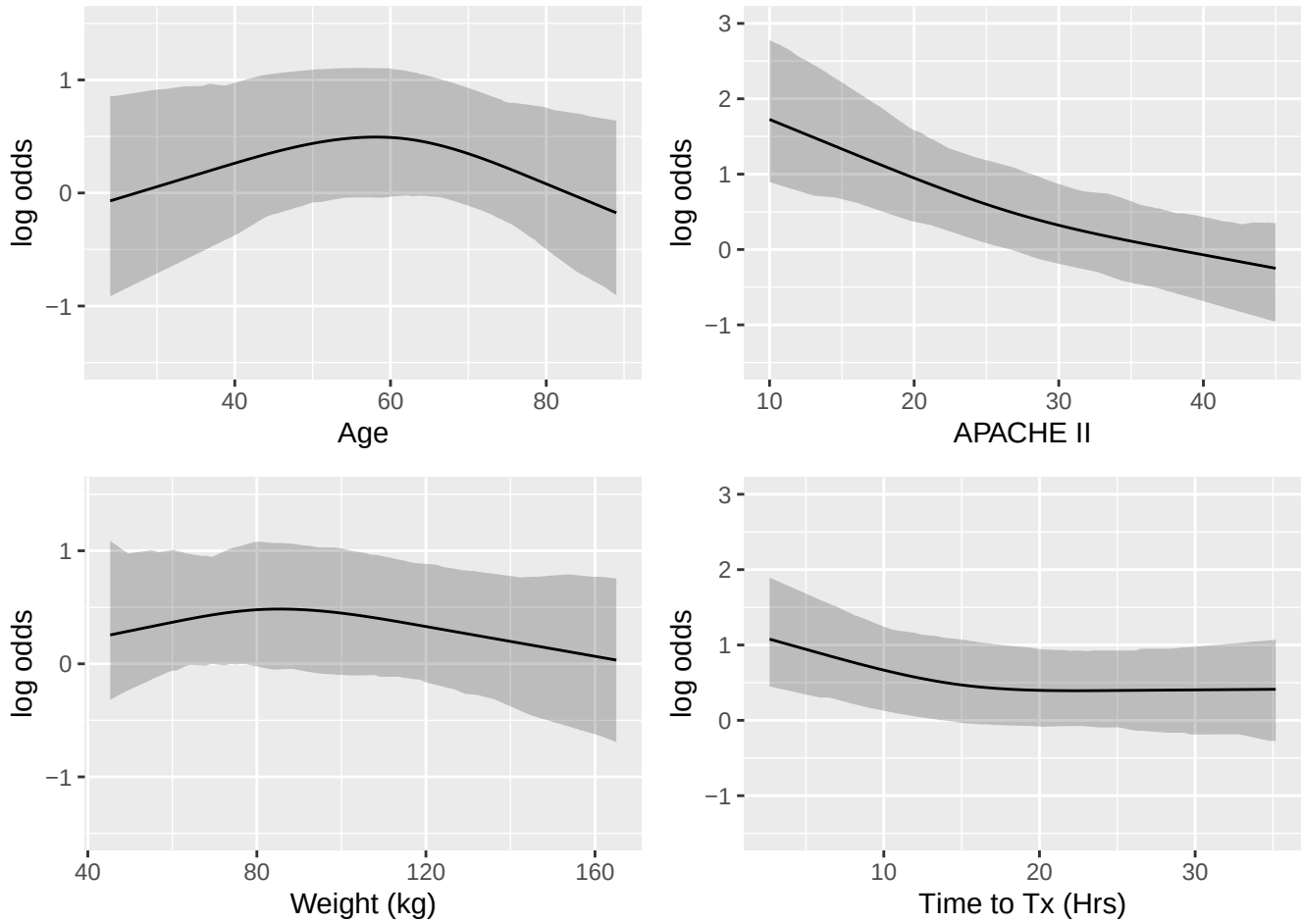
2.6.4 Partial Effect Plots

```
po2.1cc←ggplot(Predict(po.model.bootstrapcc,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Age")
```

```
po2.2cc←ggplot(Predict(po.model.bootstrapcc,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Weight (kg)")
```

```
po2.3cc←ggplot(Predict(po.model.bootstrapcc,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "APACHE II")
```

```
po2.4cc←ggplot(Predict(po.model.bootstrapcc,first.studydrugdose.hrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



2.6.5 Primary endpoint: VVFD (Proportional Odds Model) Sub-Analysis

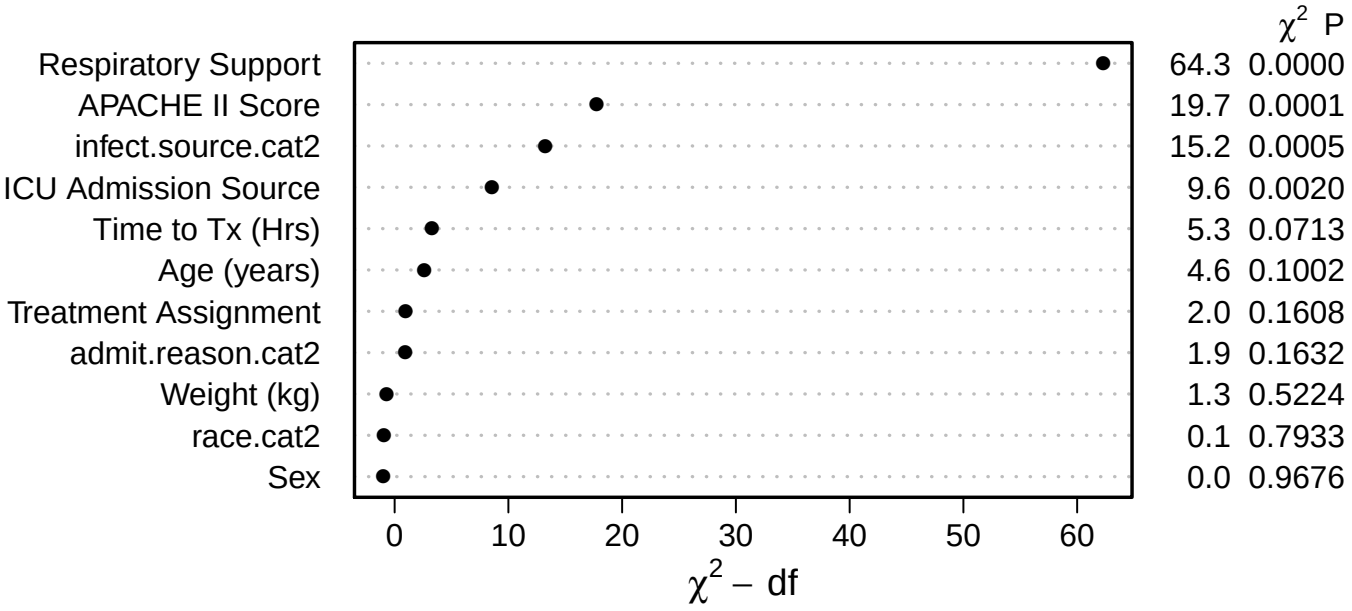
```
po.model2subcc←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                           ventilator.3grp+admit.reason.cat2+
                           ics.admit.source.cat2+rcs(ap2_total_score,3)+
                           infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                           x=TRUE,y=TRUE,data=dat.model3cc.3grp)
set.seed(31)
po.model.bootstrapsubcc←bootcov(po.model2subcc, dat.model3cc.3grp$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	458	LR χ^2	180.49	R^2	0.330	C	0.732
Cluster on `dat.model3cc.3grp$site`		d.f.	17	g	1.430	D_{xy}	0.464
Clusters	41	Pr($>\chi^2$)	<0.0001	g_r	4.177	γ	0.464
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	2×10^{-11}			g_p	0.264	τ_a	0.384
				Brier	0.196		

Table 24: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.913	0.736 - 1.105	0.100
Weight(kg) (per IQR)	1.042	0.822 - 1.28	0.522
APACHE II (per IQR)	0.495	0.354 - 0.673	0.0001
Time to Tx (Hrs) (per IQR)	0.679	0.477 - 0.964	0.071
Treatment vs. Control	1.317	0.931 - 1.989	0.161
Black vs. Non-Black	0.950	0.696 - 1.387	0.793
Male vs. Female	1.009	0.609 - 1.560	0.968
Ventilator vs. Both	0.985	0.666 - 1.599	0.945
Vasopressor vs. Both	5.585	3.488 - 9.023	<0.0001
Sepsis Primary vs. Sepsis Secondary	0.755	0.503 - 1.141	0.163
ED Admission vs. Other Admission	1.895	1.319 - 2.938	0.002
Lung Infection vs. Other Type of Infection	1.123	0.871 - 1.505	0.384
Urinary Tract Infection vs. Other Type of Infection	2.480	1.513 - 3.574	0.0001

2.6.6 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

2.6.7 Primary endpoint: VVFD (GEE Model)

```
primary.gee1cc←geeglm(log(days.vvfd+1)~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                        ics.admit.source.cat2+ap2_total_score+
                                        infect.source.cat2+first.studydrugdose.hrs,
                                        family=(link="gaussian"),
                                        data=dat.model3cc.gee1, id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

To estimate the marginal treatment effect on ventilator-and-vasopressor free days while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. To improve the distribution of the outcome variable a log transformation was implemented. The resulting point estimates from the model are summarized with the Geometric Mean (GM), 95% confidence intervals, and p-value. For the continuous variables the GM is based on the expected mean number of VVFD's per one unit increase. For the categorical variables the GM is based in comparison to their reference group (vs.).

Table 25: Primary Endpoint: GEE Model

PTable1cc	**GM**	**95% C.I.**	**P-value**
Age (per 1 year)	1.004	0.998 - 1.010	0.230
Weight(kg) (per kg)	1.001	0.998 - 1.003	0.694
APACHE II (per 1 point)	0.960	0.946 - 0.974	<0.0001
Time to Tx (Hrs) (per Hr)	0.989	0.975 - 1.003	0.115
Treatment vs. Control	1.219	0.928 - 1.602	0.155
Black vs. Non-Black	0.818	0.647 - 1.033	0.091
Male vs. Female	1.019	0.801 - 1.296	0.881
Ventilator vs. No Ventilator	0.424	0.310 - 0.580	<0.0001
Vasopressor vs. No Vasopressor	1.041	0.782 - 1.386	0.784
Sepsis Primary vs. Sepsis Secondary	0.839	0.629 - 1.119	0.232
ED Admission vs. Other Admission	1.381	1.053 - 1.813	0.020
Lung Infection vs. Other Type of Infection	1.136	0.907 - 1.423	0.268
Urinary Tract Infection vs. Other Type of Infection	1.656	1.257 - 2.182	<0.0001

2.6.8 Secondary endpoint: 30-Day Mortality (Logistic Regression Model)

```
lrm.model2cc←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                sex.cat+
                                ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3cc)
set.seed(19)
lrm.model.bootstrapcc←bootcov(lrm.model2cc, dat.model3cc$site)
```

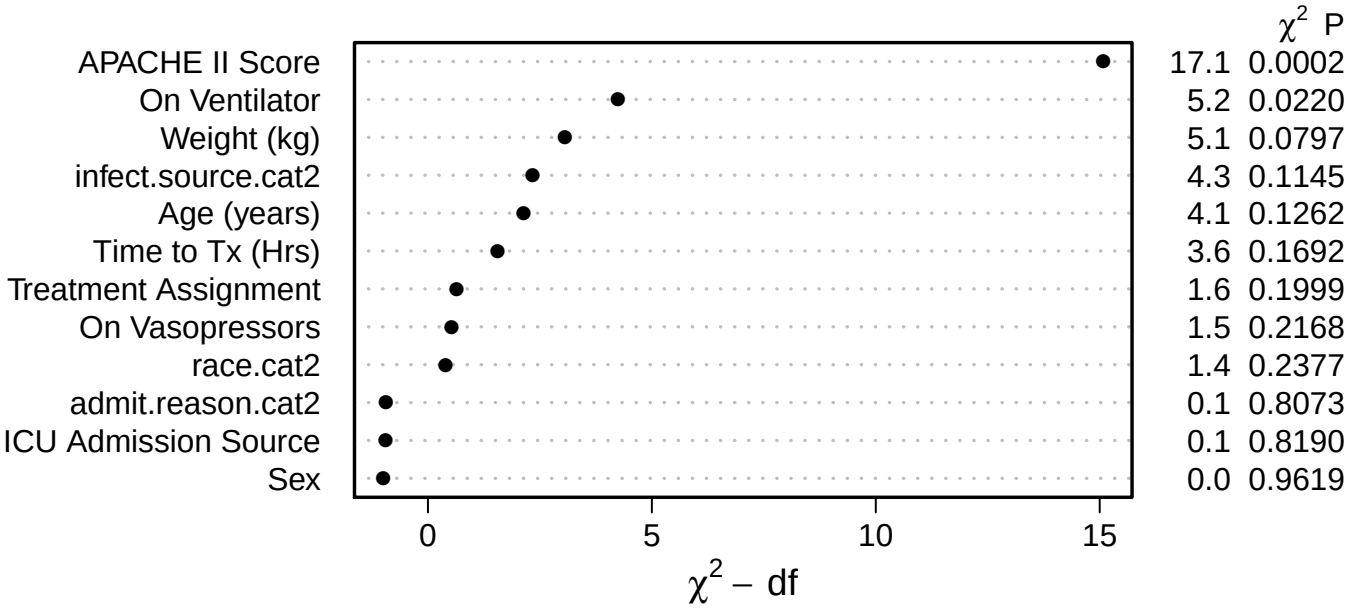
To compare 30-day mortality between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable logistic regression model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	458	LR χ^2	76.94	R^2	0.235	C	0.772
FALSE	354	d.f.	17	g	1.405	D_{xy}	0.544
TRUE	104	Pr($>\chi^2$)	<0.0001	g_r	4.075	γ	0.544
Cluster on `dat.model3cc$site`				g_p	0.189	τ_a	0.191
Clusters	41			Brier	0.146		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	4×10^{-6}						

Table 26: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.288	1.023 - 1.888	0.126
Weight(kg) (per IQR)	0.674	0.512 - 1.003	0.08
APACHE II (per IQR)	3.204	1.96 - 6.846	0.0002
Time to Tx (Hrs) (per IQR)	1.353	0.805 - 2.26	0.1692
Treatment vs. Control	0.662	0.341 - 1.069	0.200
Black vs. Non-Black	0.679	0.316 - 1.133	0.238
Male vs. Female	1.016	0.5 - 1.813	0.962
Ventilator vs. No Ventilator	2.497	1.38 - 5.728	0.022
Vasopressor vs. No Vasopressor	0.736	0.45 - 1.118	0.217
Sepsis Primary vs. Sepsis Secondary	1.069	0.673 - 1.838	0.807
ED Admission vs. Other Admission	0.931	0.513 - 1.597	0.819
Lung Infection vs. Other Type of Infection	0.810	0.520 - 1.197	0.380
Urinary Tract Infection vs. Other Type of Infection	0.349	0.114 - 0.670	0.042

2.6.9 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

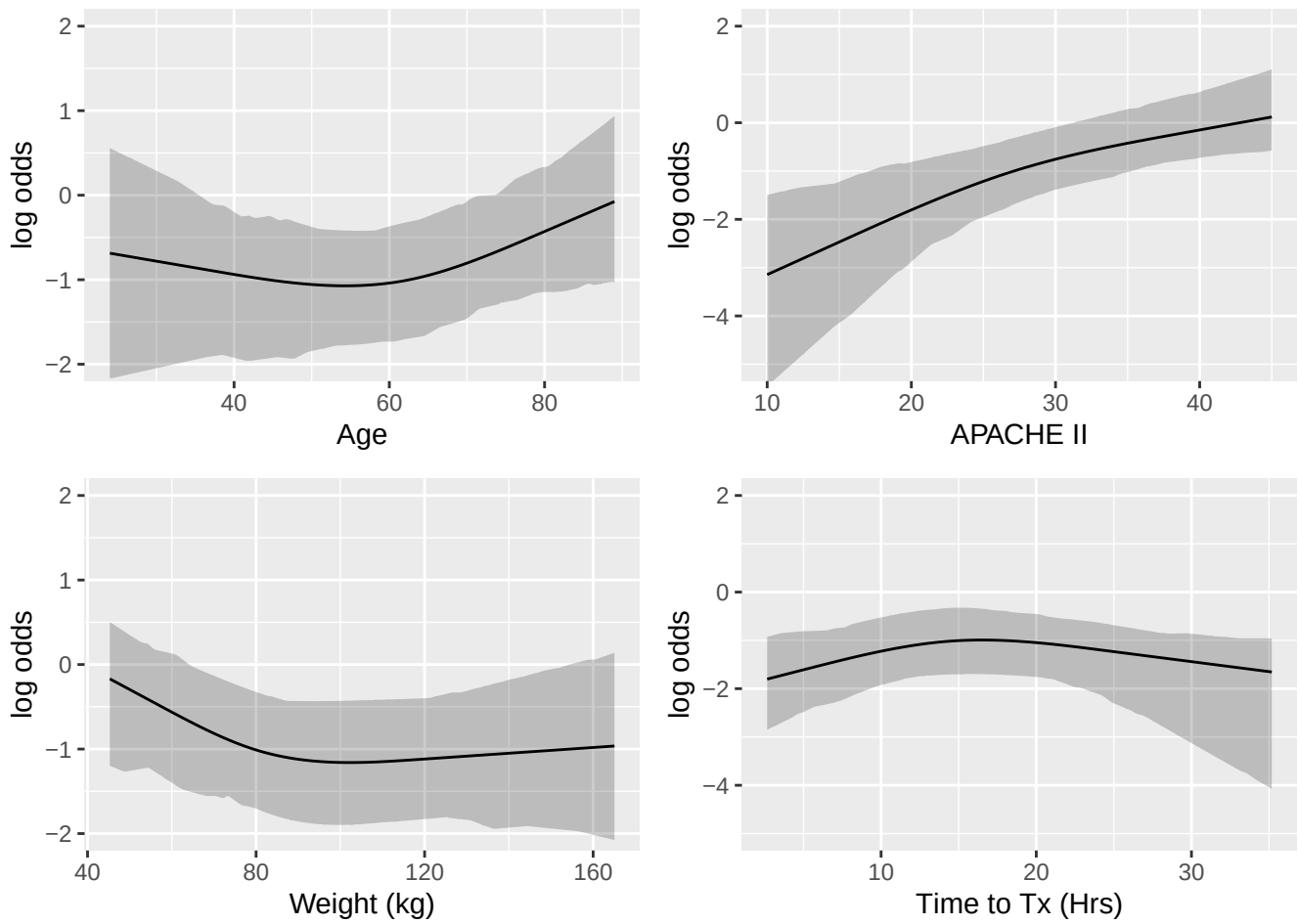
2.6.10 Partial Effect Plots

```
lrm2.1cc←ggplot(Predict(lrm.model.bootstrapcc,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-2, 2))+
             scale_x_continuous(name = "Age")
```

```
lrm2.2cc←ggplot(Predict(lrm.model.bootstrapcc,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-2, 2))+
             scale_x_continuous(name = "Weight (kg)")
```

```
lrm2.3cc←ggplot(Predict(lrm.model.bootstrapcc,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
             scale_x_continuous(name = "APACHE II")
```

```
lrm2.4cc←ggplot(Predict(lrm.model.bootstrapcc,first.studydrugdose.hrs),
             adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



2.6.11 Secondary endpoint: 30-Day Mortality (Logistic Regression Model) Sub-Analysis

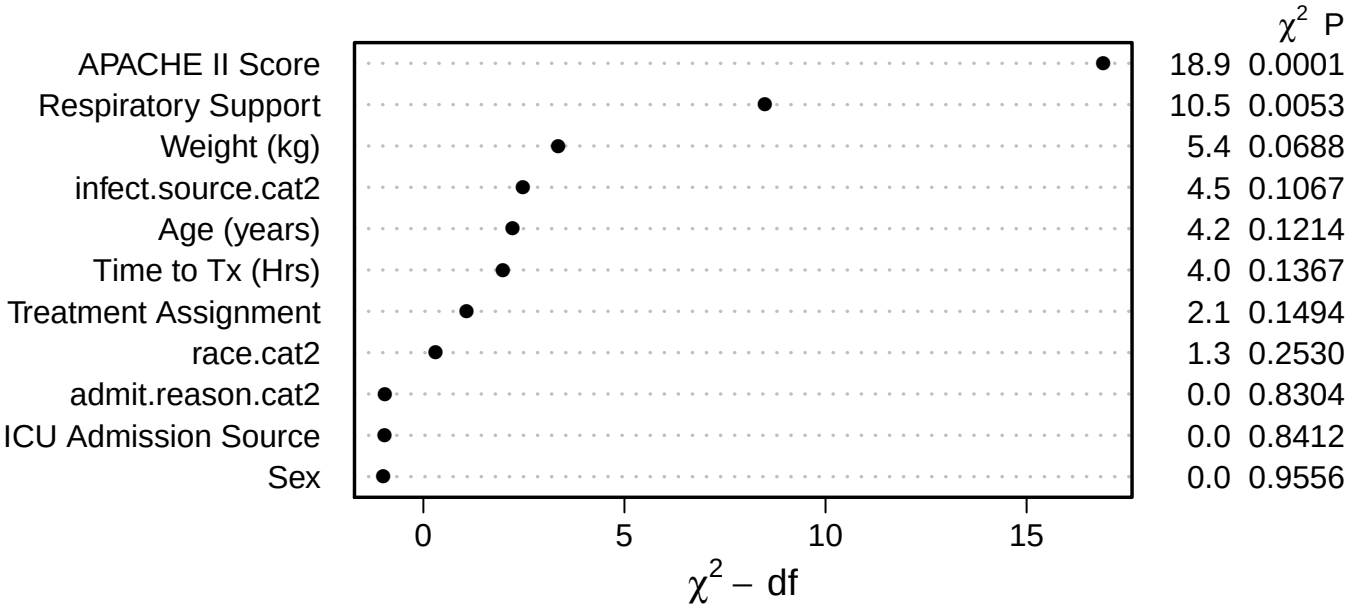
```
lrm.model2subcc←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                sex.cat+ventilator.3grp+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3cc.3grp)
set.seed(30)
lrm.model.bootstrapsubcc←bootcov(lrm.model2subcc, dat.model3cc.3grp$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	458	LR χ^2	76.80	R^2	0.235	C	0.772
FALSE	354	d.f.	17	g	1.403	D_{xy}	0.544
TRUE	104	Pr($>\chi^2$)	<0.0001	g_r	4.067	γ	0.544
Cluster on `dat.model3cc.3grp$site`				g_p	0.188	τ_a	0.191
Clusters	41			Brier	0.146		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	4×10^{-6}						

Table 27: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.288	0.973 - 1.846	0.121
Weight(kg) (per IQR)	0.674	0.514 - 1.019	0.069
APACHE II (per IQR)	3.203	1.838 - 6.372	<0.0001
Time to Tx (Hrs) (per IQR)	1.360	0.754 - 2.394	0.137
Treatment vs. Control	0.661	0.363 - 1.156	0.149
Black vs. Non-Black	0.680	0.322 - 1.159	0.253
Male vs. Female	1.016	0.623 - 1.745	0.956
Ventilator vs. Both	1.357	0.704 - 2.355	0.340
Vasopressor vs. Both	0.401	0.189 - 0.780	0.013
Sepsis Primary vs. Sepsis Secondary	1.068	0.644 - 2.093	0.830
ED Admission vs. Other Admission	0.930	0.459 - 1.820	0.841
Lung Infection vs. Other Type of Infection	0.810	0.486 - 1.344	0.428
Urinary Tract Infection vs. Other Type of Infection	0.349	0.112 - 0.738	0.041

2.6.12 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

2.6.13 Secondary endpoint: 30-day Mortality (GEE Model)

```
secondary.gee2cc←geeglm(death_30d=="1"~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+
                                        admit.reason.cat2+ics.admit.source.cat2+
                                        ap2_total_score+infect.source.cat2+
                                        first.studydrugdose.hrs,
                                        family=binomial(link="logit"),
                                        data=dat.model3cc.gee2, id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

To estimate the marginal treatment effect on 30-day mortality while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. The point estimates from the model are summarized with the Odds Ratios (OR), 95% confidence intervals, and p-value. For the continuous variables the OR is based on the odds of 30-day mortality per one unit increase. For the categorical variables the OR is based in comparison to their reference group (vs.).

Table 28: Secondary Endpoint: GEE Model

STable1cc	**OR**	**95% C.I.**	**P-value**
Age (per 1 year)	1.011	0.993 - 1.028	0.232
Weight(kg) (per kg)	0.994	0.984 - 1.004	0.226
APACHE II (per 1 point)	1.085	1.052 - 1.119	<0.0001
Time to Tx (Hrs) (per Hr)	1.001	0.981 - 1.022	0.897
Treatment vs. Control	0.634	0.364 - 1.103	0.107
Black vs. Non-Black	0.697	0.417 - 1.164	0.168
Male vs. Female	0.984	0.588 - 1.649	0.952
Ventilator vs. No Ventilator	2.527	1.248 - 5.117	0.010
Vasopressors vs. No Vasopressors	0.817	0.482 - 1.383	0.451
Sepsis Primary vs. Sepsis Secondary	1.153	0.699 - 1.903	0.578
ED Admission vs. Other Admission	0.892	0.523 - 1.521	0.675
Lung Infection vs. Other Type of Infection	0.857	0.562 - 1.306	0.473
Urinary Tract Infection vs. Other Type of Infection	0.394	0.161 - 0.963	0.041

2.6.14 Primary endpoint: VVFD (Proportional Odds Model) Excluding Open Label Steroids

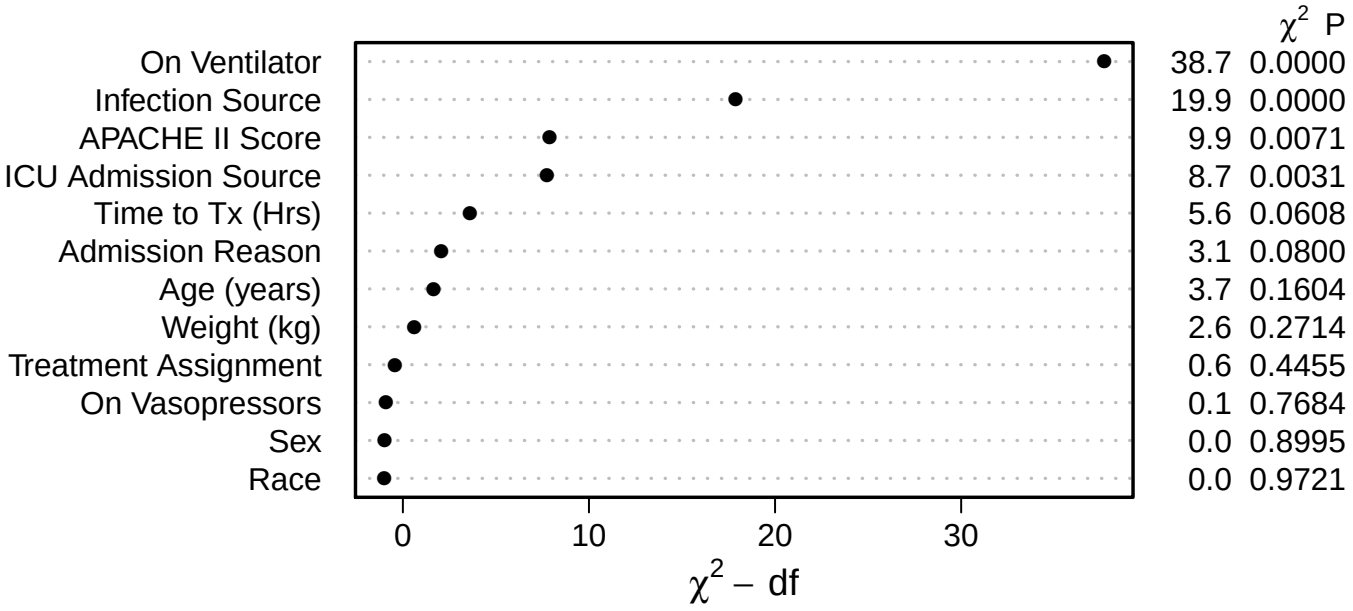
```
po.model2.ster←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                                    ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                    ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                    infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                    x=TRUE,y=TRUE,data=subset(dat.model3.impute1,
                                    record_id nin dat.steroid.control$record_id))
set.seed(50)
po.model.bootstrap.ster←bootcov(po.model2.ster, subset(dat.model3.impute1,
                                 record_id nin dat.steroid.control$record_id)$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	402	LR χ^2	166.29	R^2	0.343	C	0.735
Cluster on	site	d.f.	17	g	1.479	D_{xy}	0.471
Clusters	40	Pr($>\chi^2$)	<0.0001	g_r	4.388	γ	0.471
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	2×10^{-11}			g_p	0.265	τ_a	0.393
				Brier	0.194		

Table 29: Primary Endpoint: Proportional Odds Model (Excludes Open Label Steroids)

	OR	**95% C.I.**	**P-value**
Age (per IQR)	0.829	0.642 - 1.095	0.160
Weight(kg) (per IQR)	0.930	0.755 - 1.181	0.271
APACHE II (per IQR)	0.605	0.439 - 0.824	0.007
Time to Tx (Hrs) (per IQR)	0.657	0.440 - 0.944	0.061
Treatment vs. Control	1.176	0.741 - 1.698	0.446
Black vs. Non-Black	1.006	0.762 - 1.411	0.972
Male vs. Female	1.025	0.723 - 1.460	0.900
Ventilator vs. No Ventilator	0.136	0.068 - 0.236	<0.0001
Vasopressor vs. No Vasopressor	0.926	0.558 - 1.621	0.768
Sepsis Primary vs. Sepsis Secondary	0.633	0.381 - 1.077	0.080
ED Admission vs. Other Admission	2.057	1.339 - 3.371	0.003
Lung Infection vs. Other Type of Infection	1.443	1.066 - 1.961	0.029
Urinary Tract Infection vs. Other Type of Infection	3.035	1.850 - 4.940	<0.0001

2.6.15 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

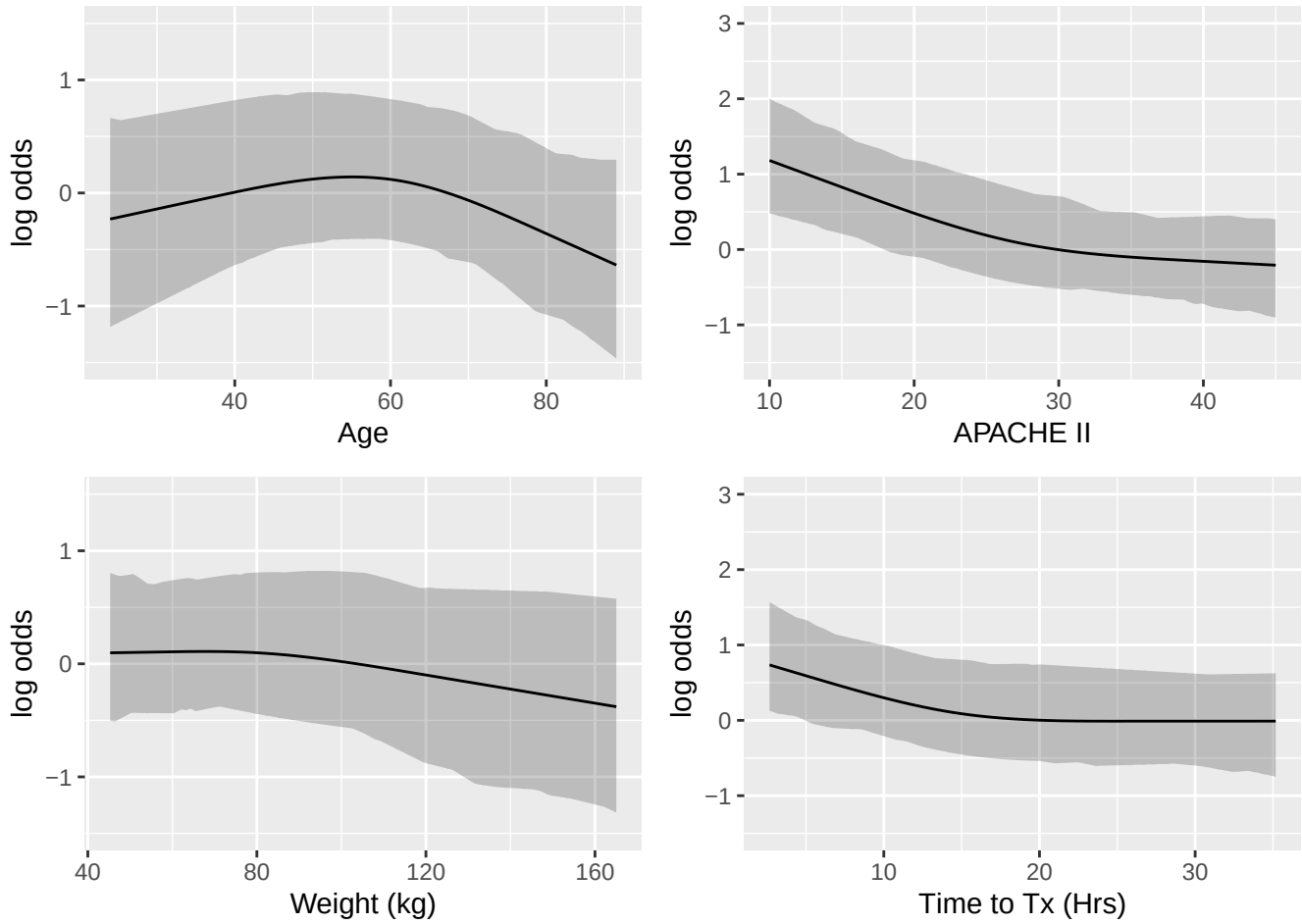
2.6.16 Partial Effect Plots

```
po2.1.ster←ggplot(Predict(po.model.bootstrap.ster,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Age")
```

```
po2.2.ster←ggplot(Predict(po.model.bootstrap.ster,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Weight (kg)")
```

```
po2.3.ster←ggplot(Predict(po.model.bootstrap.ster,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "APACHE II")
```

```
po2.4.ster←ggplot(Predict(po.model.bootstrap.ster,first.studydrugdose.hrs),adj.subtitle=FA
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



2.7 Exploratory End Points (Univariate Comparisons)

```
latex(summaryM(death.rand.icu.2+death_180d.cat.2+sofa.diff+length.icu+
               length.hosp+delirium.coma.fd+days.renal~treatment,data=dat.victas,
               overall=TRUE,test=TRUE,continuous=5),
               file="",where="!h",caption="Exploratory end points by
               treatment assignment (univariate comparisons)",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE,prtest="P",
               npct="both",digits=2, landscape=FALSE, longtable=TRUE,
               lines.page=38,what = '%',  legend.bottom = TRUE,size="footnotesize")
```

Table 30: Exploratory end points by treatment assignment (univariate comparisons)

	N	Control $N = 249$	Treatment $N = 252$	Combined $N = 501$	P-value
Mortality: Randomization and ICU discharge	501	20% $\frac{49}{249}$	21% $\frac{52}{252}$	20% $\frac{101}{501}$	0.79[1]
180-Day Mortality	501	38% $\frac{94}{249}$	40% $\frac{102}{252}$	39% $\frac{196}{501}$	0.53[1]
SOFA score change: Baseline to Day 4	501	2.0 5.0 7.0 (4.9 ±3.3)	3.0 5.0 7.0 (5.4 ±3.2)	3.0 5.0 7.0 (5.2 ±3.2)	0.1[2]
Length of ICU Stay	495	2.0 4.0 8.0 (6.4 ±6.9)	2.0 4.0 8.0 (6.7 ±7.3)	2.0 4.0 8.0 (6.5 ±7.1)	0.82[2]
Length of Hospital Stay	496	5.2 9.0 17.0 (13.5 ±25.7)	6.0 10.0 17.0 (12.6 ±10.0)	6.0 10.0 17.0 (13.0 ±19.4)	0.66[2]
Coma/Delirium Free Days	478	2.0 4.0 5.0 (3.4 ±1.9)	2.0 4.0 5.0 (3.2 ±1.9)	2.0 4.0 5.0 (3.3 ±1.9)	0.45[2]
days.renal	499	0 30 30 (21 ±13)	0 30 30 (21 ±13)	0 30 30 (21 ±13)	0.58[2]

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values. Tests used: [1]Pearson test; [2]Wilcoxon test .

3 Summary Analyses (Per-protocol analysis set)

3.1 Reasons for Protocol Deviations

```
# To create latex... --> actually calls latex.default()
latex(Table1.PD, file = "",where="!h",caption = "Descriptions of Protocol Deviations",
   col.just = c("p{7.0in}","c"),
   colheads = c("Protocol Deviation","N"),
   rowname = NULL, longtable = TRUE,size="small",
   n.rgroup=c(1, 1, 1, 1, 1, 1, 1, 1, 1,1),
   insert.bottom="Table above displays the reasons and counts for each protocol
                  deviation, there exists 103 deviations for 84 subjects.")
```

Table 31: Descriptions of Protocol Deviations

Protocol Deviation	N
Did not receive at least 4 doses	45
Found to violate any inclusion of exclusion criterion	6
Missed doses: Study Drug 1: if >1 missed dose of expected->major deviation	20
Missed doses: Study Drug 2: if >1 missed dose of expected->major deviation; open-label thiamine not considered major deviation	6
Missed doses: Study Drug 3: If >1 missed dose->major deviation if open-label steroids never ordered	3
Missed doses: Study Drug 3: If open-label steroids ordered [>200 mg]: If >1 missed dose [of study drug 3] prior to initial start time of open-label steroids->major deviation	1
Missed doses: Study Drug 3: If open-label steroids ordered [>200 mg]: If >4 doses (i.e., 200 mg hydrocortisone) given after start of open-label steroids dose ->major deviation. Note that we allowed a 24-hour window	1
If start of first round of study drugs occurs beyond 28 hours of start of respiratory or vasopressor support ->major deviation	20
Inadvertent unblinding.	1
Total number of protocol deviations	103

Table above displays the reasons and counts for each protocol deviation, there exists 103 deviations for 84 subjects.

3.2 Descriptives

```
latex(summaryM(age.yrs+race.cat+ethnicity.cat+male.cat.2+yrs.educat+weight+system.3.cat.2+
            system.4.cat.2+system.1.cat.2+system.7.cat.2+malignancy.cat.2+ventilator+
            ventilator.vent.2+ventilator.supporttype+ventilator.vaso.2+
            ics.admit.source.cat+admit.reason.cat+vitals_5+systolic_blood_pressure+
            diastolic_blood_pressure+vitals_1+vitals_7+vitals.9.celcius+wbc_value+
            platelets_value+hem_value_3+lactic_acid+creat_value+ap2_total_score+sofa_seib+
            first.studydrugdose.hrs+infect.source.cat+organism0.cat.2+organism1.cat.2+
            organism2.cat.2+organism4.cat.2+organism5.cat.2+organism6.cat.2+vvfd.zero.2~trea
            data=addMarginal(dat.victaspro,treatment,label='Total', margloc='last')),
            file="",where="!h",caption="Demographic \\& Clinical variables by Treatment Assi
            exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",digits=2,
            landscape=FALSE, longtable=TRUE,lines.page=82,what = '%',
            legend.bottom = TRUE,size="small")
```

Table 32: Demographic & Clinical variables by Treatment Assignment

	N	Control $N = 212$	Treatment $N = 205$	Total $N = 417$
Age (years)	417	49 62 72 (60 ±17)	52 62 70 (60 ±15)	51 62 71 (60 ±16)
Race	417			
Black		33% $\frac{69}{212}$	28% $\frac{58}{205}$	30% $\frac{127}{417}$
Caucasian		55% $\frac{116}{212}$	59% $\frac{121}{205}$	57% $\frac{237}{417}$
Other		13% $\frac{27}{212}$	13% $\frac{26}{205}$	13% $\frac{53}{417}$
Ethnicity	417			
Hispanic or Latino		10% $\frac{21}{212}$	11% $\frac{23}{205}$	11% $\frac{44}{417}$
Not Hispanic or Latino		85% $\frac{181}{212}$	85% $\frac{174}{205}$	85% $\frac{355}{417}$
Not Reported		5% $\frac{10}{212}$	4% $\frac{8}{205}$	4% $\frac{18}{417}$
Male	417	53% $\frac{112}{212}$	57% $\frac{117}{205}$	55% $\frac{229}{417}$
Education	417			
Less than High School		9% $\frac{19}{212}$	9% $\frac{19}{205}$	9% $\frac{38}{417}$
High School or GED		16% $\frac{33}{212}$	14% $\frac{28}{205}$	15% $\frac{61}{417}$
Some College		22% $\frac{46}{212}$	25% $\frac{52}{205}$	24% $\frac{98}{417}$
Unknown		54% $\frac{114}{212}$	52% $\frac{106}{205}$	53% $\frac{220}{417}$
Weight (kg)	417	68 80 98 (85 ±26)	68 78 94 (85 ±28)	68 80 96 (85 ±27)
Diabetes	417	31% $\frac{66}{212}$	33% $\frac{67}{205}$	32% $\frac{133}{417}$
Cardiovascular disease	417	51% $\frac{108}{212}$	52% $\frac{106}{205}$	51% $\frac{214}{417}$
Neurological disease	417	20% $\frac{42}{212}$	18% $\frac{37}{205}$	19% $\frac{79}{417}$
Respiratory illness	417	23% $\frac{48}{212}$	21% $\frac{44}{205}$	22% $\frac{92}{417}$
Current Cancer	417	21% $\frac{44}{212}$	19% $\frac{38}{205}$	20% $\frac{82}{417}$
Respiratory Support	417			
Ventilator		22% $\frac{47}{212}$	20% $\frac{42}{205}$	21% $\frac{89}{417}$
Vasopressor		40% $\frac{84}{212}$	40% $\frac{82}{205}$	40% $\frac{166}{417}$
Both		38% $\frac{81}{212}$	40% $\frac{81}{205}$	39% $\frac{162}{417}$
On Ventilator	417	60% $\frac{128}{212}$	60% $\frac{123}{205}$	60% $\frac{251}{417}$
Type of Ventilator Support	250			
Intubation		66% $\frac{84}{128}$	70% $\frac{86}{122}$	68% $\frac{170}{250}$
CPAP or BIPAP		16% $\frac{21}{128}$	18% $\frac{22}{122}$	17% $\frac{43}{250}$
Nasal Flow		18% $\frac{23}{128}$	10% $\frac{12}{122}$	14% $\frac{35}{250}$
Intubation/CPAP/BIPAP/Nasal		0% $\frac{0}{128}$	2% $\frac{2}{122}$	1% $\frac{2}{250}$
On Vasopressors	416	78% $\frac{165}{211}$	80% $\frac{163}{205}$	79% $\frac{328}{416}$
ICU Admission Source	417			
ED		75% $\frac{158}{212}$	65% $\frac{134}{205}$	70% $\frac{292}{417}$
Intermediate Care		0% $\frac{1}{212}$	1% $\frac{2}{205}$	1% $\frac{3}{417}$
Step Down Unit		4% $\frac{8}{212}$	3% $\frac{7}{205}$	4% $\frac{15}{417}$
Hospital Floor		17% $\frac{35}{212}$	20% $\frac{40}{205}$	18% $\frac{75}{417}$
Other		5% $\frac{10}{212}$	11% $\frac{22}{205}$	8% $\frac{32}{417}$
Admission Reason	417			
Sepsis		71% $\frac{151}{212}$	71% $\frac{146}{205}$	71% $\frac{297}{417}$
Other Medical		26% $\frac{55}{212}$	24% $\frac{50}{205}$	25% $\frac{105}{417}$
Other Surgical		3% $\frac{6}{212}$	4% $\frac{9}{205}$	4% $\frac{15}{417}$

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

Table 32: *(continued)*

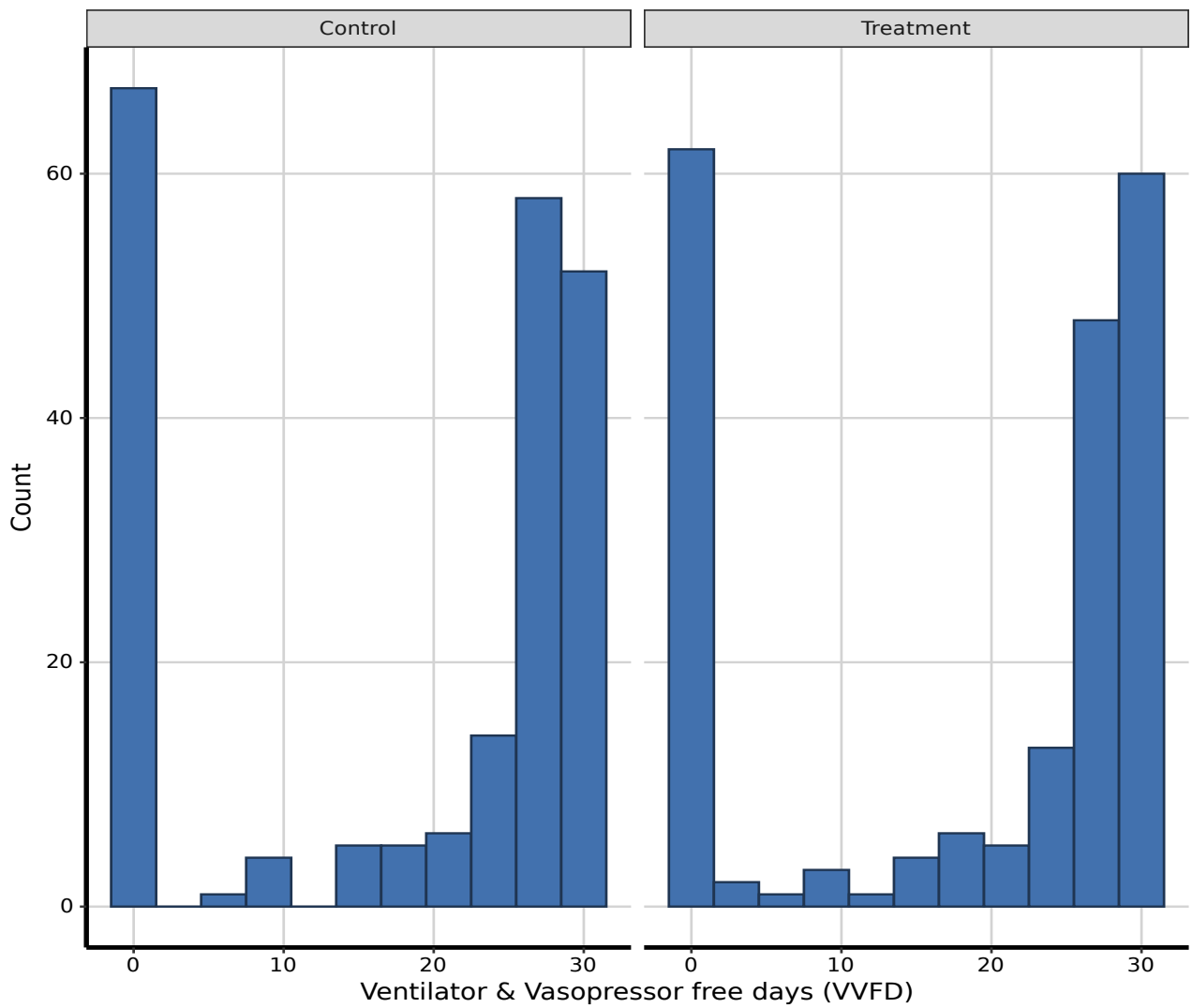
	N	Control	Treatment	Total
		$N = 212$	$N = 205$	$N = 417$
Heart Rate	417	$_{77}$ 94 $_{110}$ (95 ± 22)	$_{83}$ 102 $_{115}$ (99 ± 23)	$_{80}$ 96 $_{113}$ (97 ± 23)
Systolic Blood Pressure	417	$_{92}$ 104 $_{118}$ (106 ± 23)	$_{90}$ 103 $_{119}$ (105 ± 25)	$_{91}$ 103 $_{118}$ (106 ± 24)
Diastolic Blood Pressure	417	$_{51}$ 56 $_{66}$ (59 ±15)	$_{49}$ 58 $_{67}$ (59 ±14)	$_{50}$ 57 $_{67}$ (59 ±14)
Mean Arterial Pressure (MAP)	416	$_{66}$ 71 $_{80}$ (74 ±16)	$_{64}$ 72 $_{81}$ (74 ±14)	$_{65}$ 72 $_{81}$ (74 ±15)
Respiratory Rate	415	$_{18.0}$ 22.0 $_{27.0}$ (23.5 ± 7.5)	$_{18.0}$ 21.0 $_{26.0}$ (22.3 ± 6.9)	$_{18.0}$ 22.0 $_{27.0}$ (22.9 ± 7.3)
Temperature (celsius)	412	$_{36.5}$ 36.9 $_{37.7}$ (37.0 ± 1.4)	$_{36.4}$ 36.9 $_{37.8}$ (37.0 ± 1.3)	$_{36.5}$ 36.9 $_{37.8}$ (37.0 ± 1.3)
White Blood Cell Count	412	$_{6.3}$ 12.5 $_{19.0}$ (14.5 ± 11.5)	$_{7.1}$ 14.4 $_{21.4}$ (123.6 ±1180.3)	$_{6.6}$ 13.6 $_{19.8}$ (68.0 ± 827.3)
Platelets Count	410	$_{100}$ 177 $_{257}$ (200 ±146)	$_{108}$ 181 $_{266}$ (194 ±116)	$_{103}$ 180 $_{261}$ (198 ±132)
Hemoglobin	414	$_{8.6}$ 10.1 $_{11.9}$ (10.4 ± 2.4)	$_{8.3}$ 10.1 $_{12.1}$ (10.4 ± 2.7)	$_{8.5}$ 10.1 $_{12.0}$ (10.4 ± 2.5)
Lactic Acid	332	$_{1.7}$ 2.8 $_{4.1}$ (4.7 ±12.5)	$_{1.8}$ 2.5 $_{4.4}$ (3.6 ± 3.0)	$_{1.8}$ 2.6 $_{4.2}$ (4.1 ± 9.1)
Creatinine Value	414	$_{1.0}$ 1.6 $_{2.5}$ (2.2 ±1.9)	$_{1.1}$ 1.8 $_{3.2}$ (2.5 ±2.1)	$_{1.1}$ 1.7 $_{2.8}$ (2.3 ±2.0)
APACHE II Score	392	$_{19.0}$ 27.0 $_{32.8}$ (26.3 ± 9.0)	$_{22.0}$ 27.0 $_{33.0}$ (27.4 ± 8.2)	$_{20.0}$ 27.0 $_{33.0}$ (26.9 ± 8.6)
SOFA Score	417	$_{6.0}$ 8.5 $_{11.0}$ (8.8 ± 3.5)	$_{7.0}$ 9.0 $_{12.0}$ (9.3 ± 3.4)	$_{7.0}$ 9.0 $_{11.0}$ (9.0 ± 3.4)
Time to Tx (Hrs)	417	$_{7.7}$ 13.6 $_{19.7}$ (14.0 ± 7.1)	$_{8.4}$ 15.2 $_{20.6}$ (14.7 ± 7.4)	$_{7.8}$ 14.5 $_{20.0}$ (14.3 ± 7.2)
Infection Source	415			
Lung		36% $\frac{76}{211}$	35% $\frac{71}{204}$	35% $\frac{147}{415}$
Blood/Vascular access		10% $\frac{22}{211}$	16% $\frac{33}{204}$	13% $\frac{55}{415}$
Urinary Tract		20% $\frac{42}{211}$	12% $\frac{24}{204}$	16% $\frac{66}{415}$
Intra-abdominal		13% $\frac{27}{211}$	17% $\frac{34}{204}$	15% $\frac{61}{415}$
Skin or Soft Tissues		7% $\frac{15}{211}$	6% $\frac{12}{204}$	7% $\frac{27}{415}$
Central Nervous System (CNS)		0% $\frac{1}{211}$	1% $\frac{2}{204}$	1% $\frac{3}{415}$
Bone/Joint		1% $\frac{2}{211}$	1% $\frac{3}{204}$	1% $\frac{5}{415}$
Other		5% $\frac{10}{211}$	5% $\frac{10}{204}$	5% $\frac{20}{415}$
Unknown		8% $\frac{16}{211}$	7% $\frac{15}{204}$	7% $\frac{31}{415}$
Organism: Gram Positive	417	32% $\frac{67}{212}$	30% $\frac{62}{205}$	31% $\frac{129}{417}$
Organism: Gram Negative	417	32% $\frac{68}{212}$	28% $\frac{58}{205}$	30% $\frac{126}{417}$
Organism: Fungal	417	8% $\frac{16}{212}$	5% $\frac{11}{205}$	6% $\frac{27}{417}$
Organism: Not Identified	417	12% $\frac{26}{212}$	14% $\frac{29}{205}$	13% $\frac{55}{417}$
Organism: Other	417	15% $\frac{32}{212}$	15% $\frac{31}{205}$	15% $\frac{63}{417}$
Organism: Unknown	417	15% $\frac{32}{212}$	15% $\frac{31}{205}$	15% $\frac{63}{417}$
Zero VVFD due to death	129	69% $\frac{46}{67}$	60% $\frac{37}{62}$	64% $\frac{83}{129}$

$_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

3.3 Primary end point: VVFD

3.3.1 Histogram

```
p2 ← ggplot(dat.victaspro, aes(x = days.vvfd)) +
        geom_histogram(aes(y = ..count..), binwidth = 3,
                       colour = barlines, fill = barfill) +
        scale_x_continuous(name = "Ventilator & Vasopressor free days (VVFD)") +
        scale_y_continuous(name = "Count") +
        ggtitle("") +
        theme_bw() +
        theme(axis.line = element_line(size=1, colour = "black"),
              panel.grid.major = element_line(colour = "#d3d3d3"),
              panel.grid.minor = element_blank(),
              panel.border = element_blank(), panel.background = element_blank(),
              plot.title = element_text(size = 14, family = "Tahoma", face = "bold"),
              text=element_text(family="Tahoma"),
              axis.text.x=element_text(colour="black", size = 9),
              axis.text.y=element_text(colour="black", size = 9)) +
        facet_grid(. ~ treatment, scales = "free")
```



3.3.2 Descriptives

```
latex(summaryM(days.vvfd~treatment, data=addMarginal(dat.victaspro,treatment,
                label='Total', margloc='last')),file="",where="!h",
                caption="Ventilator and Vasopressor free days (VVFD) by
                Treatment Assignment",
                exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
                digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 33: Ventilator and Vasopressor free days (VVFD) by Treatment Assignment

	N	Control	Treatment	Total
		$N = 212$	$N = 205$	$N = 417$
VVFD	417	$_0$ 26 $_{28}$ (18 ±13)	$_0$ 26 $_{29}$ (18 ±13)	$_0$ 26 $_{29}$ (18 ±13)

$_a$ b $_c$ represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $\bar{X} \pm 1$ SD. N is the number of non-missing values.

3.3.3 Wilcoxon Rank-Sum Test

```
controlpro.vvfd←subset(dat.victaspro,treatment=="Control")$days.vvfd
treatmentpro.vvfd←subset(dat.victaspro,treatment=="Treatment")$days.vvfd
primarypro.test←wilcox.test(controlpro.vvfd,treatmentpro.vvfd,paired=FALSE,conf.int=TRUE)
set.seed(25)
MedDiffPro←Median.diff(controlpro.vvfd, treatmentpro.vvfd, conf.level=0.95,R=10000)
```

```
Tablemodel1Pro←data.frame(variable=c("{\\bf VVFD}"),
                    test.stat=c(0.24),
                    p.val=c(round(primarypro.test$p.val,3)),
                    diff.med=c(format(round((MedDiffPro)$estimate,3),nsmall=3)),
                    c.i=c(paste(format(round(MedDiffPro$conf.int[1],3),nsmall=3),
                          format(round(MedDiffPro$conf.int[2],3),nsmall=3),sep=" - ")))
```

```
latex(Tablemodel1Pro,file="", where="!h",caption = "Wilcoxon Rank-Sum Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Difference in Median',
      '{\\bf 95\\% C.I.}'), insert.bottom = "",col.just=c("l","c","c","c","c"),
      rowname=NULL)
```

Table 34: Wilcoxon Rank-Sum Test

	Test Statistic	**P-value**	**Difference in Median**	**95% C.I.**
VVFD	0.24	0.624	0.000	-3.000 - 2.000

Results indicate no statistically significant difference in number of ventilator-and-vasopressor free days between the treatment group assignments.

3.3.4 Proportional Odds Model

```
dat.model1Pro←subset(dat.victaspro,select=c(record_id,days.vvfd,treatment,age.yrs))
dat.model1Pro←upData(dat.model1Pro,treatment=factor(treatment,
                                                    levels=c("Treatment","Control")),
                                 treatment=relevel(treatment,ref="Control"))
ddist1pro ← datadist(dat.model1Pro)
options(datadist = "ddist1pro")
po.model1pro←lrm(days.vvfd~treatment,data=dat.model1Pro)
```

Per-protocol analysis set, to compare the ventilator-and-vasopressor free days between treatment groups, a univariate multivariable proportional odds model was fit due to the ordered nature of the outcome (i.e. VVFD). In the proportional odds model we assume that the relationship between each level in the outcome variable is proportional, so the coefficients that describe the relationship between the lowest category versus all higher categories of the outcome variable is the same as the relationship that describes the next lowest category and all higher categories and continues for each addtional category. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of having an increased number of VVFDs when compared to the reference control group.

	Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	0.24	R^2	0.001	C	0.508
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	8×10^{-12}	d.f.	1	g	0.043	D_{xy}	0.016
		Pr($>\chi^2$)	0.6228	g_r	1.044	γ	0.033
				g_p	0.010	τ_a	0.014
				Brier	0.234		

Table 35: Proportional Odds Model

	OR	**95% C.I.**	**P-value**
Treatment vs. Control	1.089	0.775 - 1.529	0.623

In the univariate model, although results indicate that treatment group is not statistically associated with ventilator and vasopressor free days. When comparing treatment group to the control group the odds of having an increased number of ventilator and vasopressor free days increases by approximately 9% (OR=1.089 and p-value=0.623)

3.4 Secondary end point: 30-Day Mortality

3.4.1 Descriptives

```
latex(summaryM(death_30d.cat.2~treatment, data=addMarginal(dat.victaspro,treatment,
               label='Total', margloc='last')),file="",where="!h",
               caption="30-Day Mortality by Treatment Assignment",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
               digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 36: 30-Day Mortality by Treatment Assignment

	N	Control	Treatment	Total
		$N = 212$	$N = 205$	$N = 417$
30-Day Mortality	417	22% $\frac{46}{212}$	18% $\frac{37}{205}$	20% $\frac{83}{417}$

N is the number of non-missing values.

3.4.2 Pearson Chi-Square Test

```
tbl1pro←table(dat.victaspro$treatment,dat.victaspro$death_30d.cat)
secondary.test1pro←chisq.test(tbl1pro,correct=FALSE)
secondary.test2pro←prop.test(table(dat.victaspro$treatment,dat.victaspro$death_30d.cat),
                                    correct=FALSE)
```

```
latex(Tablemodel3pro,file="", where="!h",caption = "Pearson Chi-Square Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Control Prop',
      '\\bf Treatment Prop','{\\bf 95\\% C.I.}'),
      insert.bottom = "",col.just=c("l","c","c","c","c","c"),rowname=NULL)
```

Table 37: Pearson Chi-Square Test

	Test Statistic	**P-value**	**Control Prop**	**Treatment Prop**	**95% C.I.**
30-Day Mortality	0.871	0.351	0.217	0.180	-0.04 - 0.113

Results indicate no statistically significant difference in proportions between treatment group on 30-day mortality.

3.4.3 Logistic Regression Model

```
dat.model2pro←subset(dat.victaspro,select=c(record_id,treatment,death_30d,
                                             death_30d.cat,death_30days))
dat.model2pro←upData(dat.model2pro,treatment=factor(treatment,
                                                 levels=c("Treatment","Control")),
                                 treatment=relevel(treatment,ref="Control"),
                                 Srv_mortality=Surv(death_30days,death_30d))
ddist2pro ← datadist(dat.model2pro)
options(datadist = "ddist2pro")
lrm.model1pro←lrm(death_30d.cat=="Yes"~treatment,data=dat.model2pro)
```

Per-protocol analysis set, to compare 30-day mortality between treatment groups, a univariate logistic regression model was fit due to the binary nature of the outcome (i.e. 30-day mortality). The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	0.87	R^2	0.003	C	0.529
FALSE	334	d.f.	1	g	0.115	D_{xy}	0.057
TRUE	83	Pr($>\chi^2$)	0.3503	g_r	1.122	γ	0.114
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	5×10^{-10}			g_p	0.018	τ_a	0.018
				Brier	0.159		

Table 38: Logistic Regresion Model

	OR	**95% C.I.**	**P-value**
Treatment vs. Control	0.795	0.49 - 1.288	0.351

In the univariate model, although results indicate that treatment group is not statistically associated with 30-day mortality. When comparing treatment group to the control group the odds of an 30-day mortality decreases by approximately 20% (OR=0.795 and p-value=0.351).

3.4.4 Cox Proportional Hazard Model

```
cph.model1pro←cph(Surv(death_30days,death_30d)~treatment,data=dat.model2pro)
```

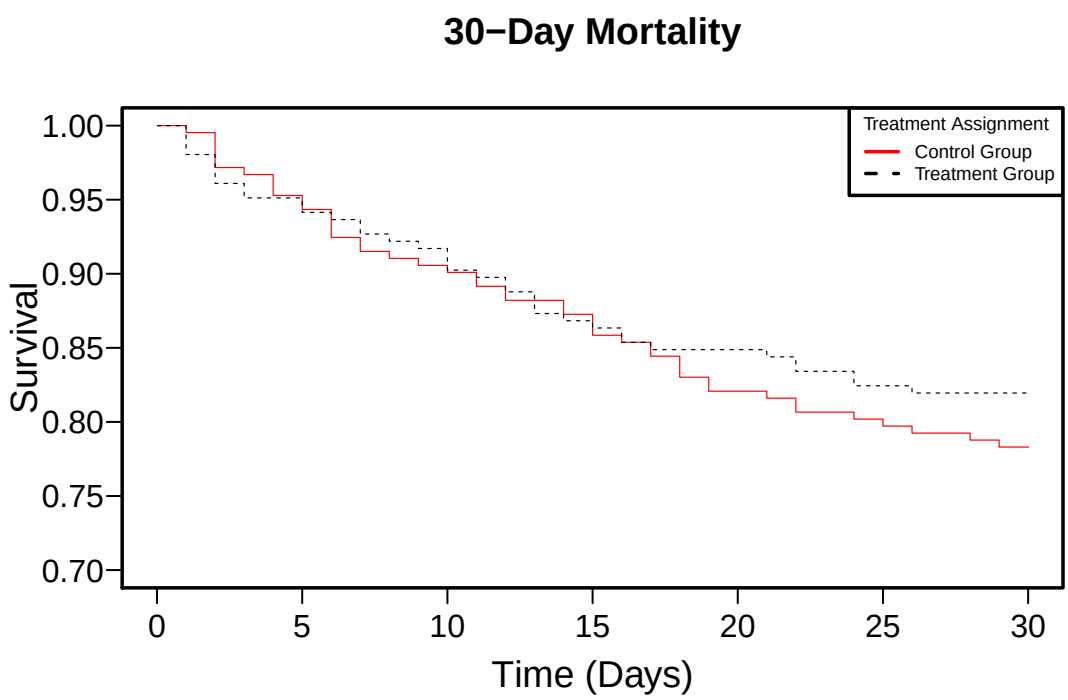
Per-protocol analysis set, to investigate the time to 30-day mortality between treatment groups, a univariate cox regression model was fit to the data. The point estimates from the model are summarized with Hazard Ratios (HR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the hazard ratio (HR) is the risk of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Tests		Discrimination Indexes	
Obs	417	LR χ^2	0.75	R^2	0.002
Events	83	d.f.	1	D_{xy}	0.044
Center	-0.0935	Pr($>\chi^2$)	0.3879	g	0.095
		Score χ^2	0.74	g_r	1.100
		Pr($>\chi^2$)	0.3884		

Table 39: Cox Regresion Model

	HR	95% C.I.	P-value
Treatment vs. Control	0.827	0.536 - 1.275	0.389

In the univariate model, although results indicate that treatment group is not statistically associated with time to death within 30-days. When comparing treatment group to the control group the risk of an death decreases by approximately 17% (HR=0.827 and p-value=0.389).



3.5 Secondary end point: 180-Day Mortality

3.5.1 Descriptives

```
latex(summaryM(death_180d.cat.2~treatment, data=addMarginal(dat.victaspro,treatment,
               label='Total', margloc='last')),file="",where="!h",
               caption="180-Day Mortality by Treatment Assignment",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE, npct="both",
               digits=2,landscape=FALSE,what = '%',legend.bottom = TRUE)
```

Table 40: 180-Day Mortality by Treatment Assignment

	N	Control	Treatment	Total
		$N = 212$	$N = 205$	$N = 417$
180-Day Mortality	417	37% $\frac{78}{212}$	40% $\frac{81}{205}$	38% $\frac{159}{417}$

N is the number of non-missing values.

3.5.2 Pearson Chi-Square Test

```
tbl1pro.180←table(dat.victaspro$treatment,dat.victaspro$death_180d.cat)
secondary.test1pro.180←chisq.test(tbl1pro.180,correct=FALSE)
secondary.test2pro.180←prop.test(table(dat.victaspro$treatment,dat.victaspro$death_180d.cat
                                       correct=FALSE)
```

```
latex(Tablemodel3pro.180,file="", where="!h",caption = "Pearson Chi-Square Test",
      colheads=c('','\\bf Test Statistic','\\bf P-value','\\bf Control Prop',
      '\\bf Treatment Prop','{\\bf 95\\% C.I.}'),
      insert.bottom = "",col.just=c("l","c","c","c","c","c"),rowname=NULL)
```

Table 41: Pearson Chi-Square Test

	Test Statistic	**P-value**	**Control Prop**	**Treatment Prop**	**95% C.I.**
180-Day Mortality	0.327	0.568	0.368	0.395	-0.12 - 0.066

Results indicate no statistically significant difference in proportions between treatment group on 180-day mortality.

3.5.3 Logistic Regression Model

```
dat.model2pro.180 ← subset(dat.victaspro,select=c(record_id,treatment,death_180d,
                                                  death_180d.cat,death_180days))
dat.model2pro.180 ← upData(dat.model2pro.180,treatment=factor(treatment,
                                                    levels=c("Treatment","Control")),
                           treatment=relevel(treatment,ref="Control"),
                           Srv_mortality=Surv(death_180days,death_180d))
ddist2pro180 ← datadist(dat.model2pro.180)
options(datadist = "ddist2pro180")
lrm.model1pro.180 ← lrm(death_180d.cat=="Yes"~treatment,data=dat.model2pro.180)
```

Per-protocol analysis set, to compare 180-day mortality between treatment groups, a univariate logistic regression model was fit due to the binary nature of the outcome (i.e. 180-day mortality). The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the odds ratio (OR) is the odds of incurring an death within 30 days from randomization when compared to the reference control group.

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	0.33	R^2	0.001	C	0.514
FALSE	258	d.f.	1	g	0.058	D_{xy}	0.029
TRUE	159	Pr($>\chi^2$)	0.5676	g_r	1.059	γ	0.058
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	4×10^{-14}			g_p	0.014	τ_a	0.014
				Brier	0.236		

Table 42: Logistic Regresion Model

	OR	95% C.I.	P-value
Treatment vs. Control	1.122	0.756 - 1.666	0.568

In the univariate model results indicate that treatment group is not statistically associated with 180-day mortality.

3.5.4 Cox Proportional Hazard Model

```
cph.model1pro.180 ← cph(Surv(death_180days,death_180d)~treatment,
                        data=dat.model2pro.180)
```

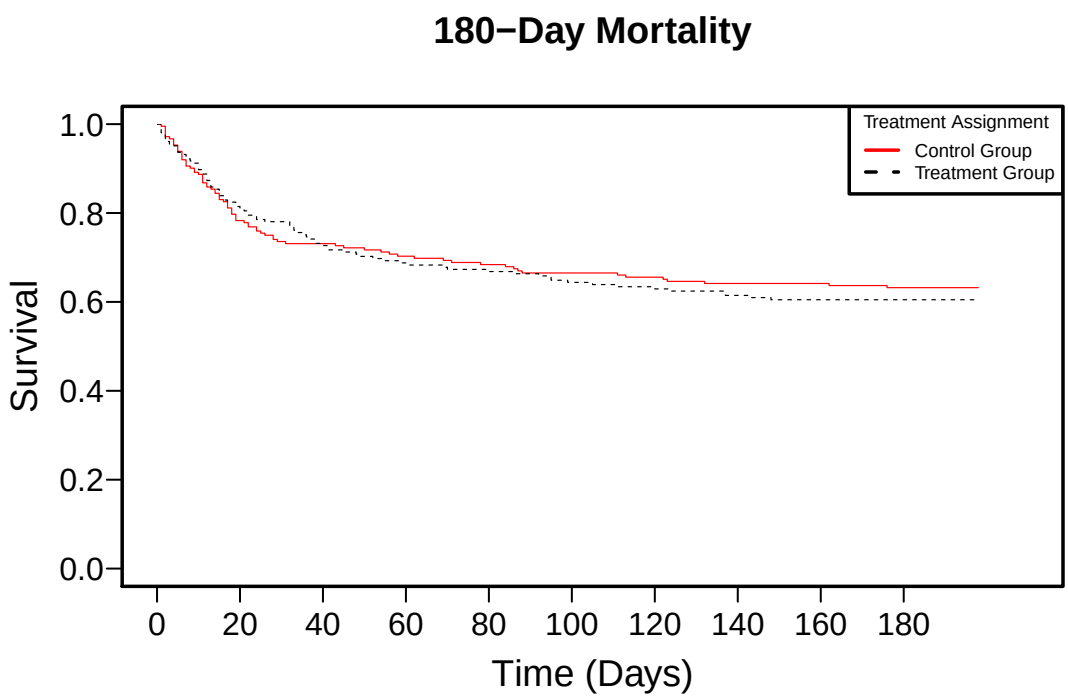
Per-protocol analysis set, to investigate the time to 180-day mortality between treatment groups, a univariate cox regression model was fit to the data. The point estimates from the model are summarized with Hazard Ratios (HR), 95% confidence intervals, and p-value. For the binary predictor (i.e. treatment assignment), the hazard ratio (HR) is the risk of incurring an death within 180 days from randomization when compared to the reference control group.

		Model Tests		Discrimination Indexes	
Obs	417	LR χ^2	0.18	R^2	0.000
Events	159	d.f.	1	D_{xy}	0.011
Center	0.0333	Pr($>\chi^2$)	0.6691	g	0.034
		Score χ^2	0.18	g_r	1.035
		Pr($>\chi^2$)	0.6690		

Table 43: Cox Regresion Model

	HR	95% C.I.	P-value
Treatment vs. Control	1.070	0.784 - 1.460	0.669

In the univariate model results indicate that treatment group is not statistically associated with time to death within 180-days.



3.6 Adjusted Analyses

3.6.1 Primary endpoint: VVFD (Proportional Odds Model)

```
po.model2pro←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                            ventilator.vent+ventilator.vaso+admit.reason.cat2+
                            ics.admit.source.cat2+rcs(ap2_total_score,3)+
                            infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                            x=TRUE,y=TRUE,data=dat.model3.impute1pro)
set.seed(23)
po.model.bootstrappro←bootcov(po.model2pro, dat.model3.impute1pro$site)
```

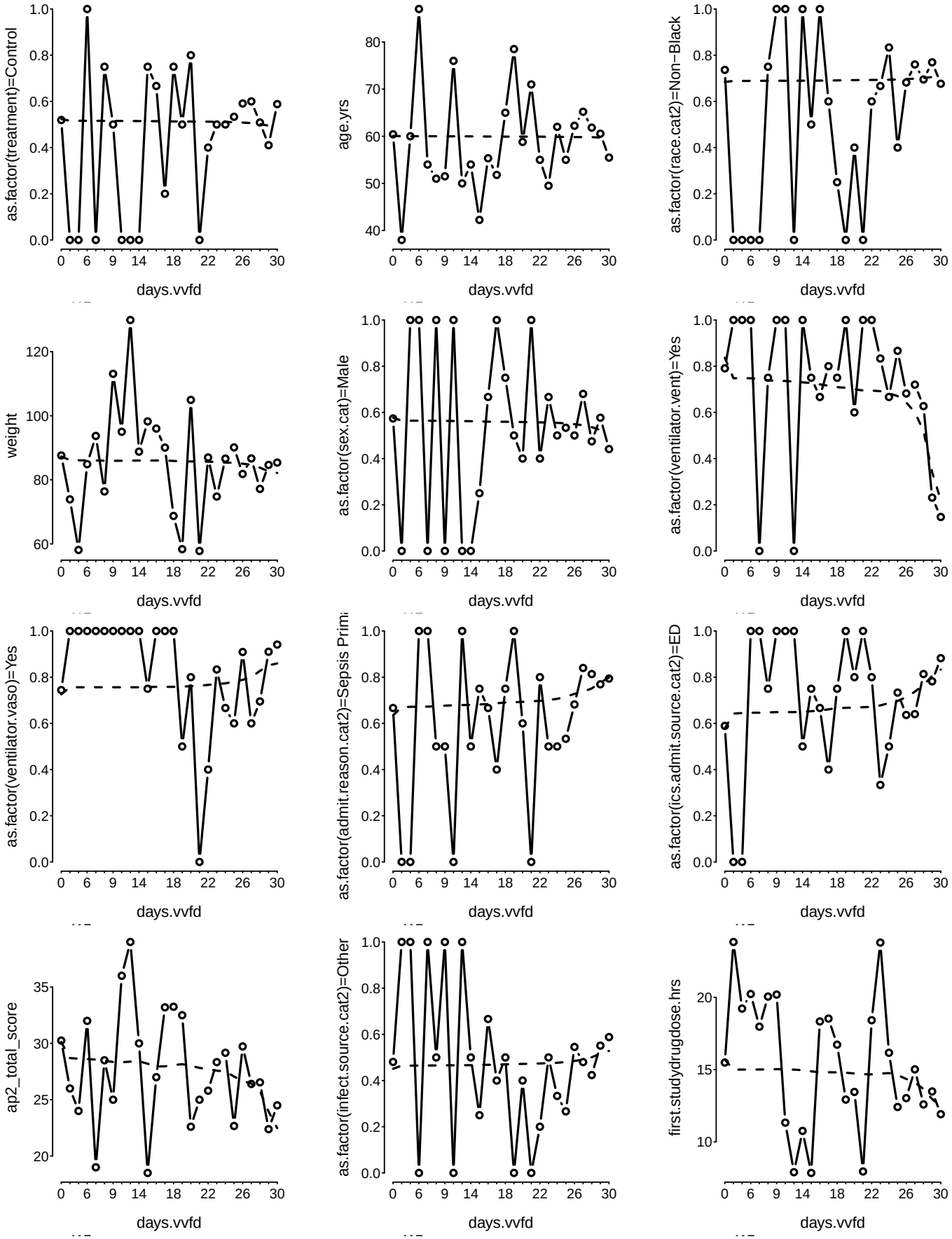
Per-protocol analysis set, to compare the ventilator-and-vasopressor free days between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable proportional odds model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	146.20	R^2	0.299	C	0.723
Cluster on `dat.model3.impute1pro$site`		d.f.	17	g	1.323	D_{xy}	0.446
Clusters	39	Pr($>\chi^2$)	<0.0001	g_r	3.756	γ	0.446
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	7×10^{-6}			g_p	0.247	τ_a	0.373
				Brier	0.194		

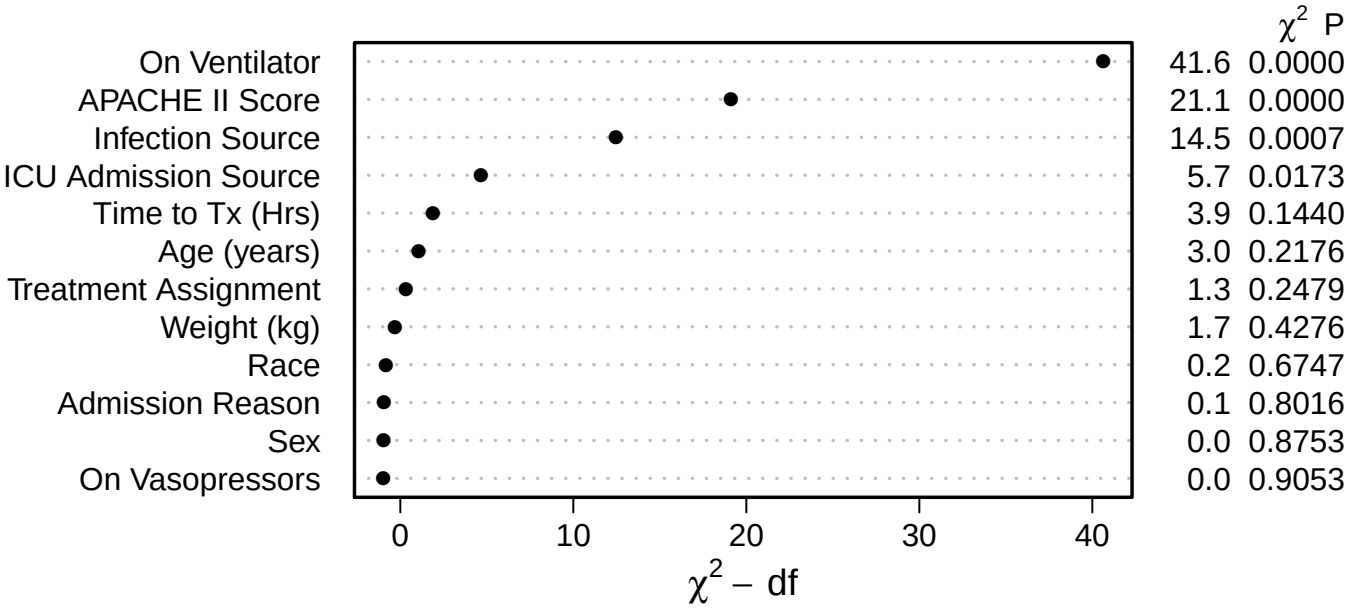
Table 44: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.916	0.753 - 1.164	0.218
Weight(kg) (per IQR)	1.017	0.805 - 1.227	0.428
APACHE II (per IQR)	0.515	0.363 - 0.657	<0.0001
Time to Tx (Hrs) (per IQR)	0.740	0.527 - 0.983	0.144
Treatment vs. Control	1.266	0.786 - 1.810	0.248
Black vs. Non-Black	0.924	0.637 - 1.312	0.675
Male vs. Female	1.030	0.727 - 1.483	0.875
Ventilator vs. No Ventilator	0.194	0.114 - 0.302	<0.0001
Vasopressor vs. No Vasopressor	0.977	0.685 - 1.477	0.905
Sepsis Primary vs. Sepsis Secondary	0.932	0.542 - 1.517	0.802
ED Admission vs. Other Admission	1.743	1.165 - 3.038	0.017
Lung Infection vs. Other Type of Infection	1.120	0.754 - 1.649	0.578
Urinary Tract Infection vs. Other Type of Infection	2.358	1.560 - 3.803	0.0002

3.6.2 PO Plots


as.factor(treatment)=Control
age.yrs
as.factor(race.cat2)=Non−Black
weight
as.factor(sex.cat)=Male
as.factor(ventilator.vent)=Yes
as.factor(ventilator.vaso)=Yes
as.factor(admit.reason.cat2)=Sepsis Prim
as.factor(ics.admit.source.cat2)=ED
ap2_total_score
as.factor(infect.source.cat2)=Other
first.studydrugdose.hrs
days.vvfd

3.6.3 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

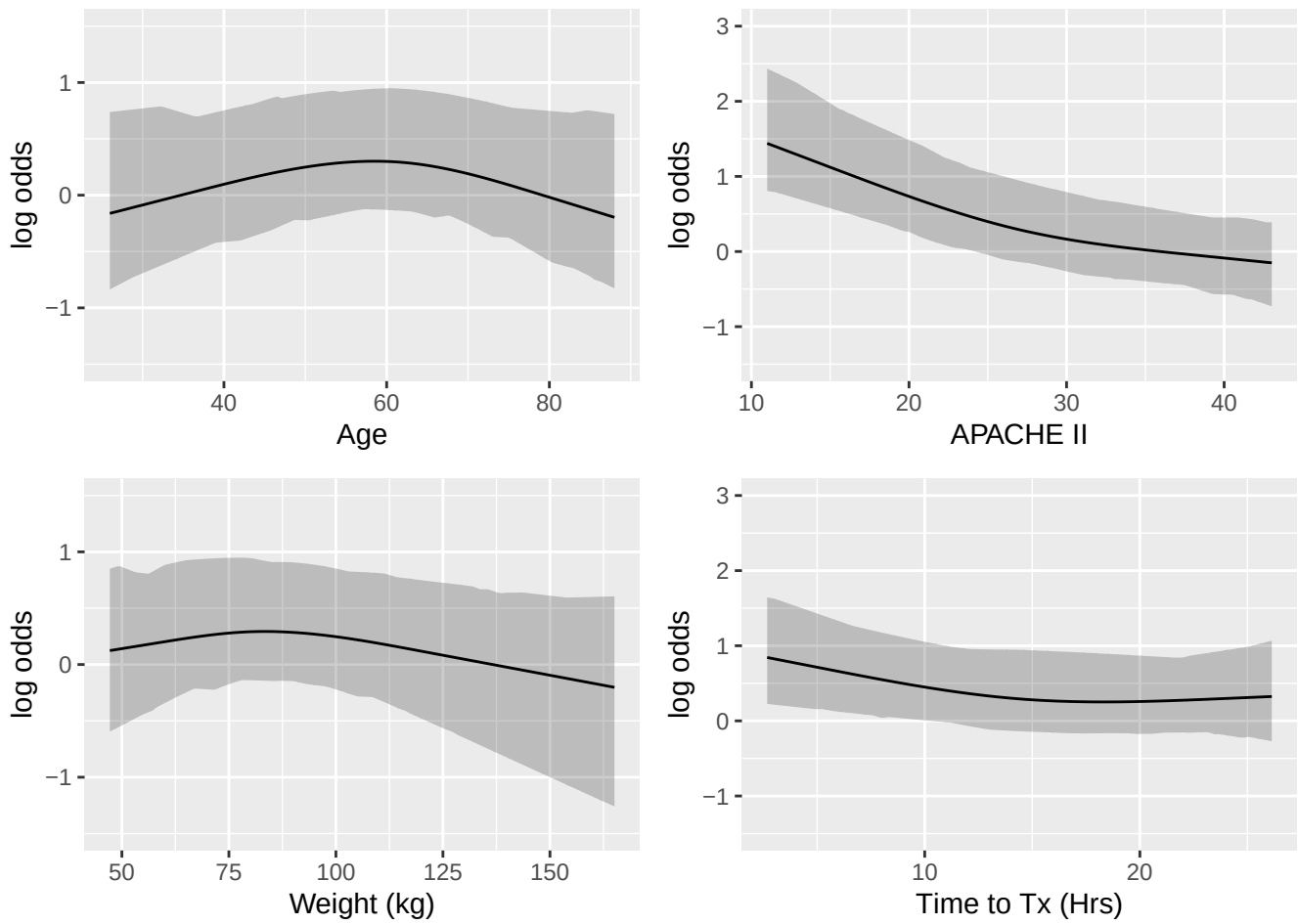
3.6.4 Partial Effect Plots

```
po2.1pro←ggplot(Predict(po.model.bootstrappro,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Age")
```

```
po2.2pro←ggplot(Predict(po.model.bootstrappro,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Weight (kg)")
```

```
po2.3pro←ggplot(Predict(po.model.bootstrappro,ap2_total_score),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "APACHE II")
```

```
po2.4pro←ggplot(Predict(po.model.bootstrappro,first.studydrugdose.hrs),
             adj.subtitle=FALSE,legend.position='top')+
             coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



3.6.5 Primary endpoint: VVFD (Interaction Table)

```
po.model2pro.interact←lrm((days.vvfd)~treatment*(rcs(age.yrs,3)+race.cat2+
                                    rcs(weight,3)+sex.cat+ventilator.vent+
                                    ventilator.vaso+admit.reason.cat2+
                                    ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                    infect.source.cat2+rcs(first.studydrugdose.hrs,3)),
                                    x=TRUE,y=TRUE,data=dat.model3.impute1pro)
set.seed(723)
po.model2pro.interact.bootstrap←bootcov(po.model2pro.interact,
                                        dat.model3.impute1pro$site)
```

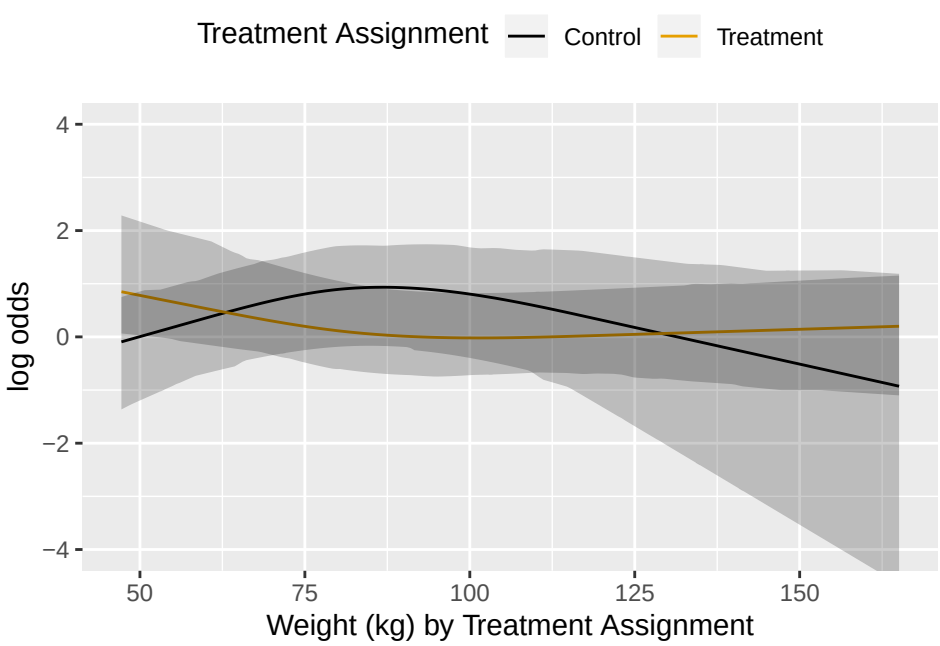
Table 45: Primary Endpoint: Proportional Odds Model (Interaction Table)

po.model2pro.anova	Chi-Square	d.f.	P
treatment * Age	0.165	2	0.921
treatment * Race	0.080	1	0.777
treatment * Weight	9.581	2	0.008
treatment * Sex	0.187	1	0.665
treatment * On Ventilator	1.098	1	0.295
treatment * On Vasopressor	0.270	1	0.603
treatment * Admission Reason	0.475	1	0.491
treatment * ICU Admission Source	0.063	1	0.802
treatment * APACHE II Score	0.862	2	0.650
treatment * Infection Source	1.000	2	0.607
treatment * Time to Tx	2.046	2	0.360
TOTAL INTERACTION	41.235	16	0.001

Per SAP, results indicate the interaction terms with p-value≤0.2 are Treatment Assignment by Weight.

3.6.6 Partial Effect Plots

```
po2.2pro.interact←ggplot(Predict(po.model2pro.interact.bootstrap,weight,treatment),
adj.subtitle=FALSE,legend.position='top')+coord_cartesian(ylim = c(-4.0, 4.0))+
scale_x_continuous(name = "Weight (kg) by Treatment Assignment")
```



3.6.7 Primary endpoint: VVFD (Proportional Odds Model) Sub-Analysis

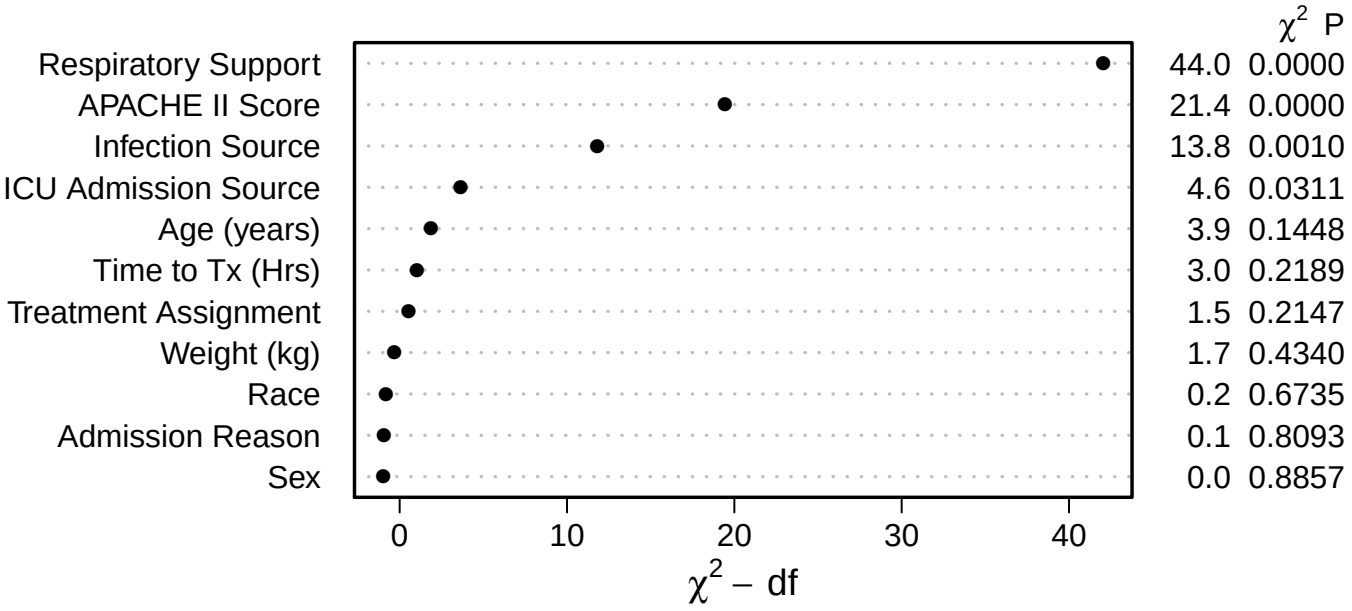
```
po.model2prosub←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                            sex.cat+ventilator.3grp+admit.reason.cat2+
                            ics.admit.source.cat2+rcs(ap2_total_score,3)+
                            infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                            x=TRUE,y=TRUE,data=dat.model3.impute1pro)
set.seed(73)
po.model.bootstrapprosub←bootcov(po.model2prosub, dat.model3.impute1pro$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	146.20	R^2	0.299	C	0.723
Cluster on `dat.model3.impute1pro$site`		d.f.	17	g	1.323	D_{xy}	0.446
Clusters	39	Pr($>\chi^2$)	<0.0001	g_r	3.756	γ	0.446
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	7×10^{-6}			g_p	0.247	τ_a	0.373
				Brier	0.194		

Table 46: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.916	0.714 - 1.136	0.145
Weight(kg) (per IQR)	1.017	0.772 - 1.267	0.434
APACHE II (per IQR)	0.515	0.369 - 0.655	<0.0001
Time to Tx (Hrs) (per IQR)	0.740	0.51 - 1.030	0.219
Treatment vs. Control	1.266	0.901 - 1.807	0.215
Black vs. Non-Black	0.924	0.653 - 1.333	0.674
Male vs. Female	1.030	0.715 - 1.588	0.886
Ventilator vs. Both	1.024	0.661 - 1.591	0.921
Vasopressor vs. Both	5.143	3.406 - 9.804	<0.0001
Sepsis Primary vs. Sepsis Secondary	0.932	0.536 - 1.536	0.809
ED Admission vs. Other Admission	1.743	1.100 - 3.277	0.031
Lung Infection vs. Other Type of Infection	1.120	0.743 - 1.623	0.570
Urinary Tract Infection vs. Other Type of Infection	2.358	1.546 - 3.683	0.0002

3.6.8 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

3.6.9 Primary endpoint: VVFD (GEE Model)

```
primary.gee1pro←geeglm(log(days.vvfd+1)~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                        ics.admit.source.cat2+ap2_total_score+
                                        infect.source.cat2+first.studydrugdose.hrs,
                                        family=(link="gaussian"),
                                        data=dat.model3.impute1pro,id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

Per-protocol analysis set, to estimate the marginal treatment effect on ventilator-and-vasopressor free days while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. To improve the distribution of the outcome variable a log transformation was implemented. The resulting point estimates from the model are summarized with the Geometric Mean (GM), 95% confidence intervals, and p-value. For the continuous variables the GM is based on the expected mean number of VVFD's per one unit increase. For the categorical variables the GM is based in comparison to their reference group (vs.).

Table 47: Primary Endpoint: GEE Model

PTable1pro	**GM**	**95% C.I.**	**P-value**
Age (per 1 year)	1.002	0.994 - 1.010	0.602
Weight(kg) (per Kg)	0.999	0.995 - 1.002	0.493
APACHE II (per 1 point)	0.964	0.950 - 0.978	<0.0001
Time to Tx (Hrs) (per Hr)	0.988	0.970 - 1.006	0.177
Treatment vs. Control	1.184	0.877 - 1.598	0.271
Black vs. Non-Black	1.006	0.811 - 1.247	0.958
Male vs. Female	1.051	0.824 - 1.340	0.690
Ventilator vs. No Ventilator	0.490	0.355 - 0.675	<0.0001
Vasopressor vs. No Vasopressor	1.075	0.776 - 1.490	0.663
Sepsis Primary vs. Sepsis Secondary	0.916	0.641 - 1.308	0.628
ED Admission vs. Other Admission	1.387	1.024 - 1.878	0.034
Lung Infection vs. Other Type of Infection	1.112	0.890 - 1.389	0.351
Urinary Tract Infection vs. Other Type of Infection	1.839	1.401 - 2.415	<0.0001

3.6.10 Secondary endpoint: 30-Day Mortality (Logistic Regression Model)

```
lrm.model2pro←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                sex.cat+ventilator.vent+ventilator.vaso+
                                admit.reason.cat2+ics.admit.source.cat2+
                                rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3.impute1pro)
set.seed(27)
lrm.model.bootstrappro←bootcov(lrm.model2pro, dat.model3.impute1pro$site)
```

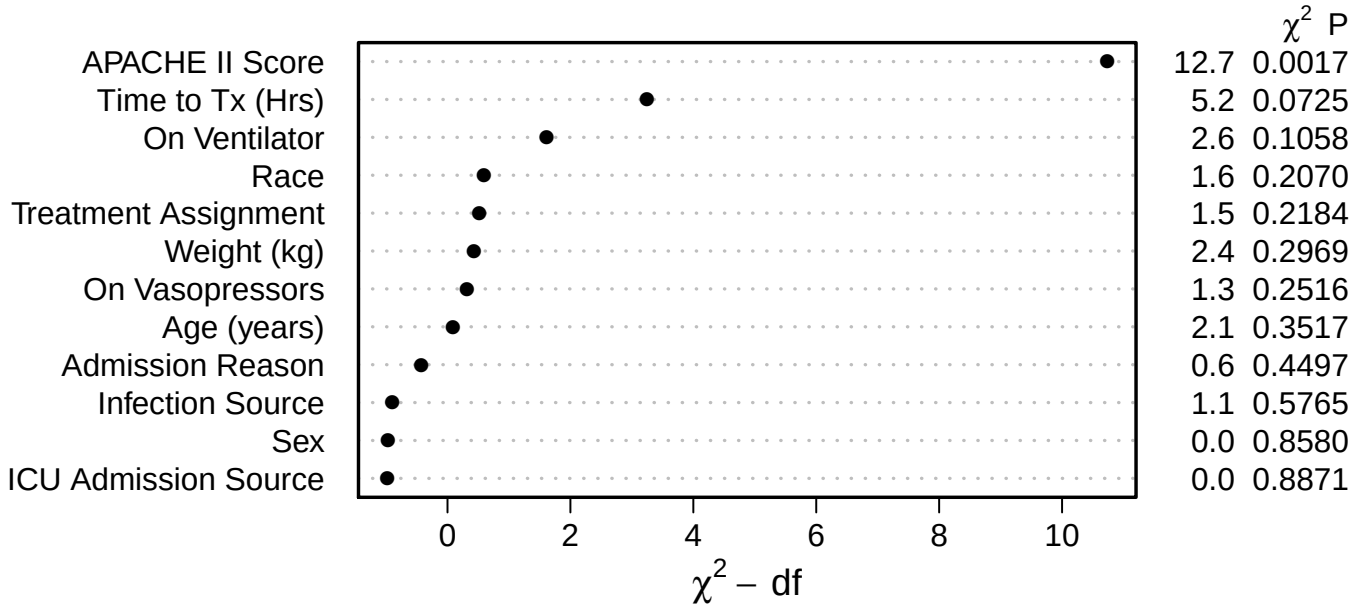
Per-protocol analysis set, to compare 30-day mortality between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable logistic regression model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	55.33	R^2	0.197	C	0.753
FALSE	334	d.f.	17	g	1.267	D_{xy}	0.505
TRUE	83	Pr($>\chi^2$)	<0.0001	g_r	3.551	γ	0.505
Cluster on `dat.model3.impute1pro$site`				g_p	0.160	τ_a	0.161
Clusters	39			Brier	0.138		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	5×10^{-7}						

Table 48: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.391	0.901 - 2.472	0.352
Weight(kg) (per IQR)	0.698	0.517 - 1.298	0.297
APACHE II (per IQR)	2.898	1.626 - 6.08	0.002
Time to Tx (Hrs) (per IQR)	1.307	0.765 - 2.591	0.073
Treatment vs. Control	0.662	0.308 - 1.223	0.218
Black vs. Non-Black	0.624	0.306 - 1.348	0.207
Male vs. Female	0.947	0.52 - 1.736	0.858
Ventilator vs. No Ventilator	2.145	0.945 - 6.159	0.106
Vasopressor vs. No Vasopressor	0.743	0.459 - 1.263	0.252
Sepsis Primary vs. Sepsis Secondary	0.782	0.377 - 1.391	0.450
ED Admission vs. Other Admission	1.052	0.485 - 1.840	0.887
Lung Infection vs. Other Type of Infection	0.908	0.404 - 1.421	0.766
Urinary Tract Infection vs. Other Type of Infection	0.292	0.054 - 0.796	0.295

3.6.11 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

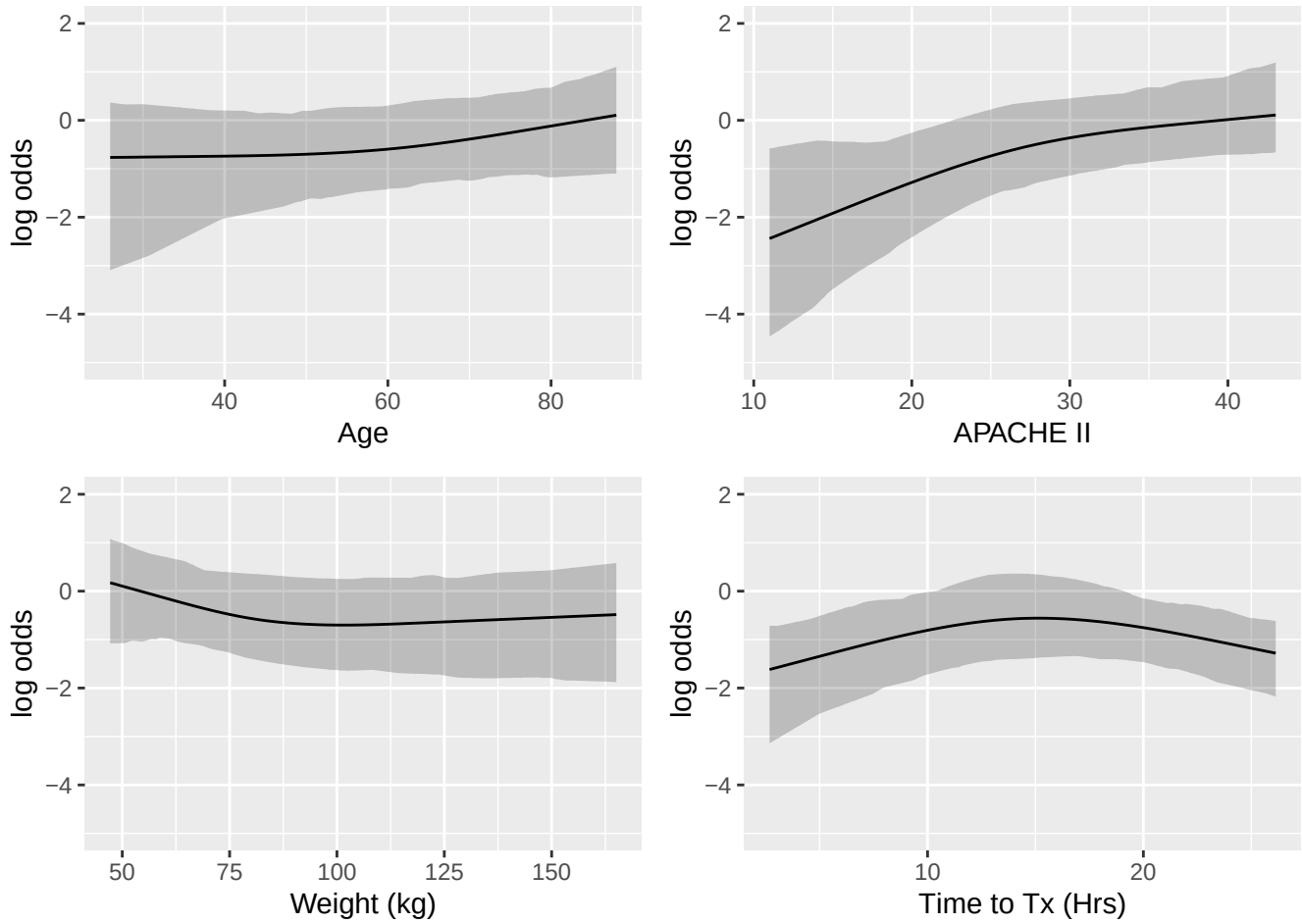
3.6.12 Partial Effect Plots

```
lrm2.1pro←ggplot(Predict(lrm.model.bootstrappro,age.yrs),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2))+
            scale_x_continuous(name = "Age")
```

```
lrm2.2pro←ggplot(Predict(lrm.model.bootstrappro,weight),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2))+
            scale_x_continuous(name = "Weight (kg)")
```

```
lrm2.3pro←ggplot(Predict(lrm.model.bootstrappro,ap2_total_score),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
            scale_x_continuous(name = "APACHE II")
```

```
lrm2.4pro←ggplot(Predict(lrm.model.bootstrappro,first.studydrugdose.hrs),
adj.subtitle=FALSE,legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
scale_x_continuous(name = "Time to Tx (Hrs)")
```



3.6.13 Secondary endpoint: 30-Day Mortality (Interaction Table)

```
lrm.model2pro.interact←lrm(death_30d=="1"~treatment*(rcs(age.yrs,3)+race.cat2+
                                    rcs(weight,3)+sex.cat+ventilator.vent+
                                    ventilator.vaso+admit.reason.cat2+
                                    ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                    infect.source.cat2+rcs(first.studydrugdose.hrs,3)),
                                    x=TRUE,y=TRUE,data=dat.model3.impute1pro)
set.seed(743)
lrm.model2pro.interact.bootstrap←bootcov(lrm.model2pro.interact,
                                         dat.model3.impute1pro$site,maxit=25)
```

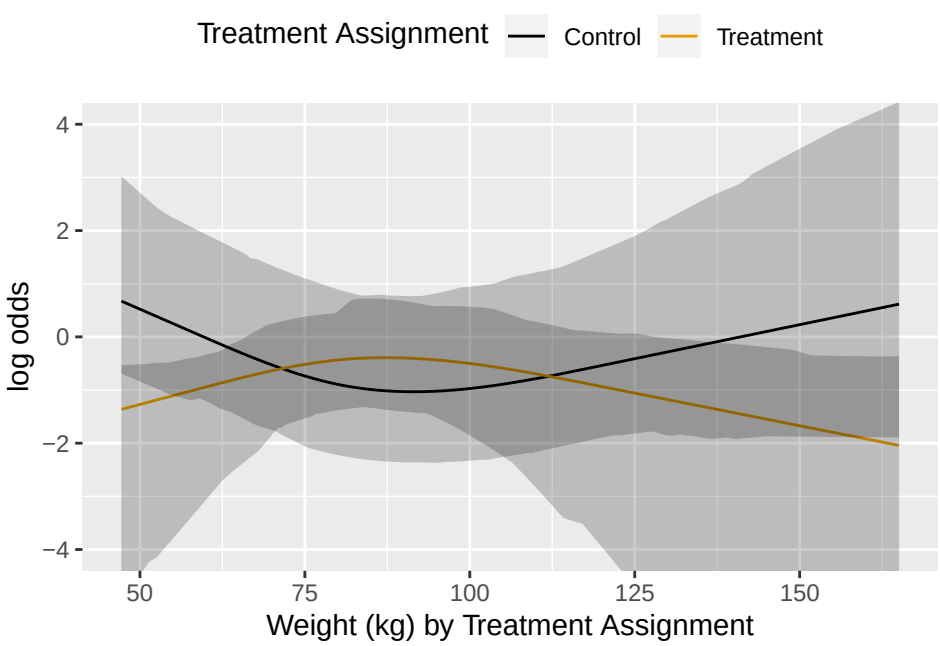
Table 49: Secondary Endpoint: Logistic Regression Model (Interaction Table)

lrm.model2pro.anova	Chi-Square	d.f.	P
treatment * Age	0.033	2	0.984
treatment * Race	0.014	1	0.905
treatment * Weight	2.122	2	0.346
treatment * Sex	0.000	1	0.987
treatment * On Ventilator	0.010	1	0.921
treatment * On Vasopressor	0.312	1	0.576
treatment * Admission Reason	0.858	1	0.354
treatment * ICU Admission Source	0.006	1	0.940
treatment * APACHE II Score	0.868	2	0.648
treatment * Infection Source	0.602	2	0.740
treatment * Time to Tx	0.335	2	0.846
TOTAL INTERACTION	11.959	16	0.747

Per SAP, results indicate no interaction terms with p-value≤0.2.

3.6.14 Partial Effect Plots

```
lrm2.2pro.interact←ggplot(Predict(lrm.model2pro.interact.bootstrap,weight,treatment),
adj.subtitle=FALSE, legend.position='top')+coord_cartesian(ylim = c(-4.0, 4.0))+
scale_x_continuous(name = "Weight (kg) by Treatment Assignment")
```



3.6.15 Secondary endpoint: 30-Day Mortality (Logistic Regression Model) Sub-Analysis

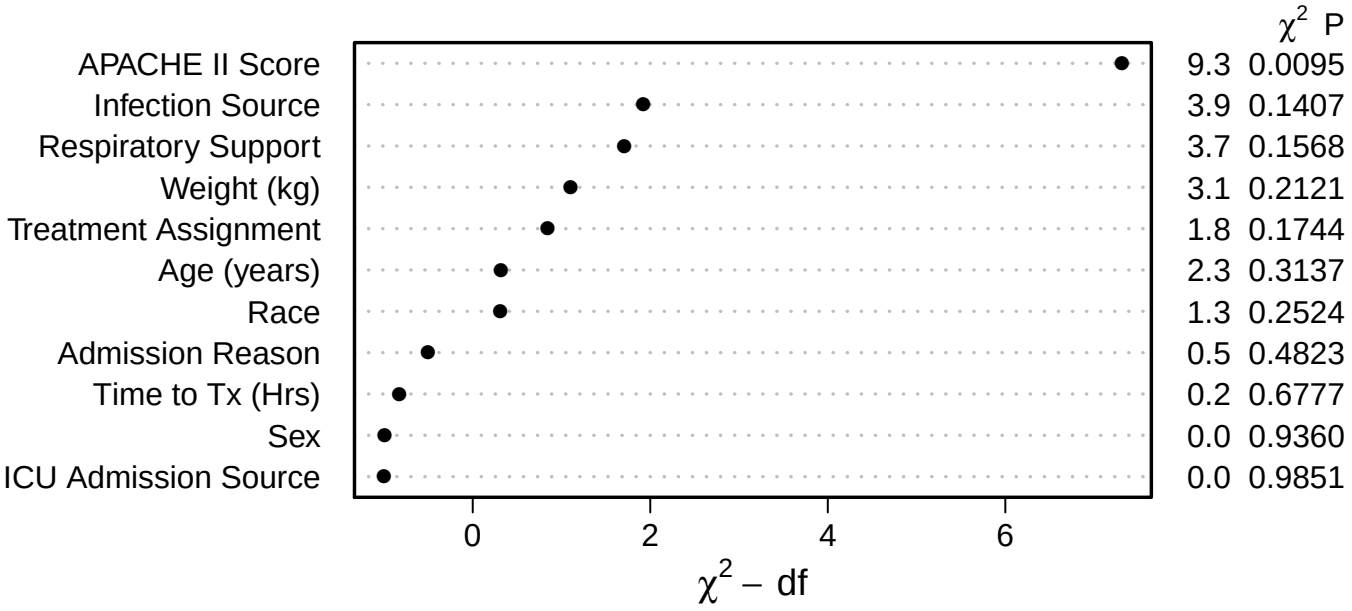
```
lrm.model2prosub←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.ca
                                ventilator.3grp+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+first.studydrugdose.hrs,
                                x=TRUE,y=TRUE,
                                data=dat.model3.impute1pro)
set.seed(77)
lrm.model.bootstrapprosub←bootcov(lrm.model2prosub, dat.model3.impute1pro$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	417	LR χ^2	50.44	R^2	0.180	C	0.745
FALSE	334	d.f.	16	g	1.195	D_{xy}	0.489
TRUE	83	Pr($>\chi^2$)	<0.0001	g_r	3.304	γ	0.490
Cluster on `dat.model3.impute1pro$site`				g_p	0.154	τ_a	0.156
Clusters	39			Brier	0.140		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	2×10^{-7}						

Table 50: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.425	0.889 - 2.302	0.314
Weight(kg) (per IQR)	0.720	0.52 - 1.103	0.212
APACHE II (per IQR)	2.880	1.660 - 6.597	0.010
Time to Tx (Hrs) (per IQR)	1.100	0.727 - 1.763	0.678
Treatment vs. Control	0.650	0.321 - 1.164	0.174
Black vs. Non-Black	0.653	0.384 - 1.638	0.252
Male vs. Female	0.972	0.553 - 1.938	0.936
Ventilator vs. Both	1.192	0.695 - 1.939	0.542
Vasopressor vs. Both	0.477	0.149 - 1.022	0.120
Sepsis Primary vs. Sepsis Secondary	0.783	0.459 - 1.687	0.482
ED Admission vs. Other Admission	0.993	0.422 - 1.652	0.985
Lung Infection vs. Other Type of Infection	0.881	0.471 - 1.285	0.630
Urinary Tract Infection vs. Other Type of Infection	0.317	0.078 - 0.746	0.047

3.6.16 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

3.6.17 Secondary endpoint: 30-day Mortality (GEE Model)

```
secondary.gee2pro←geeglm(death_30d=="1"~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                        ics.admit.source.cat2+ap2_total_score+
                                        infect.source.cat2+first.studydrugdose.hrs,
                                        family=binomial(link="logit"),
                                        data=dat.model3.impute1pro,id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

Per-protocol analysis set, to estimate the marginal treatment effect on 30-day mortality while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. The point estimates from the model are summarized with the Odds Ratios (OR), 95% confidence intervals, and p-value. For the continuous variables the OR is based on the odds of 30-day mortality per one unit increase. For the categorical variables the OR is based in comparison to their reference group (vs.).

Table 51: Secondary Endpoint: GEE Model

STable1pro	**OR**	**95% C.I.**	**P-value**
Age (per 1 year)	1.018	0.994 - 1.042	0.143
Weight(kg) (per kg)	0.996	0.986 - 1.005	0.374
APACHE II (per 1 point)	1.065	1.031 - 1.100	<0.0001
Time to Tx (Hrs) (per Hr)	1.007	0.974 - 1.041	0.668
Treatment vs. Control	0.675	0.396 - 1.148	0.147
Black vs. Non-Black	0.596	0.318 - 1.118	0.107
Male vs. Female	0.930	0.545 - 1.584	0.789
Ventilator vs. No Ventilator	2.091	0.928 - 4.708	0.075
Vasopressors vs. No Vasopressors	0.867	0.543 - 1.384	0.550
Sepsis Primary vs. Sepsis Secondary	0.822	0.471 - 1.436	0.492
ED Admission vs. Other Admission	1.009	0.548 - 1.858	0.977
Lung Infection vs. Other Type of Infection	0.932	0.599 - 1.449	0.754
Urinary Tract Infection vs. Other Type of Infection	0.338	0.117 - 0.980	0.046

3.7 Adjusted Analyses (Complete Case)

3.7.1 Descriptives

```
latex(summaryM(age.yrs+race.cat+ethnicity.cat+male.cat.2+yrs.educat+weight+bmi+system.3.cat
            system.4.cat.2+system.1.cat.2+system.7.cat.2+malignancy.cat.2+ventilator+
            ventilator.vent.2+ventilator.supporttype+ventilator.vaso.2+
            ics.admit.source.cat+admit.reason.cat+vitals_5+systolic_blood_pressure+
            diastolic_blood_pressure+vitals_1+vitals_7+vitals.9.celcius+wbc_value+
            platelets_value+hem_value_3+lactic_acid+creat_value+ap2_total_score+sofa_seib+
            first.studydrugdose.hrs+infect.source.cat+organism0.cat.2+organism1.cat.2+
            organism2.cat.2+organism4.cat.2+organism5.cat.2+organism6.cat.2+
            vvfd.zero.2~incl.excl,
            data=addMarginal(dat.victaspro.cc,incl.excl,label='Total', margloc='last')),
            file="",where="!h",caption="Demographic \\& Clinical variables by
            Inclusion/Exclusion", exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE,
            npct="both",digits=2, landscape=FALSE, longtable=TRUE,
            lines.page=82,what = '%',  legend.bottom = TRUE,size="footnotesize")
```

Table 52: Demographic & Clinical variables by Inclusion/Exclusion

	N	Inclusion Group $N = 389$	Exclusion Group $N = 28$	Total $N = 417$
Age (years)	417	51 62 71 (60 ±16)	53 58 64 (58 ±16)	51 62 71 (60 ±16)
Race	417			
Black		31% $\frac{120}{389}$	25% $\frac{7}{28}$	30% $\frac{127}{417}$
Caucasian		56% $\frac{218}{389}$	68% $\frac{19}{28}$	57% $\frac{237}{417}$
Other		13% $\frac{51}{389}$	7% $\frac{2}{28}$	13% $\frac{53}{417}$
Ethnicity	417			
Hispanic or Latino		11% $\frac{43}{389}$	4% $\frac{1}{28}$	11% $\frac{44}{417}$
Not Hispanic or Latino		85% $\frac{330}{389}$	89% $\frac{25}{28}$	85% $\frac{355}{417}$
Not Reported		4% $\frac{16}{389}$	7% $\frac{2}{28}$	4% $\frac{18}{417}$
Male	417	54% $\frac{212}{389}$	61% $\frac{17}{28}$	55% $\frac{229}{417}$
Education	417			
Less than High School		9% $\frac{36}{389}$	7% $\frac{2}{28}$	9% $\frac{38}{417}$
High School or GED		14% $\frac{54}{389}$	25% $\frac{7}{28}$	15% $\frac{61}{417}$
Some College		24% $\frac{93}{389}$	18% $\frac{5}{28}$	24% $\frac{98}{417}$
Unknown		53% $\frac{206}{389}$	50% $\frac{14}{28}$	53% $\frac{220}{417}$
Weight (kg)	417	68 80 96 (85 ±27)	65 77 89 (82 ±29)	68 80 96 (85 ±27)
BMI	408	23.7 27.4 33.0 (29.3 ± 9.3)	22.7 25.8 31.7 (28.2 ± 9.2)	23.5 27.2 33.0 (29.2 ± 9.3)
Diabetes	417	32% $\frac{126}{389}$	25% $\frac{7}{28}$	32% $\frac{133}{417}$
Cardiovascular disease	417	51% $\frac{200}{389}$	50% $\frac{14}{28}$	51% $\frac{214}{417}$
Neurological disease	417	19% $\frac{72}{389}$	25% $\frac{7}{28}$	19% $\frac{79}{417}$
Respiratory illness	417	22% $\frac{87}{389}$	18% $\frac{5}{28}$	22% $\frac{92}{417}$
Current Cancer	417	20% $\frac{76}{389}$	21% $\frac{6}{28}$	20% $\frac{82}{417}$
Respiratory Support	417			
Ventilator		21% $\frac{81}{389}$	29% $\frac{8}{28}$	21% $\frac{89}{417}$
Vasopressor		39% $\frac{153}{389}$	46% $\frac{13}{28}$	40% $\frac{166}{417}$
Both		40% $\frac{155}{389}$	25% $\frac{7}{28}$	39% $\frac{162}{417}$
On Ventilator	417	61% $\frac{236}{389}$	54% $\frac{15}{28}$	60% $\frac{251}{417}$
Type of Ventilator Support	250			
Intubation		68% $\frac{160}{235}$	67% $\frac{10}{15}$	68% $\frac{170}{250}$
CPAP or BIPAP		17% $\frac{40}{235}$	20% $\frac{3}{15}$	17% $\frac{43}{250}$
Nasal Flow		14% $\frac{33}{235}$	13% $\frac{2}{15}$	14% $\frac{35}{250}$
Intubation/CPAP/BIPAP/Nasal		1% $\frac{2}{235}$	0% $\frac{0}{15}$	1% $\frac{2}{250}$
On Vasopressors	416	79% $\frac{308}{389}$	74% $\frac{20}{27}$	79% $\frac{328}{416}$
ICU Admission Source	417			
ED		70% $\frac{271}{389}$	75% $\frac{21}{28}$	70% $\frac{292}{417}$
Intermediate Care		1% $\frac{3}{389}$	0% $\frac{0}{28}$	1% $\frac{3}{417}$
Step Down Unit		4% $\frac{14}{389}$	4% $\frac{1}{28}$	4% $\frac{15}{417}$
Hospital Floor		18% $\frac{71}{389}$	14% $\frac{4}{28}$	18% $\frac{75}{417}$
Other		8% $\frac{30}{389}$	7% $\frac{2}{28}$	8% $\frac{32}{417}$
Admission Reason	417			
Sepsis		71% $\frac{276}{389}$	75% $\frac{21}{28}$	71% $\frac{297}{417}$
Other Medical		25% $\frac{98}{389}$	25% $\frac{7}{28}$	25% $\frac{105}{417}$
Other Surgical		4% $\frac{15}{389}$	0% $\frac{0}{28}$	4% $\frac{15}{417}$
Heart Rate	417	80 96 113 (97 ± 23)	82 104 117 (98 ± 24)	80 96 113 (97 ± 23)
Systolic Blood Pressure	417	91 103 118 (106 ± 24)	93 106 120 (106 ± 23)	91 103 118 (106 ± 24)
Diastolic Blood Pressure	417	50 57 67 (59 ±14)	48 55 66 (58 ±18)	50 57 67 (59 ±14)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values.

Table 52: *(continued)*

	N	Inclusion Group $N = 389$	Exclusion Group $N = 28$	Total $N = 417$
Mean Arterial Pressure (MAP)	416	65 72 81 (74 ±15)	66 72 85 (73 ±18)	65 72 81 (74 ±15)
Respiratory Rate	415	18.0 22.0 27.0 (23.0 ± 7.4)	17.0 20.5 26.0 (21.7 ± 5.0)	18.0 22.0 27.0 (22.9 ± 7.3)
Temperature (celsius)	412	36.44 36.90 37.80 (37.03 ± 1.37)	36.60 36.78 37.11 (36.93 ± 0.93)	36.50 36.90 37.78 (37.02 ± 1.35)
White Blood Cell Count	412	6.5 13.6 20.2 (71.4 ±853.5)	7.8 14.0 18.4 (15.3 ± 11.7)	6.6 13.6 19.8 (68.0 ±827.3)
Platelets Count	410	103 178 259 (196 ±130)	119 194 299 (219 ±154)	103 180 261 (198 ±132)
Hemoglobin	414	8.5 10.1 12.0 (10.3 ± 2.5)	8.2 10.1 13.1 (10.6 ± 3.0)	8.5 10.1 12.0 (10.4 ± 2.5)
Lactic Acid	332	1.8 2.7 4.2 (4.2 ±9.3)	1.2 2.2 3.5 (3.0 ±2.4)	1.8 2.6 4.2 (4.1 ±9.1)
Creatinine Value	414	1.0 1.7 2.8 (2.3 ±2.0)	1.3 2.2 3.7 (2.8 ±2.1)	1.1 1.7 2.8 (2.3 ±2.0)
APACHE II Score	392	20.0 27.0 33.0 (26.9 ± 8.6)	15.0 22.0 25.5 (19.7 ±10.7)	20.0 27.0 33.0 (26.9 ± 8.6)
SOFA Score	417	7.0 9.0 12.0 (9.1 ± 3.4)	6.8 8.0 9.2 (8.0 ± 3.2)	7.0 9.0 11.0 (9.0 ± 3.4)
Time to Tx (Hrs)	417	8.6 14.9 20.2 (14.7 ± 7.1)	4.3 7.3 11.8 (9.0 ± 6.4)	7.8 14.5 20.0 (14.3 ± 7.2)
Infection Source	415			
Lung		36% $\frac{139}{389}$	31% $\frac{8}{26}$	35% $\frac{147}{415}$
Blood/Vascular access		14% $\frac{54}{389}$	4% $\frac{1}{26}$	13% $\frac{55}{415}$
Urinary Tract		16% $\frac{63}{389}$	12% $\frac{3}{26}$	16% $\frac{66}{415}$
Intra-abdominal		14% $\frac{56}{389}$	19% $\frac{5}{26}$	15% $\frac{61}{415}$
Skin or Soft Tissues		6% $\frac{25}{389}$	8% $\frac{2}{26}$	7% $\frac{27}{415}$
Central Nervous System (CNS)		1% $\frac{3}{389}$	0% $\frac{0}{26}$	1% $\frac{3}{415}$
Bone/Joint		1% $\frac{5}{389}$	0% $\frac{0}{26}$	1% $\frac{5}{415}$
Other		4% $\frac{17}{389}$	12% $\frac{3}{26}$	5% $\frac{20}{415}$
Unknown		7% $\frac{27}{389}$	15% $\frac{4}{26}$	7% $\frac{31}{415}$
Organism: Gram Positive	417	31% $\frac{122}{389}$	25% $\frac{7}{28}$	31% $\frac{129}{417}$
Organism: Gram Negative	417	31% $\frac{119}{389}$	25% $\frac{7}{28}$	30% $\frac{126}{417}$
Organism: Fungal	417	7% $\frac{27}{389}$	0% $\frac{0}{28}$	6% $\frac{27}{417}$
Organism: Not Identified	417	13% $\frac{51}{389}$	14% $\frac{4}{28}$	13% $\frac{55}{417}$
Organism: Other	417	15% $\frac{59}{389}$	14% $\frac{4}{28}$	15% $\frac{63}{417}$
Organism: Unknown	417	14% $\frac{56}{389}$	25% $\frac{7}{28}$	15% $\frac{63}{417}$
Zero VVFD due to death	129	65% $\frac{79}{121}$	50% $\frac{4}{8}$	64% $\frac{83}{129}$

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values.

3.7.2 Primary endpoint: VVFD (Proportional Odds Model)

```
po.model2procc←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                            ventilator.vent+ventilator.vaso+admit.reason.cat2+
                            ics.admit.source.cat2+rcs(ap2_total_score,3)+
                            infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                            x=TRUE,y=TRUE,data=dat.model3procc)
set.seed(237)
po.model.bootstrapprocc←bootcov(po.model2procc, dat.model3procc$site)
```

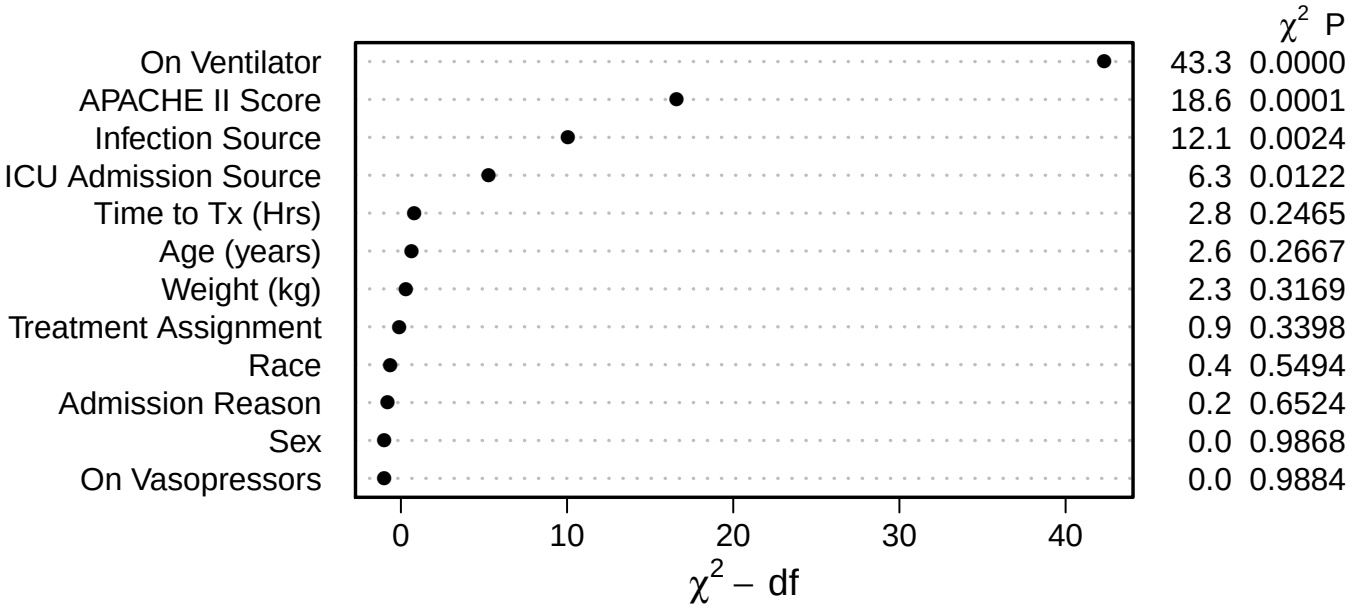
Per-protocol analysis set, to compare the ventilator-and-vasopressor free days between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable proportional odds model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	389	LR χ^2	145.82	R^2	0.316	C	0.729
Cluster on `dat.model3procc$site`		d.f.	17	g	1.384	D_{xy}	0.458
Clusters	39	Pr($>\chi^2$)	<0.0001	g_r	3.991	γ	0.458
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	3×10^{-12}			g_p	0.254	τ_a	0.382
				Brier	0.193		

Table 53: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.918	0.717 - 1.144	0.267
Weight(kg) (per IQR)	0.978	0.745 - 1.218	0.317
APACHE II (per IQR)	0.499	0.356 - 0.714	<0.0001
Time to Tx (Hrs) (per IQR)	0.771	0.551 - 1.023	0.247
Treatment vs. Control	1.227	0.832 - 1.833	0.340
Black vs. Non-Black	0.877	0.541 - 1.379	0.549
Male vs. Female	0.996	0.613 - 1.555	0.987
Ventilator vs. No Ventilator	0.181	0.102 - 0.284	<0.0001
Vasopressor vs. No Vasopressor	1.003	0.626 - 1.497	0.988
Sepsis Primary vs. Sepsis Secondary	0.910	0.609 - 1.311	0.652
ED Admission vs. Other Admission	1.799	1.275 - 3.159	0.012
Lung Infection vs. Other Type of Infection	1.061	0.767 - 1.458	0.737
Urinary Tract Infection vs. Other Type of Infection	2.347	1.311 - 3.455	<0.0001

3.7.3 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

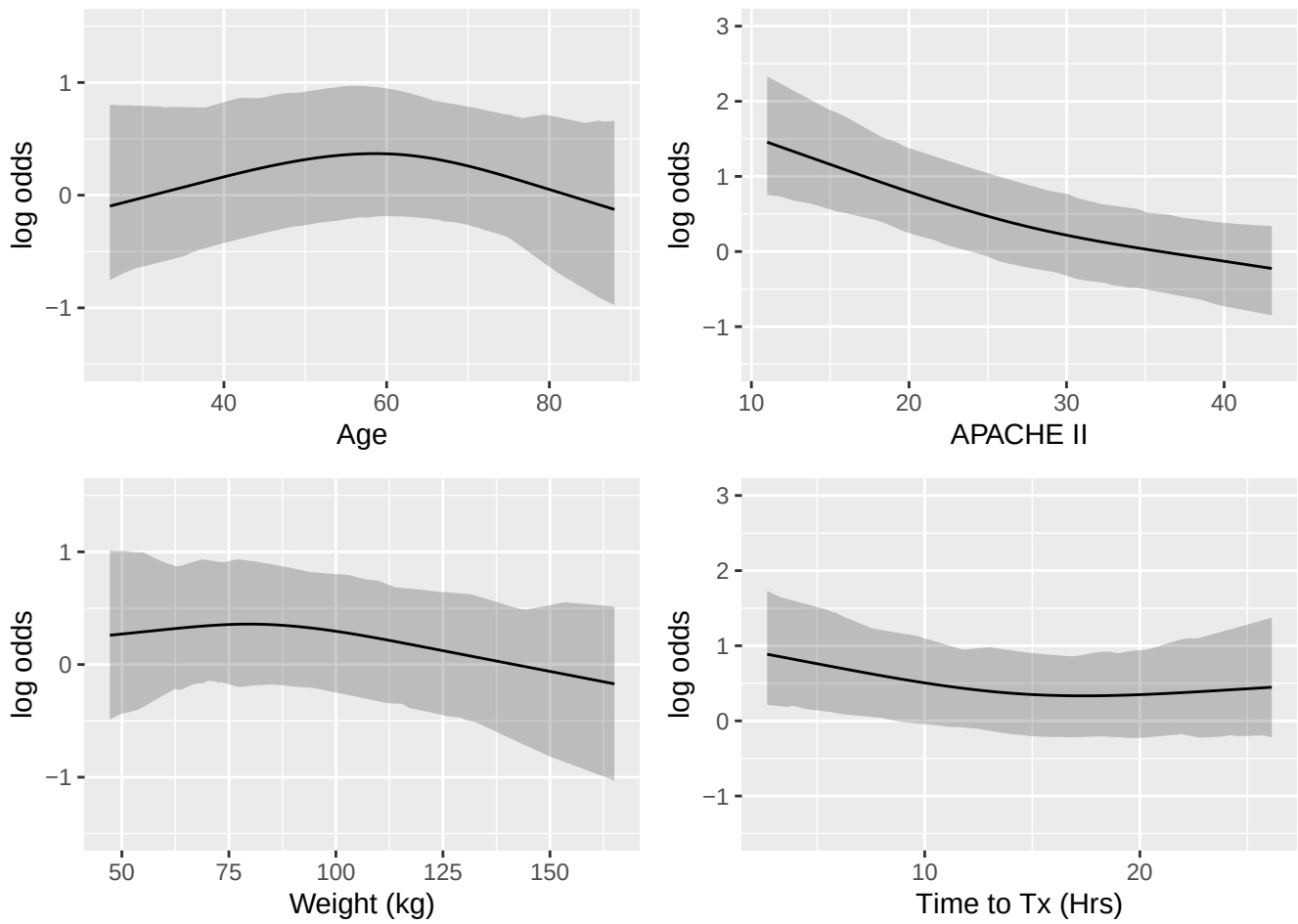
3.7.4 Partial Effect Plots

```
po2.1procc←ggplot(Predict(po.model.bootstrapprocc,age.yrs),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
            scale_x_continuous(name = "Age")
```

```
po2.2procc←ggplot(Predict(po.model.bootstrapprocc,weight),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
            scale_x_continuous(name = "Weight (kg)")
```

```
po2.3procc←ggplot(Predict(po.model.bootstrapprocc,ap2_total_score),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
            scale_x_continuous(name = "APACHE II")
```

```
po2.4procc←ggplot(Predict(po.model.bootstrapprocc,first.studydrugdose.hrs),
           adj.subtitle=FALSE,legend.position='top')+
           coord_cartesian(ylim = c(-1.5, 3)) +
           scale_x_continuous(name = "Time to Tx (Hrs)")
```



3.7.5 Primary endpoint: VVFD (Proportional Odds Model) Sub-Analysis

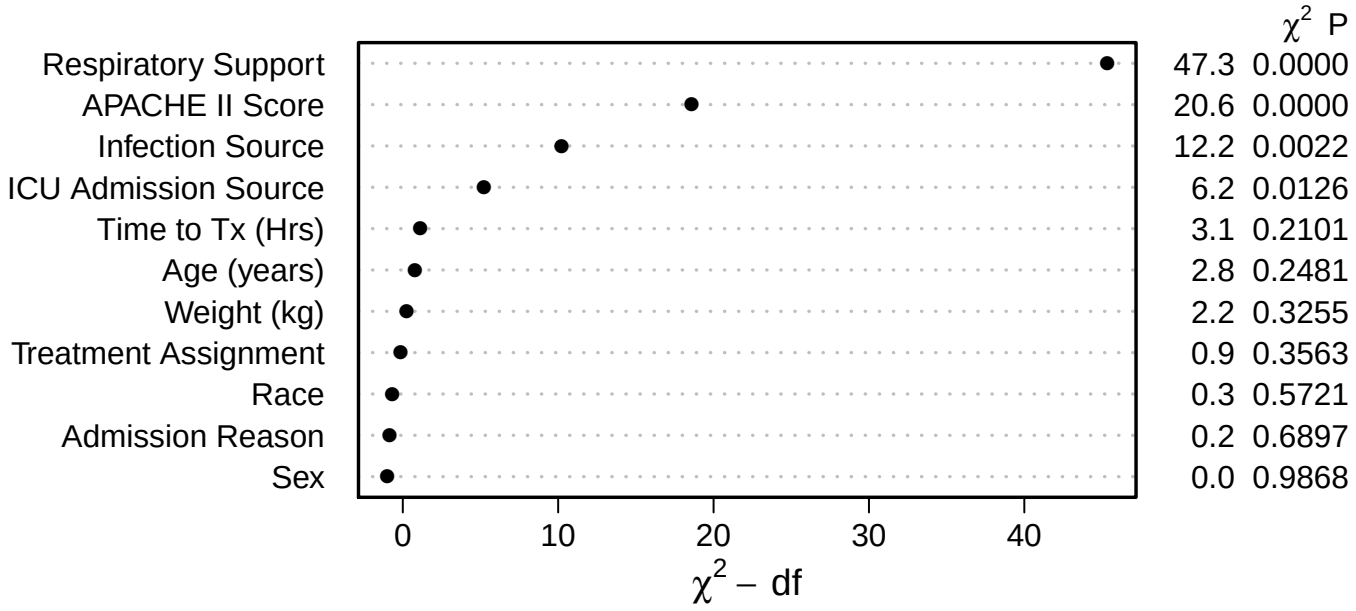
```
po.model2prosubcc←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                          sex.cat+ventilator.3grp+admit.reason.cat2+
                          ics.admit.source.cat2+rcs(ap2_total_score,3)+
                          infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                          x=TRUE,y=TRUE,data=dat.model3procc.3grp)
set.seed(737)
po.model.bootstrapprosubcc←bootcov(po.model2prosubcc, dat.model3procc.3grp$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	389	LR χ^2	145.88	R^2	0.316	C	0.729
Cluster on `dat.model3procc.3grp$site`		d.f.	17	g	1.385	D_{xy}	0.458
Clusters	39	Pr($>\chi^2$)	<0.0001	g_r	3.993	γ	0.458
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	7×10^{-12}			g_p	0.254	τ_a	0.382
				Brier	0.193		

Table 54: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.918	0.736 - 1.204	0.248
Weight(kg) (per IQR)	0.979	0.715 - 1.210	0.325
APACHE II (per IQR)	0.499	0.368 - 0.653	<0.0001
Time to Tx (Hrs) (per IQR)	0.766	0.568 - 1.069	0.210
Treatment vs. Control	1.227	0.739 - 1.923	0.356
Black vs. Non-Black	0.877	0.563 - 1.369	0.572
Male vs. Female	0.996	0.636 - 1.445	0.987
Ventilator vs. Both	0.996	0.660 - 1.650	0.985
Vasopressor vs. Both	5.509	3.58 - 10.455	<0.0001
Sepsis Primary vs. Sepsis Secondary	0.910	0.618 - 1.573	0.690
ED Admission vs. Other Admission	1.799	1.216 - 3.113	0.013
Lung Infection vs. Other Type of Infection	1.060	0.697 - 1.523	0.774
Urinary Tract Infection vs. Other Type of Infection	2.347	1.463 - 3.656	0.0005

3.7.6 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

3.7.7 Primary endpoint: VVFD (GEE Model)

```
primary.gee1procc←geeglm(log(days.vvfd+1)~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+
                                        admit.reason.cat2+ics.admit.source.cat2+
                                        ap2_total_score+
                                        infect.source.cat2+first.studydrugdose.hrs,
                                        family=(link="gaussian"),
                                        data=dat.model3procc.gee1,id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

Per-protocol analysis set, to estimate the marginal treatment effect on ventilator-and-vasopressor free days while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. To improve the distribution of the outcome variable a log transformation was implemented. The resulting point estimates from the model are summarized with the Geometric Mean (GM), 95% confidence intervals, and p-value. For the continuous variables the GM is based on the expected mean number of VVFD's per one unit increase. For the categorical variables the GM is based in comparison to their reference group (vs.).

Table 55: Primary Endpoint: GEE Model

PTable1procc	**GM**	**95% C.I.**	**P-value**
Age (per 1 year)	1.003	0.995 - 1.011	0.449
Weight(kg) (per Kg)	0.998	0.994 - 1.001	0.204
APACHE II (per 1 point)	0.962	0.947 - 0.976	<0.0001
Time to Tx (Hrs) (per Hr)	0.991	0.973 - 1.009	0.330
Treatment vs. Control	1.149	0.842 - 1.570	0.381
Black vs. Non-Black	0.983	0.753 - 1.282	0.897
Male vs. Female	1.044	0.816 - 1.337	0.730
Ventilator vs. No Ventilator	0.472	0.341 - 0.654	<0.0001
Vasopressor vs. No Vasopressor	1.082	0.757 - 1.547	0.665
Sepsis Primary vs. Sepsis Secondary	0.876	0.640 - 1.200	0.409
ED Admission vs. Other Admission	1.436	1.051 - 1.963	0.023
Lung Infection vs. Other Type of Infection	1.082	0.845 - 1.385	0.532
Urinary Tract Infection vs. Other Type of Infection	1.706	1.286 - 2.263	<0.0001

3.7.8 Secondary endpoint: 30-Day Mortality (Logistic Regression Model)

```
lrm.model2procc←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+
                                sex.cat+ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                x=TRUE,y=TRUE,data=dat.model3procc)
set.seed(27)
lrm.model.bootstrapprocc←bootcov(lrm.model2procc, dat.model3procc$site)
```

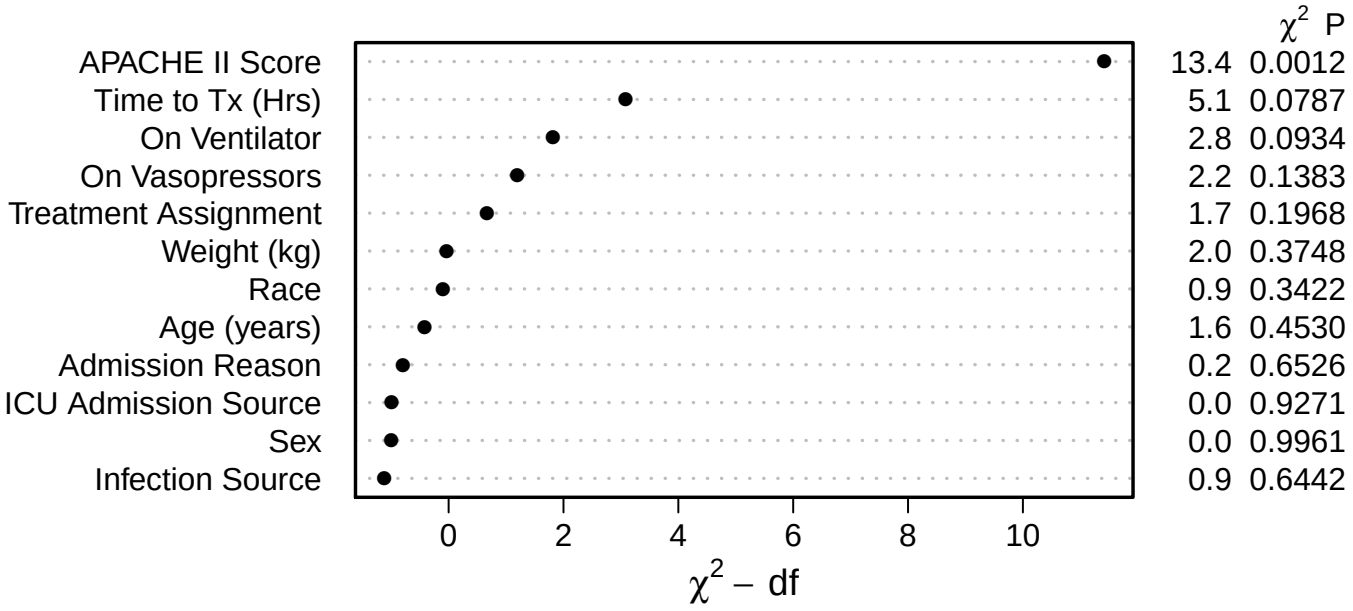
Per-protocol analysis set, to compare 30-day mortality between treatment groups while adjusting for the effects of the demographic/clincial characteristics and site location, a mixed effects multivariable logistic regression model was fit. The point estimates from the model are summarized with Odds Ratios (OR), 95% confidence intervals, and p-value. Since the continuous variables are modeled as non-linear effects the OR's are based on the change from the interquartile range (IQR) (i.e. 25% to 75%) and for categorical variables the OR's are based in comparison to their reference group (vs.).

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	389	LR χ^2	53.43	R^2	0.202	C	0.756
FALSE	310	d.f.	17	g	1.288	D_{xy}	0.512
TRUE	79	Pr($>\chi^2$)	<0.0001	g_r	3.624	γ	0.512
Cluster on `dat.model3procc$site`				g_p	0.164	τ_a	0.166
Clusters	39			Brier	0.140		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	6×10^{-7}						

Table 56: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.309	0.845 - 2.375	0.453
Weight(kg) (per IQR)	0.730	0.555 - 1.318	0.375
APACHE II (per IQR)	3.102	1.659 - 6.357	0.001
Time to Tx (Hrs) (per IQR)	1.236	0.701 - 2.375	0.079
Treatment vs. Control	0.649	0.291 - 1.172	0.197
Black vs. Non-Black	0.693	0.331 - 1.625	0.342
Male vs. Female	0.998	0.524 - 1.738	0.996
Ventilator vs. No Ventilator	2.198	0.956 - 6.411	0.093
Vasopressor vs. No Vasopressor	0.657	0.356 - 1.092	0.138
Sepsis Primary vs. Sepsis Secondary	0.869	0.453 - 1.521	0.653
ED Admission vs. Other Admission	0.967	0.421 - 1.704	0.927
Lung Infection vs. Other Type of Infection	0.978	0.460 - 1.586	0.947
Urinary Tract Infection vs. Other Type of Infection	0.978	0.065 - 0.864	0.349

3.7.9 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

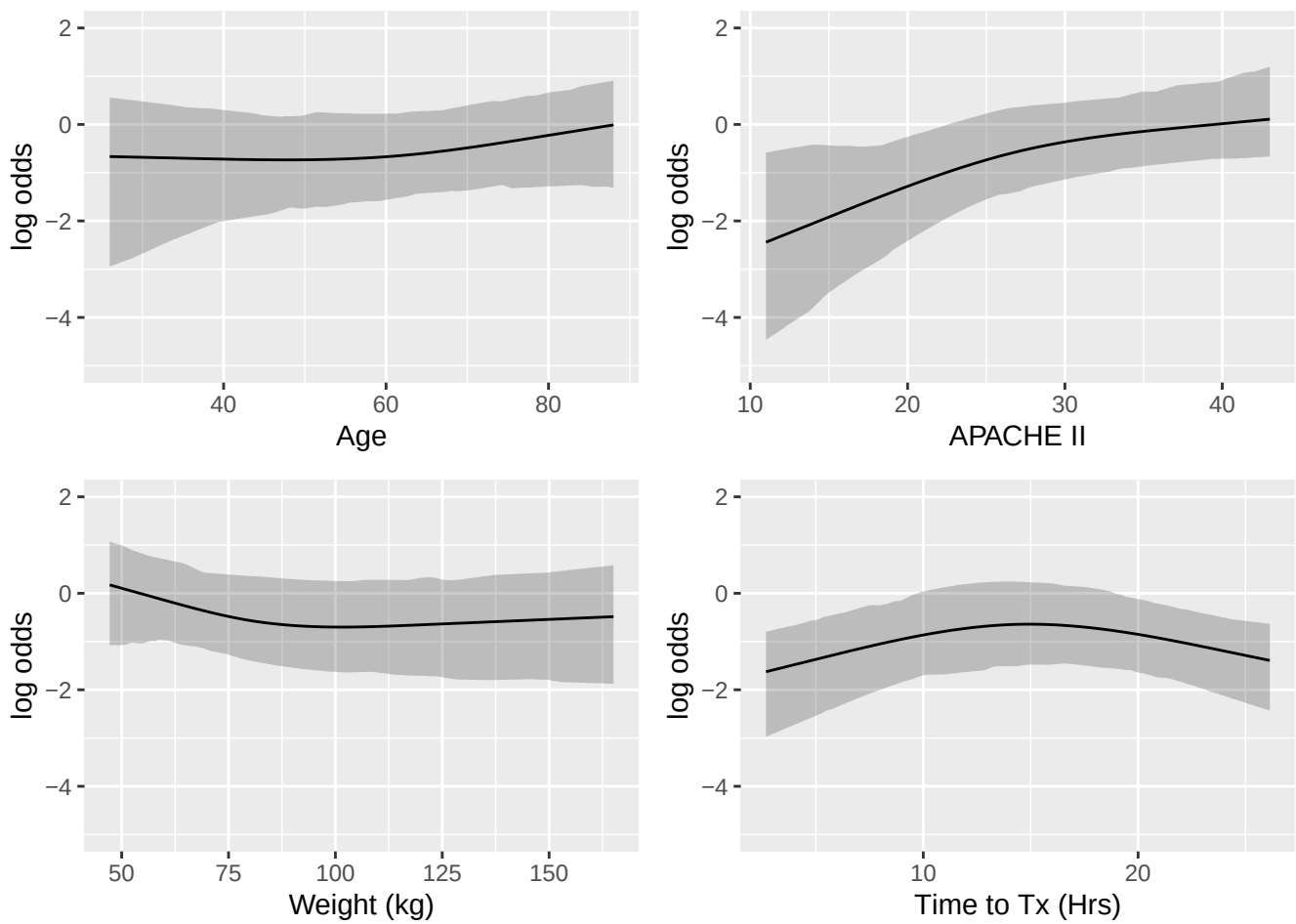
3.7.10 Partial Effect Plots

```
lrm2.1procc←ggplot(Predict(lrm.model.bootstrapprocc,age.yrs),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2))+
            scale_x_continuous(name = "Age")
```

```
lrm2.2procc←ggplot(Predict(lrm.model.bootstrapprocc,weight),adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2))+
            scale_x_continuous(name = "Weight (kg)")
```

```
lrm2.3procc←ggplot(Predict(lrm.model.bootstrapprocc,ap2_total_score),
            adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
            scale_x_continuous(name = "APACHE II")
```

```
lrm2.4procc←ggplot(Predict(lrm.model.bootstrapprocc,first.studydrugdose.hrs),
            adj.subtitle=FALSE,
            legend.position='top')+coord_cartesian(ylim = c(-5, 2)) +
            scale_x_continuous(name = "Time to Tx (Hrs)")
```



3.7.11 Secondary endpoint: 30-Day Mortality (Logistic Regression Model) Sub-Analysis

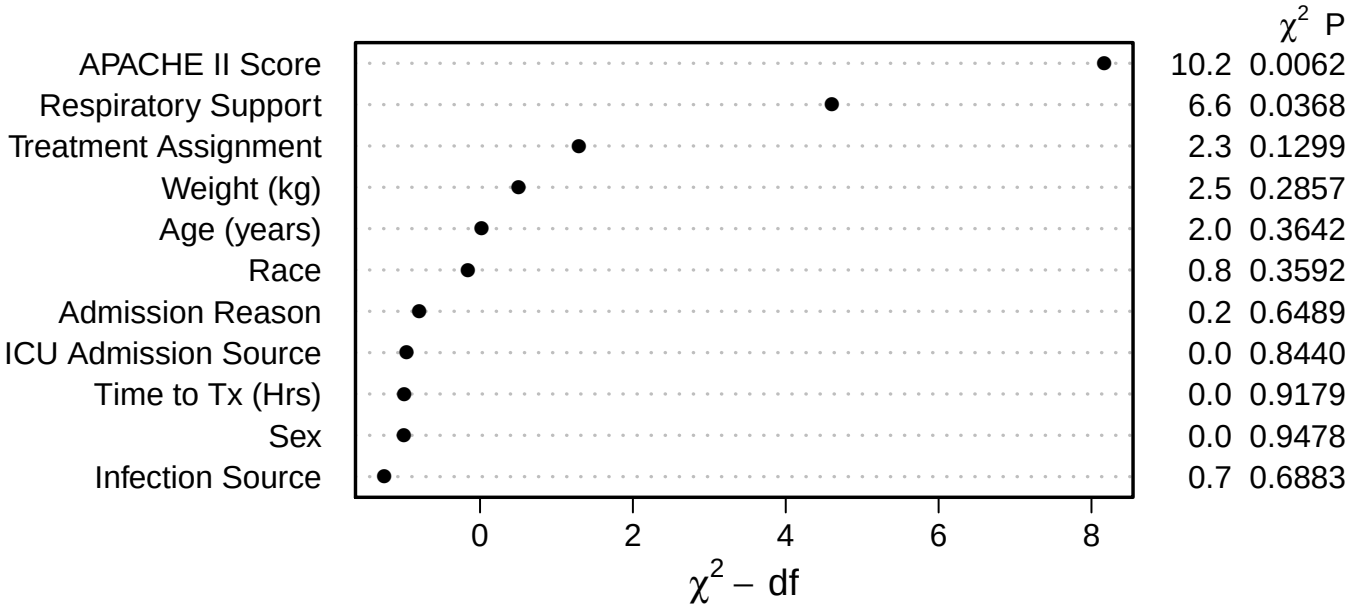
```
lrm.model2prosubcc←lrm(death_30d=="1"~treatment+rcs(age.yrs,3)+race.cat2+
                                rcs(weight,3)+sex.cat+ventilator.3grp+
                                admit.reason.cat2+ics.admit.source.cat2+
                                rcs(ap2_total_score,3)+
                                infect.source.cat2+first.studydrugdose.hrs,
                                x=TRUE,y=TRUE,
                                data=dat.model3procc.3grp)
set.seed(777)
lrm.model.bootstrapprosubcc←bootcov(lrm.model2prosubcc, dat.model3procc.3grp$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	389	LR χ^2	49.05	R^2	0.186	C	0.747
FALSE	310	d.f.	16	g	1.219	D_{xy}	0.494
TRUE	79	Pr($>\chi^2$)	<0.0001	g_r	3.382	γ	0.494
Cluster on `dat.model3procc.3grp$site`				g_p	0.158	τ_a	0.160
Clusters	39			Brier	0.142		
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	3×10^{-7}						

Table 57: Secondary Endpoint: Logistic Regression Model

	OR	95% C.I.	P-value
Age (per IQR)	1.332	0.973 - 2.050	0.364
Weight(kg) (per IQR)	0.750	0.562 - 1.198	0.286
APACHE II (per IQR)	3.097	1.528 - 7.031	0.006
Time to Tx (Hrs) (per IQR)	1.025	0.596 - 1.566	0.918
Treatment vs. Control	0.632	0.325 - 1.070	0.130
Black vs. Non-Black	0.718	0.347 - 1.457	0.359
Male vs. Female	1.023	0.516 - 2.011	0.948
Ventilator vs. Both	1.365	0.649 - 2.529	0.358
Vasopressor vs. Both	0.469	0.159 - 0.978	0.096
Sepsis Primary vs. Sepsis Secondary	0.872	0.503 - 1.571	0.649
ED Admission vs. Other Admission	0.931	0.452 - 1.813	0.844
Lung Infection vs. Other Type of Infection	0.937	0.517 - 1.536	0.810
Urinary Tract Infection vs. Other Type of Infection	0.359	0.035 - 3.675	0.388

3.7.12 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

3.7.13 Secondary endpoint: 30-day Mortality (GEE Model)

```
secondary.gee2procc←geeglm(death_30d=="1"~treatment+age.yrs+race.cat2+weight+sex.cat+
                                        ventilator.vent+ventilator.vaso+
                                        admit.reason.cat2+ics.admit.source.cat2+
                                        ap2_total_score+
                                        infect.source.cat2+first.studydrugdose.hrs,
                                        family=binomial(link="logit"),
                                        data=dat.model3procc.gee2,id=site,
                                        corstr = "exchangeable", std.err="san.se")
```

Per-protocol analysis set, to estimate the marginal treatment effect on 30-day mortality while adjusting for the effects of the demographic/clincial characteristics and site location, a multivariable generalized estimating equation model was fit. The point estimates from the model are summarized with the Odds Ratios (OR), 95% confidence intervals, and p-value. For the continuous variables the OR is based on the odds of 30-day mortality per one unit increase. For the categorical variables the OR is based in comparison to their reference group (vs.).

Table 58: Secondary Endpoint: GEE Model

STable1procc	**OR**	**95% C.I.**	**P-value**
Age (per 1 year)	1.014	0.992 - 1.037	0.225
Weight(kg) (per kg)	0.997	0.987 - 1.007	0.518
APACHE II (per 1 point)	1.071	1.034 - 1.111	0.0002
Time to Tx (Hrs) (per Hr)	1.000	0.967 - 1.034	0.997
Treatment vs. Control	0.655	0.387 - 1.107	0.114
Black vs. Non-Black	0.649	0.344 - 1.226	0.183
Male vs. Female	0.999	0.575 - 1.737	0.998
Ventilator vs. No Ventilator	2.124	0.944 - 4.776	0.068
Vasopressors vs. No Vasopressors	0.743	0.426 - 1.295	0.295
Sepsis Primary vs. Sepsis Secondary	0.914	0.546 - 1.533	0.734
ED Admission vs. Other Admission	0.947	0.507 - 1.770	0.864
Lung Infection vs. Other Type of Infection	0.976	0.620 - 1.539	0.918
Urinary Tract Infection vs. Other Type of Infection	0.383	0.136 - 1.077	0.069

3.7.14 Primary endpoint: VVFD (Proportional Odds Model) Excluding Open Label Steroids

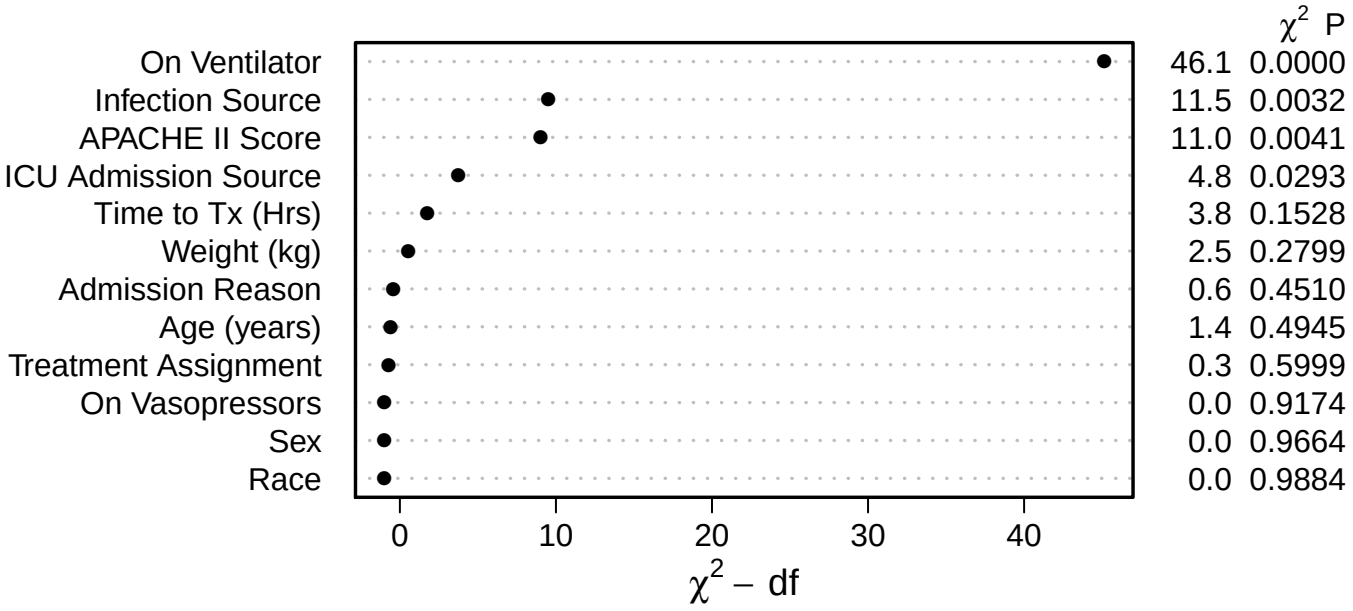
```
po.model2pro.ster←lrm((days.vvfd)~treatment+rcs(age.yrs,3)+race.cat2+rcs(weight,3)+sex.cat+
                                  ventilator.vent+ventilator.vaso+admit.reason.cat2+
                                  ics.admit.source.cat2+rcs(ap2_total_score,3)+
                                  infect.source.cat2+rcs(first.studydrugdose.hrs,3),
                                  x=TRUE,y=TRUE,data=subset(dat.model3.impute1pro,
                                  record_id nin dat.steroid.control.pro$record_id))
set.seed(52)
po.model.bootstrappro.ster←bootcov(po.model2pro.ster, subset(dat.model3.impute1pro,
                            record_id nin dat.steroid.control.pro$record_id)$site)
```

		Model Likelihood Ratio Test		Discrimination Indexes		Rank Discrim. Indexes	
Obs	332	LR χ^2	134.55	R^2	0.337	C	0.733
Cluster on	site	d.f.	17	g	1.470	D_{xy}	0.467
Clusters	39	Pr($>\chi^2$)	<0.0001	g_r	4.351	γ	0.467
$\max\lvert\frac{\partial \log L}{\partial \beta}\rvert$	1×10^{-11}			g_p	0.257	τ_a	0.393
				Brier	0.187		

Table 59: Primary Endpoint: Proportional Odds Model

	OR	95% C.I.	P-value
Age (per IQR)	0.860	0.620 - 1.199	0.495
Weight(kg) (per IQR)	0.873	0.625 - 1.145	0.280
APACHE II (per IQR)	0.599	0.432 - 0.816	0.004
Time to Tx (Hrs) (per IQR)	0.699	0.485 - 1.003	0.153
Treatment vs. Control	1.134	0.709 - 1.682	0.600
Black vs. Non-Black	1.004	0.608 - 1.729	0.988
Male vs. Female	0.990	0.571 - 1.493	0.966
Ventilator vs. No Ventilator	0.135	0.068 - 0.207	<0.0001
Vasopressor vs. No Vasopressor	1.025	0.659 - 1.643	0.917
Sepsis Primary vs. Sepsis Secondary	0.762	0.372 - 1.463	0.451
ED Admission vs. Other Admission	2.069	1.205 - 4.366	0.029
Lung Infection vs. Other Type of Infection	1.464	0.973 - 2.151	0.087
Urinary Tract Infection vs. Other Type of Infection	2.885	1.482 - 5.089	0.001

3.7.15 Anova Plot



The results of the anova plot display the most important to least important covariates in descending order.

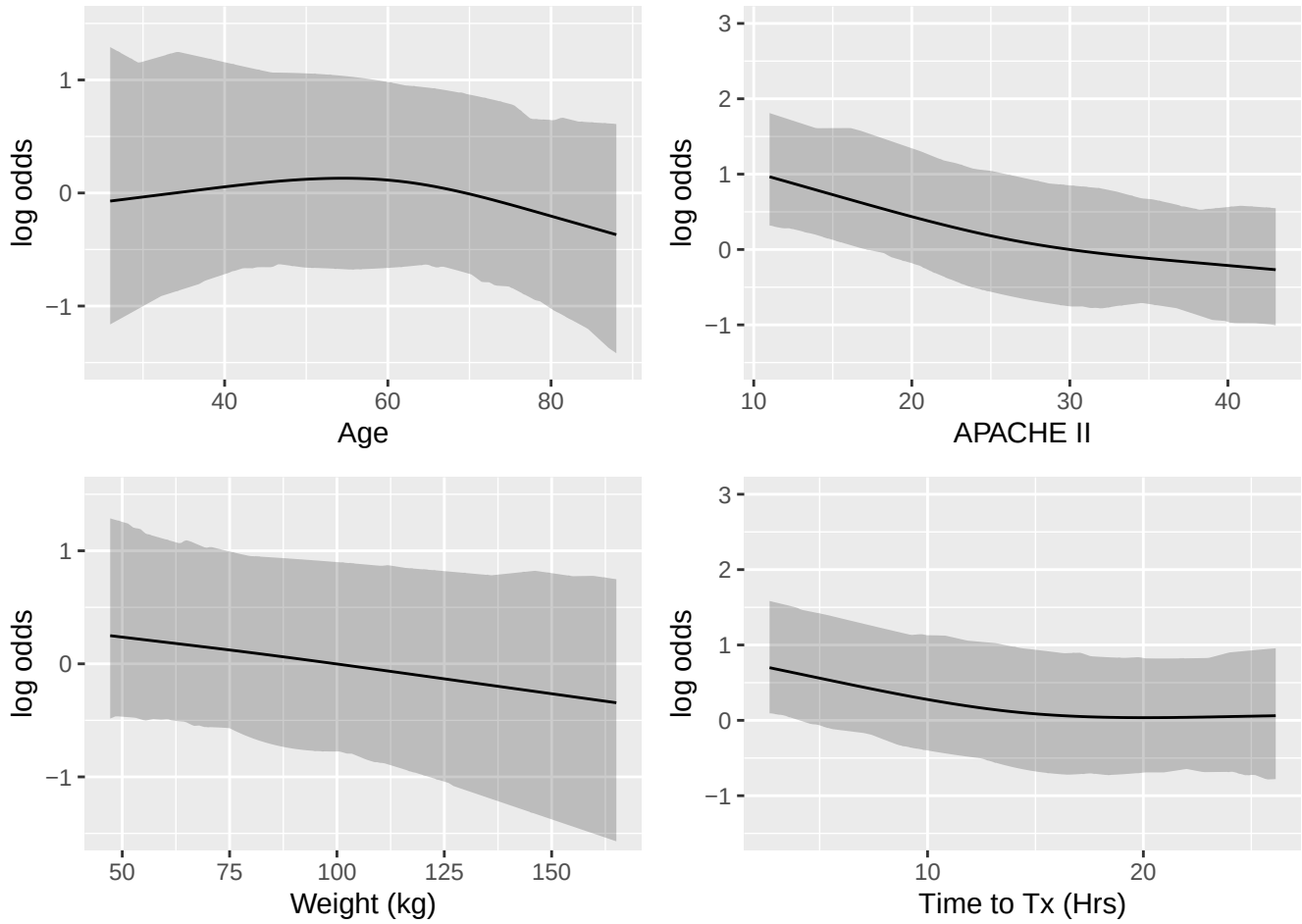
3.7.16 Partial Effect Plots

```
po2.1pro.ster←ggplot(Predict(po.model.bootstrappro.ster,age.yrs),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Age")
```

```
po2.2pro.ster←ggplot(Predict(po.model.bootstrappro.ster,weight),adj.subtitle=FALSE,
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 1.5))+
             scale_x_continuous(name = "Weight (kg)")
```

```
po2.3pro.ster←ggplot(Predict(po.model.bootstrappro.ster,ap2_total_score),adj.subtitle=FALSE
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "APACHE II")
```

```
po2.4pro.ster←ggplot(Predict(po.model.bootstrappro.ster,first.studydrugdose.hrs),adj.subti
             legend.position='top')+coord_cartesian(ylim = c(-1.5, 3)) +
             scale_x_continuous(name = "Time to Tx (Hrs)")
```



3.8 Exploratory End Points (Univariate Comparisons)

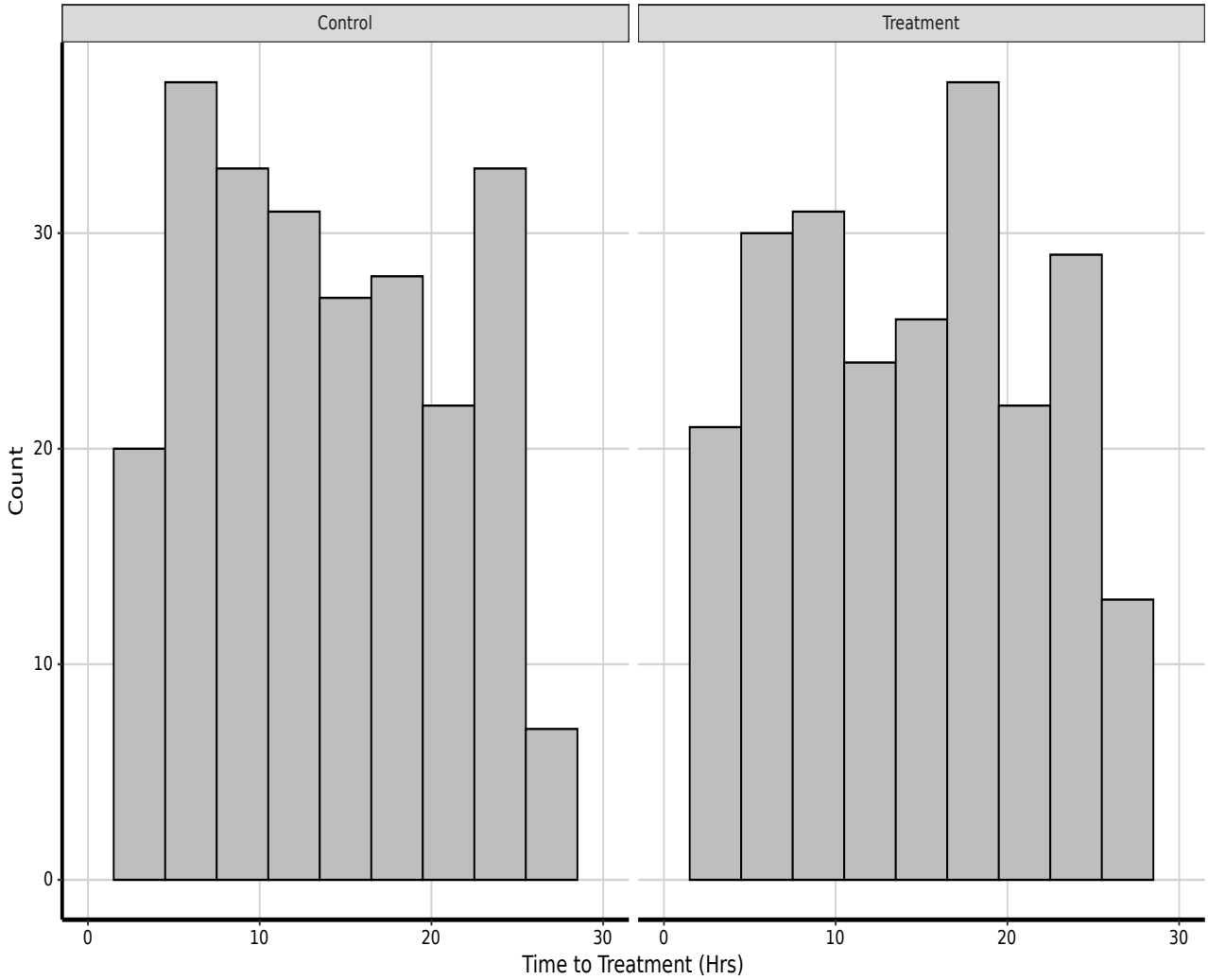
```
latex(summaryM(death.rand.icu.2+death_180d.cat.2+sofa.diff+length.icu+
               length.hosp+delirium.coma.fd+days.renal~treatment,data=dat.victaspro,
               overall=TRUE,test=TRUE,continuous=5),
               file="",where="!h",caption="Exploratory end points by
               treatment assignment (univariate comparisons)",
               exclude1=TRUE,prn=TRUE,prmsd=TRUE,long=TRUE,prtest="P",
               npct="both",digits=2, landscape=FALSE, longtable=TRUE,
               lines.page=38,what = '%',  legend.bottom = TRUE,size="footnotesize")
```

Table 60: Exploratory end points by treatment assignment (univariate comparisons)

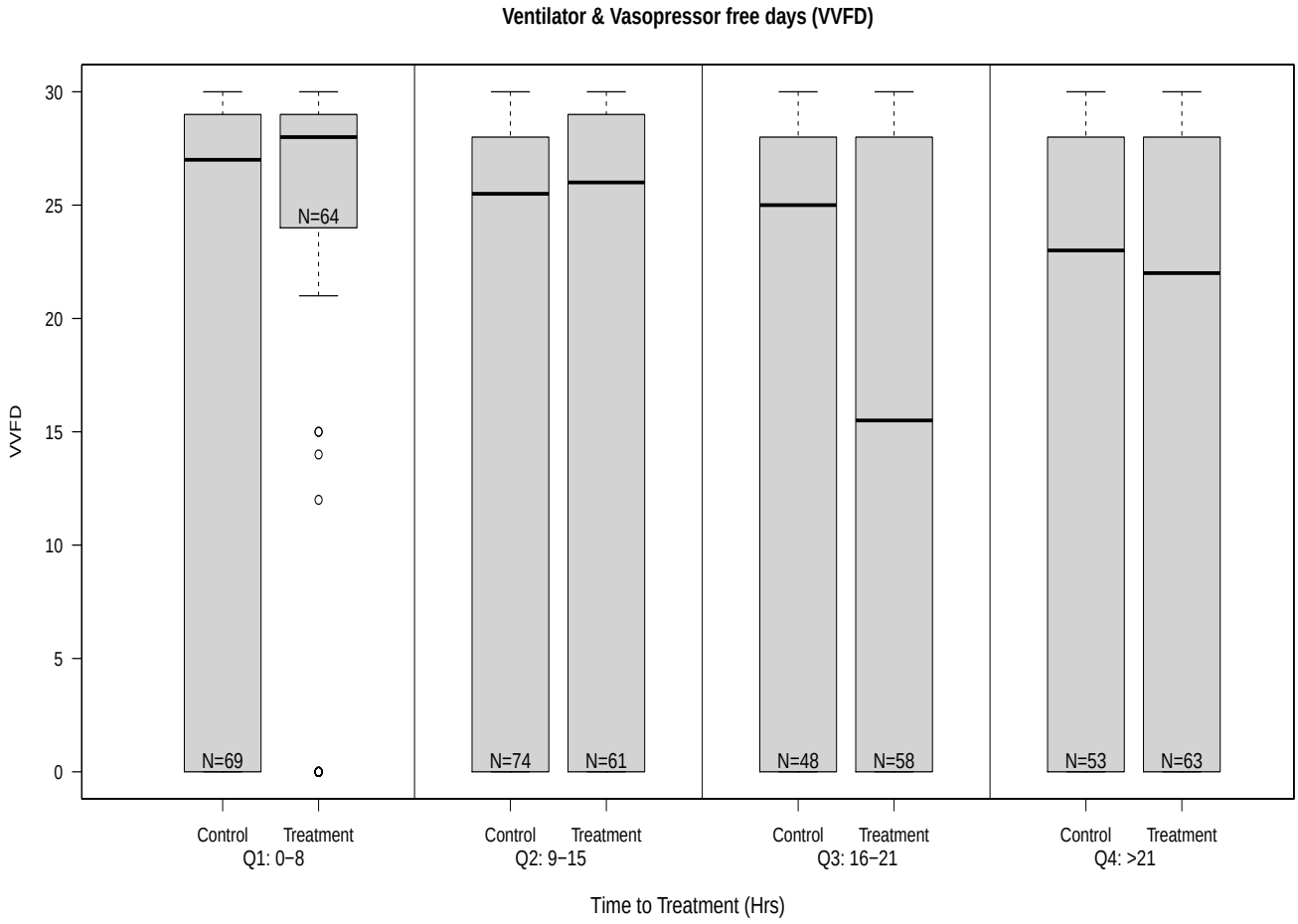
	N	Control $N = 212$	Treatment $N = 205$	Combined $N = 417$	P-value
Mortality: Randomization and ICU discharge	417	17% $\frac{36}{212}$	17% $\frac{34}{205}$	17% $\frac{70}{417}$	0.91[1]
180-Day Mortality	417	37% $\frac{78}{212}$	40% $\frac{81}{205}$	38% $\frac{159}{417}$	0.57[1]
SOFA score change: Baseline to Day 4	417	2.0 5.0 7.0 (4.8 ±3.1)	3.0 5.0 7.0 (5.4 ±3.2)	3.0 5.0 7.0 (5.1 ±3.1)	0.073[2]
Length of ICU Stay	414	2.0 4.0 8.0 (6.8 ±7.1)	2.0 4.0 9.0 (7.2 ±7.5)	2.0 4.0 8.0 (7.0 ±7.3)	0.52[2]
Length of Hospital Stay	414	6 10 18 (14 ±27)	6 11 19 (14 ±10)	6 11 18 (14 ±21)	0.48[2]
Coma/Delirium Free Days	409	2.0 4.0 5.0 (3.3 ±1.9)	2.0 4.0 5.0 (3.2 ±1.9)	2.0 4.0 5.0 (3.2 ±1.9)	0.53[2]
days.renal	416	7.0 30.0 30.0 (21.9 ±13.0)	13.0 30.0 30.0 (22.0 ±12.6)	9.2 30.0 30.0 (22.0 ±12.8)	0.78[2]

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. $x \pm s$ represents $X \pm 1$ SD. N is the number of non-missing values. Tests used: [1]Pearson test; [2]Wilcoxon test .

4 Exploratory Analyses



Plot was truncated to 30 hours. Subjects with 30+ hours had an N=6 in the Control group and an N=11 in the Treatment group.


Ventilator & Vasopressor free days (VVFD)
VVFD
30
25
20
15
10
5
0
N=64
N=69
N=74
N=61
N=48
N=58
N=53
N=63
Control
Treatment
Q1: 0−8
Control
Treatment
Q2: 9−15
Control
Treatment
Q3: 16−21
Control
Treatment
Q4: >21
Time to Treatment (Hrs)