Supplementary material for:

Sodium bicarbonate administration for metabolic acidosis in the intensive care: a target trial emulation

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INTENSIVE CARE MEDICINE

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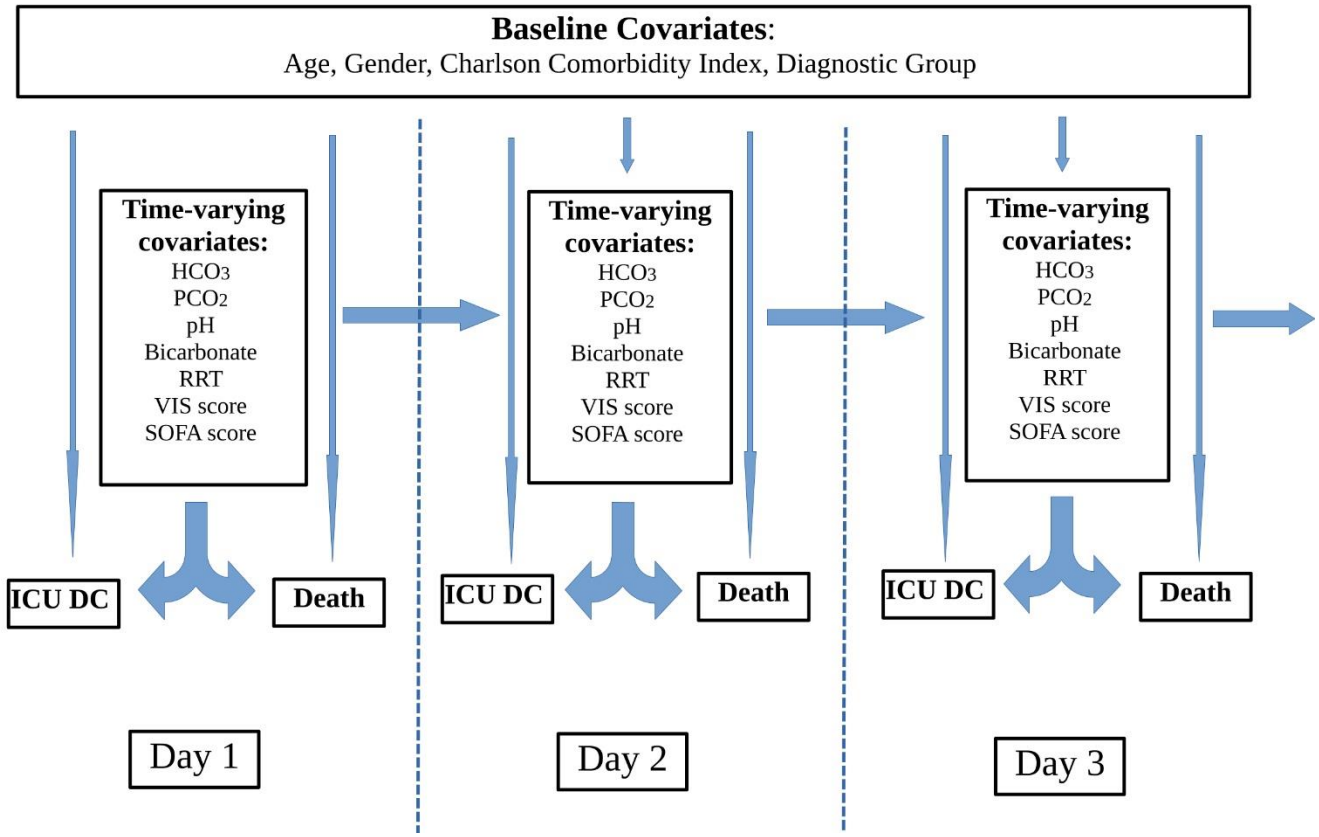
Table S1 – Overview of Protocol for Target Trial Emulation

Component	Potential randomised trial	Target trial emulation
Eligibility	Inclusion criteria • Adult (≥18 yr) • pH<7.3 and PCO_2≤45mmHg on arterial or venous blood gas in first 3 days of admission to ICU. Exclusion criteria • Admission for DKA or toxicology • History of End Stage Renal Failure • Previous enrolment.	Additional exclusions • No lactate measurement in first 2 days in ICU • Transfer from another hospital • Discharge from ICU to another ICU
Treatment strategies	Treatment group: administer bicarbonate with aim to restore pH > 7.3 as long as PCO_2≤45mmHg Control group: no bicarbonate administration	Treatment group: administer bicarbonate on days where pH<7.3 and PCO_2≤45 Control group: no bicarbonate administration.
Follow up	Follow-up starts at enrolment into trial. Completed when patient dies, undergoes administrative censoring or is lost to follow up.	Follow-up starts at ICU admission Censored at day 30 in ICU or discharge from ICU
Primary end-point	• All cause 30-day mortality • ICU mortality • Pre-specified subgroups	• ICU mortality • Pre-specified subgroups
Analysis	Intention-to-treat	Per protocol
Statistical analysis	Intention-to-treat analysis	Adjustment for baseline and time varying confounders using sequential G-computation. Monte Carlo simulation is used to simulate each patient twice – once for each treatment strategy.

Figure S1 – Schematic illustration of model used in G-formulation



Visual representation of the modelling utilized in the g-computation.

Day 1: baseline covariates and observed values of time-varying covariates on day 1 modelled to predict outcome (mortality/ICU discharge vs ongoing admission)

Day 2 and beyond:

Step 1 = time-varying covariates modelled using results over preceding days as well as baseline covariates

Step 2 = outcomes (mortality/ICU discharge) are predicted using both baseline covariates and time-varying covariates up to that day

*RRT = renal replacement therapy VIS = vasoactive-inotropic score
SOFA = Sequential Organ Failure Score ICU DC = discharge from intensive care unit

Table S2 – Covariates used in G-formulation mortality models

Baseline Covariates:			
Variable		**Distribution assumption**	
Age		Normal	
Gender		Binary	
Charlson Co-morbidity Index (CCI)		Categorical	
Diagnostic group		Categorical	
Year of admission		Categorical	
Time varying covariates:			
	Distribution assumption	**Transformation**	**Independent variables used in model**
PCO_2	Normal		Lag1 PCO_2
HCO_3	Normal		Lag1 HCO_3 ,lag1 bicarbonate treatment, lag1 RRT
pH	Normal	Cubic	HCO_3, PCO_2 , interaction HCO_3 & PCO_2
Bicarbonate treatment	Binary		HCO_3, pH, PCO_2 , Admission year
Maximal lactate	Normal	Reciprocal square root	Lag1 SOFA, HCO_3
VIS – score	Zero-inflated	Square root	Bicarbonate, cum_avg lag1 SOFA, pH, lactate
SOFA – score	Normal		Bicarbonate, PCO_2, HCO_3 , interaction HCO_3 & PCO2
RRT	Binary		Bicarbonate, SOFA, lactate, year of admission
Outcome & competing event models			
ICU discharge (competing event)	Binary		VIS, Cum avg RRT, pH, PCO_2, cum_avg lactate, age, diagnostic group, year of admission,
Mortality	Binary		Bicarbonate, SOFA, pH, cum_avg lactate, cum_avg RRT, HCO_3, cum_avg VIS, diagnostic group, age, gender , year of admission, CCI
All models contain time as a covariate. **Continues variables are modelled using natural splines as required (3-4 knots per variable)**			

LagX – value X days ago.
Cum_avg – cumulative average, can be combined with lagX to specify time of the average.

*RRT = renal replacement therapy VIS = vasoactive-inotropic score
SOFA = Sequential Organ Failure Score ICU DC = discharge from intensive care unit

Table S3 – Covariates used in G-formulation secondary outcome (renal replacement) model

Baseline Covariates:			
Variable		**Distribution assumption**	
Age		Normal	
Gender		Binary	
Charlson Co-morbidity Index (CCI)		Categorical	
Diagnostic group		Categorical	
Year of admission		Categorical	
Time varying covariates:			
	Distribution assumption	**Transformation**	**Independent variables used in model**
PCO_2	Normal		Lag1 PCO_2
HCO_3	Normal		Lag1 HCO_3 ,lag1 bicarbonate treatment
pH	Normal	Cubic	HCO_3, PCO_2 , interaction HCO_3 & PCO_2
Bicarbonate treatment	Binary		HCO_3, pH, PCO_2 , Admission year
Maximal lactate	Normal	Reciprocal square root	Lag1 SOFA, PCO_2, HCO_3, interaction HCO3 & PCO_2
VIS – score	Zero-inflated	Square root	Bicarbonate, cum_avg lag1 SOFA, pH, lactate
SOFA – score	Normal		Bicarbonate, PCO_2, HCO_3 , interaction HCO_3 & PCO2
Outcome & competing event models			
Mortality or ICU discharge (competing event)	Binary		SOFA, pH, PCO_2, HCO_3, PCO2, cum_avg lactate, cum_avg VIS, age, diagnostic group, gender, year of admission,
RRT	Binary		Bicarbonate, SOFA, pH, HCO_3, cum_avg lactate, cum_avg VIS, diagnostic group, CCI, age, Gender, year of admission
All models contain time as a covariate. **Continues variables are modelled using natural splines as required (3-4 knots per variable)**			

LagX – value X days ago.
Cum_avg – cumulative average, can be combined with lagX to specify time of the average.

*RRT = renal replacement therapy VIS = vasoactive-inotropic score
SOFA = Sequential Organ Failure Score ICU DC = discharge from intensive care unit

Figure S2 – Flow chart of patient selection

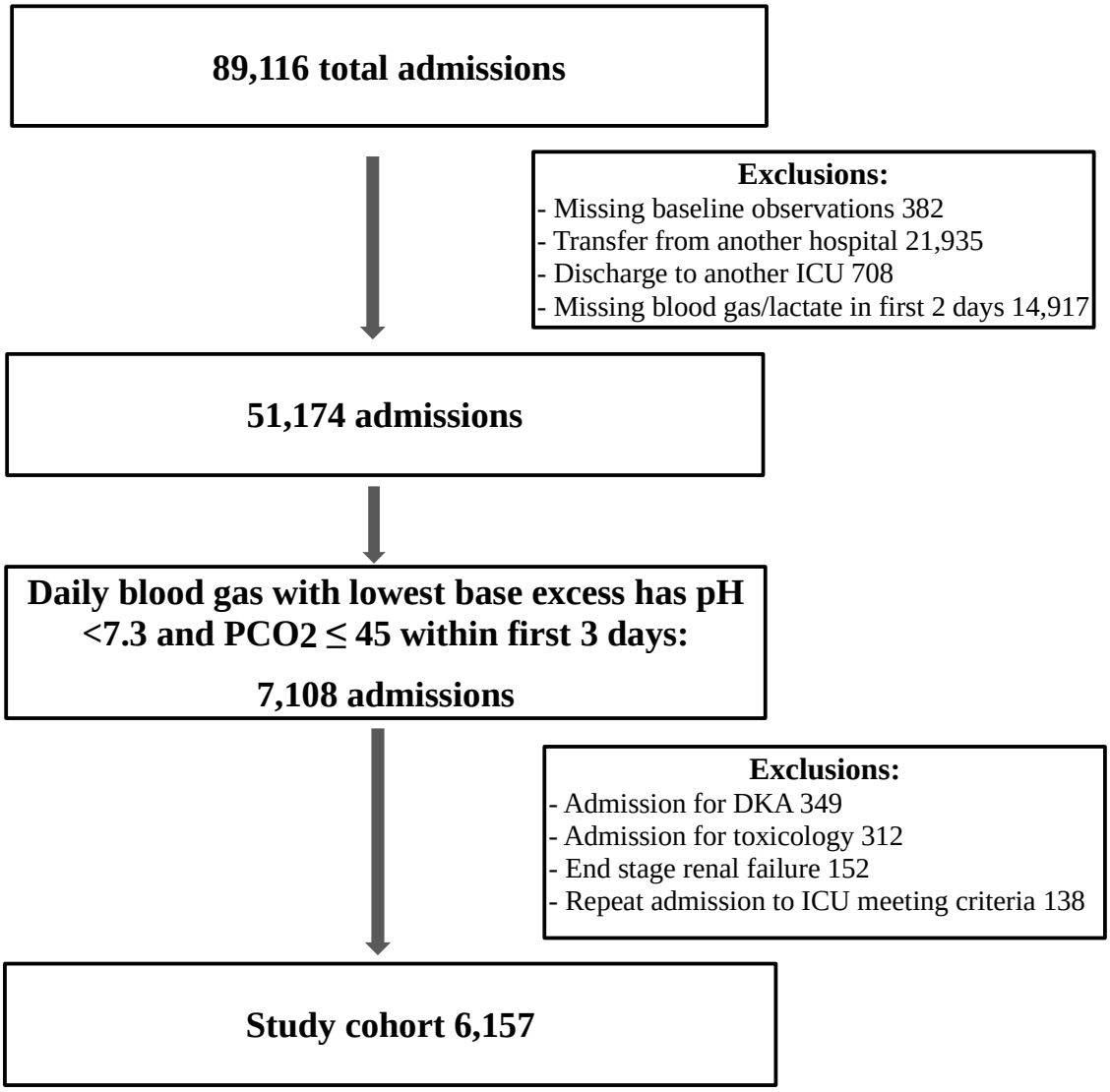


Table S4: Dose and timing of bicarbonate administration

	Primary model	Subgroup analysis: pH<7.3 + AKI	Subgroup analysis: pH<7.3 + vasoactive support	Subgroup analysis: severe acidosis pH<7.2	Subgroup analysis: 7.2 ≤ pH <7.3, no AKI or vasoactive support
Total bicarbonate administration	1764/6157 (29%)	835/1982 (42%)	682/1656 (41%)	670/1353 (50%)	479/2851 (17%)
Bicarbonate administration by day of admission:					
Day 1	1159/6157 (19%)	564/1982 (28%)	480/1656 (29%)	527/1353 (39%)	280/2851 (9%)
Day 2	877/5880 (15%)	386/1889 (20%)	325/1565 (21%)	311/1236 (25%)	255/2744 (9%)
Day 3	201/ 4360 (5%)	108/1561 (7%)	85/1328 (6%)	63/939 (7%)	45/1796 (3%)
Day 4	80/ 3234 (2%)	40/1234 (3%)	26/1083 (2%)	17/705 (2%)	25/1238 (2%)
Day 5 and beyond	118/2521 (5%)	64/990 (6%)	39/895 (4%)	30/554 (5%)	28/921 (3%)
Median daily dose[a]	100 (100-200)	100 (100-200)	100 (100-200)	100 (100-200)	100 (88-150)
Median cumulative dose[b]	150 (100-250)	200 (100-300)	200 (100-300)	200 (100-300)	100 (100-200)

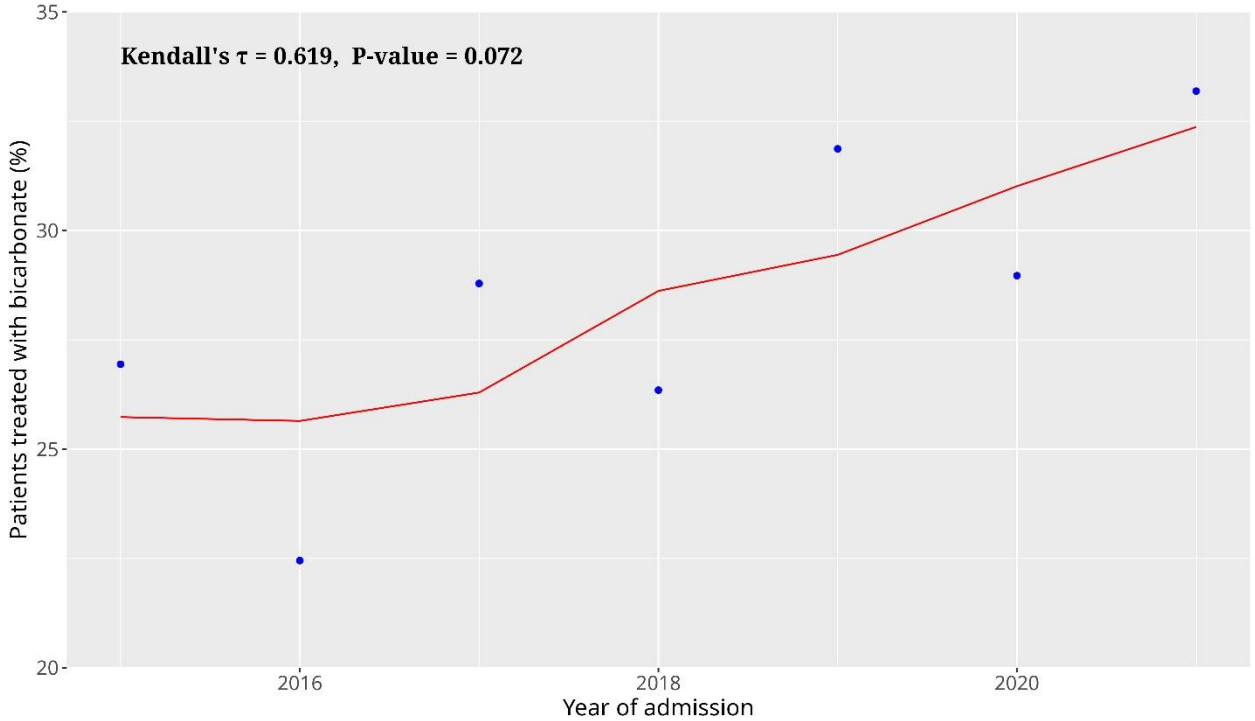
Data presented as n (%) and median (interquartile range)
[a] median daily dose on days that bicarbonate is administered
[b] median cumulative dose over the whole admission
AKI = acute kidney injury
Vasoactive support = mean daily vasoactive-inotropic score ≥10 = 0.1mcg/kg/min noradrenaline
Information on the daily administration of bicarbonate can also be found in the co-variate plots of the respective g-formula model

Table S5: Eligible admissions and bicarbonate administration per site

Site	1	2	3	4	5	6	7
Bicarbonate treatment	463/1057 (44%)	81/558 (15%)	44/205 (21%)	113/260 (43%)	32/133 (24%)	227/1097 (21%)	175/781 (22%)

Site	8	9	10	11	12	13
Bicarbonate treatment	457/1340 (34%)	46/279 (16%)	68/251 (27%)	55/172 (32%)	2/21 (10%)	1/3 (33%)

Figure S3 – Bicarbonate administration over time.



P value calculated using Mann-Kendall test

Figure S4 – Covariate plot for primary model (pH<7.3 and $PCO_2 \leq 45$)

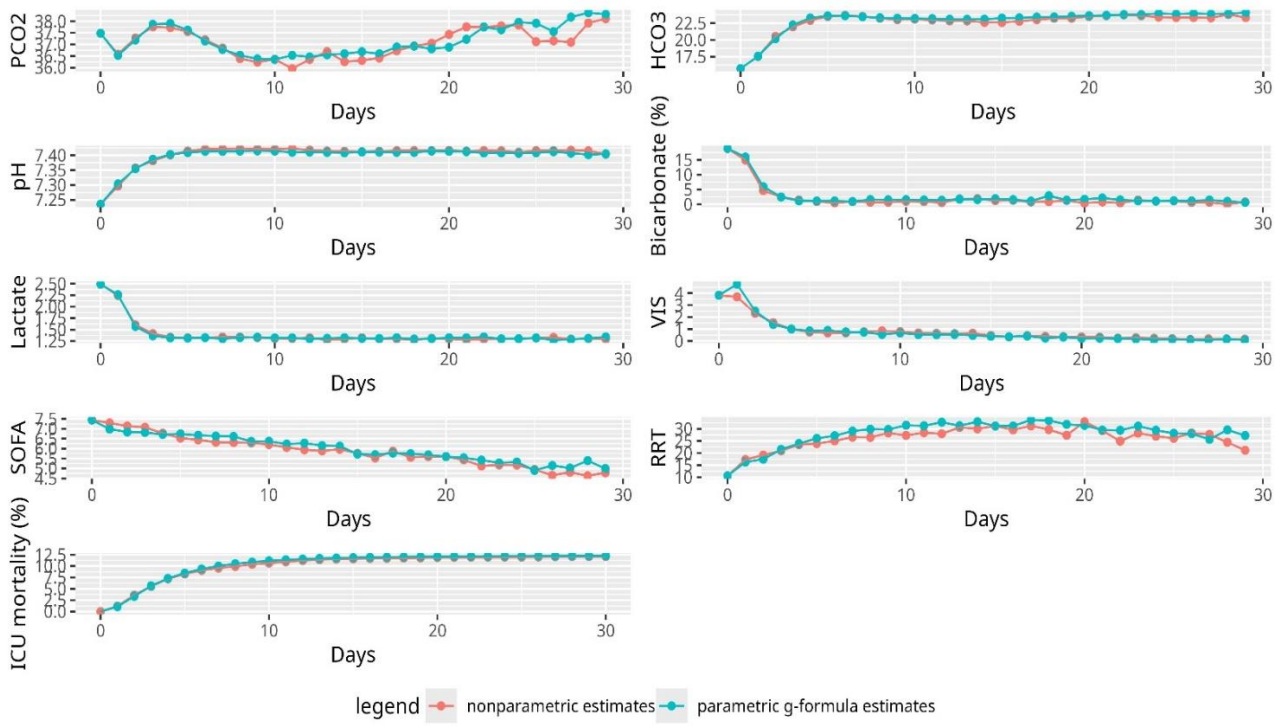


Fig S5 – Covariate plot for cumulative risk of renal replacement therapy (secondary outcome)

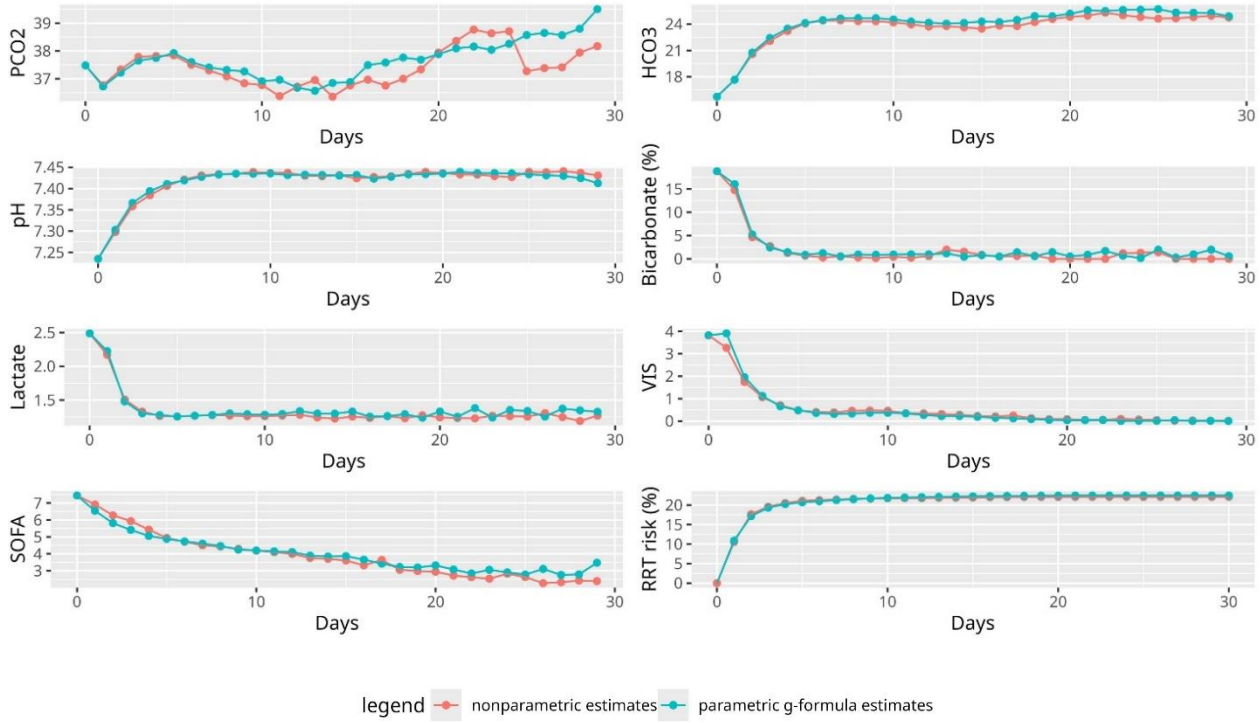


Fig S6 – Cumulative risk curves for renal replacement therapy (secondary outcome)

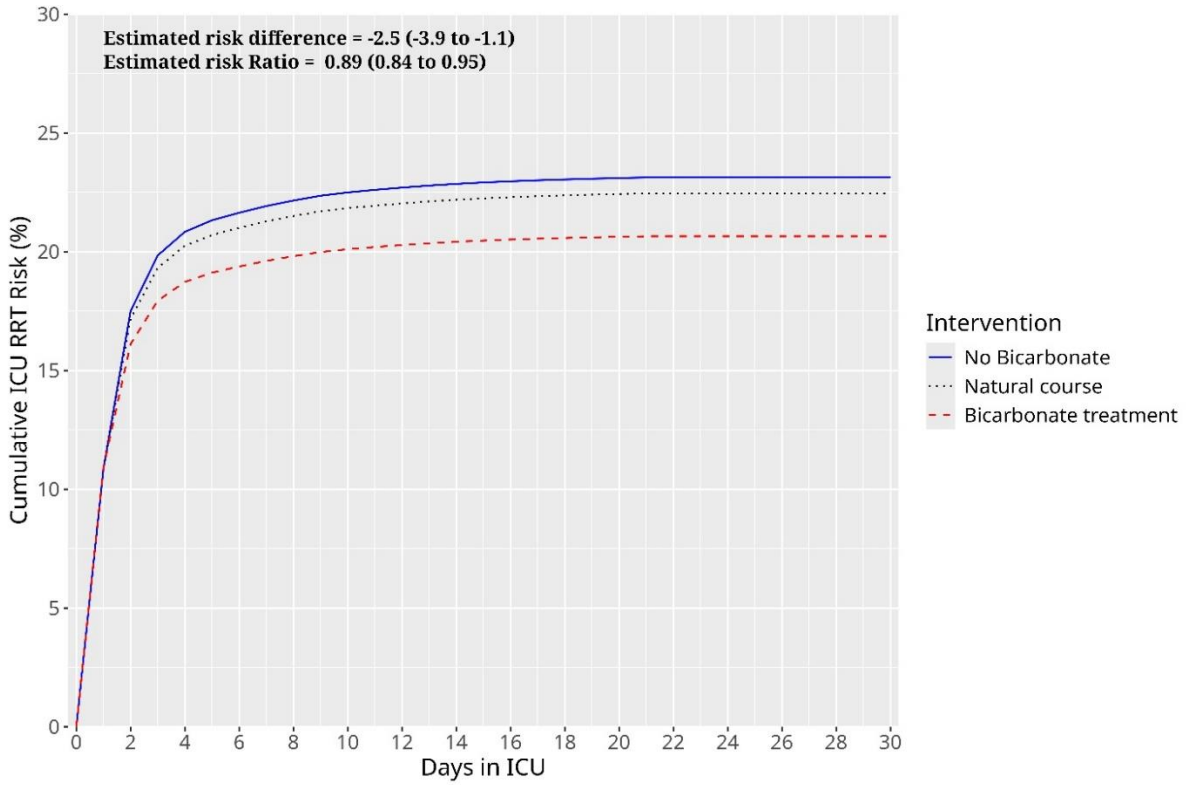


Fig S7 – Covariate plot for subgroup analysis – pH<7.3 plus acute kidney injury (AKI)

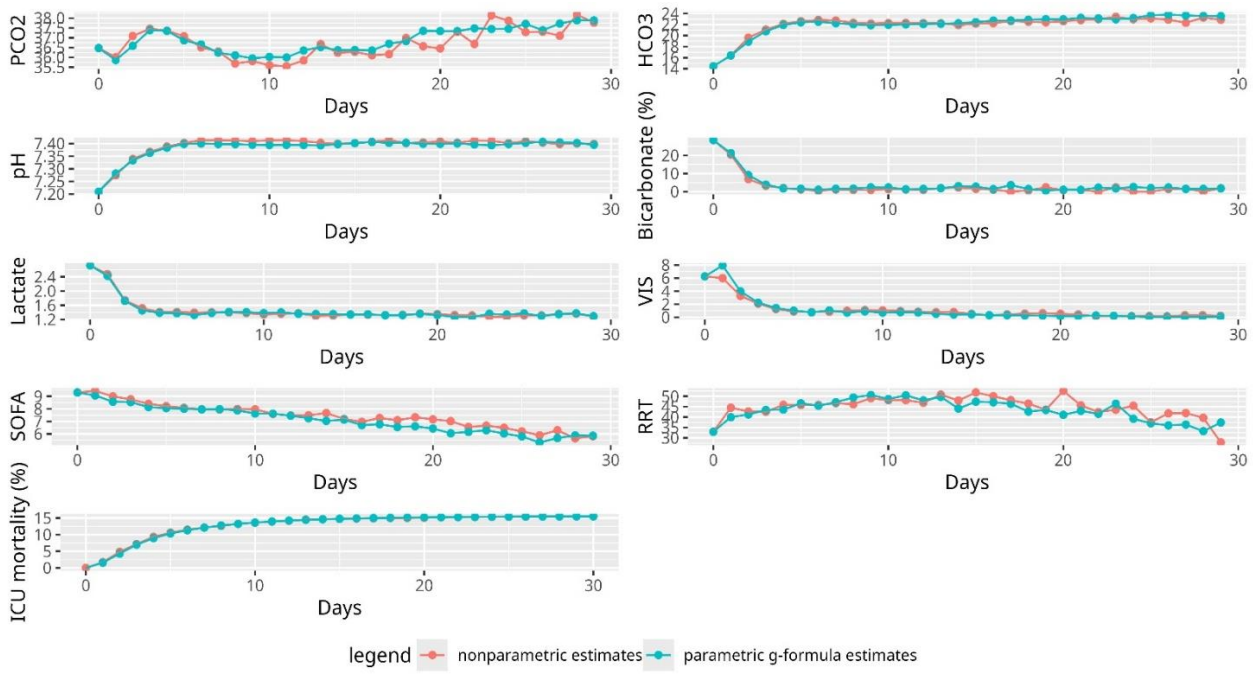
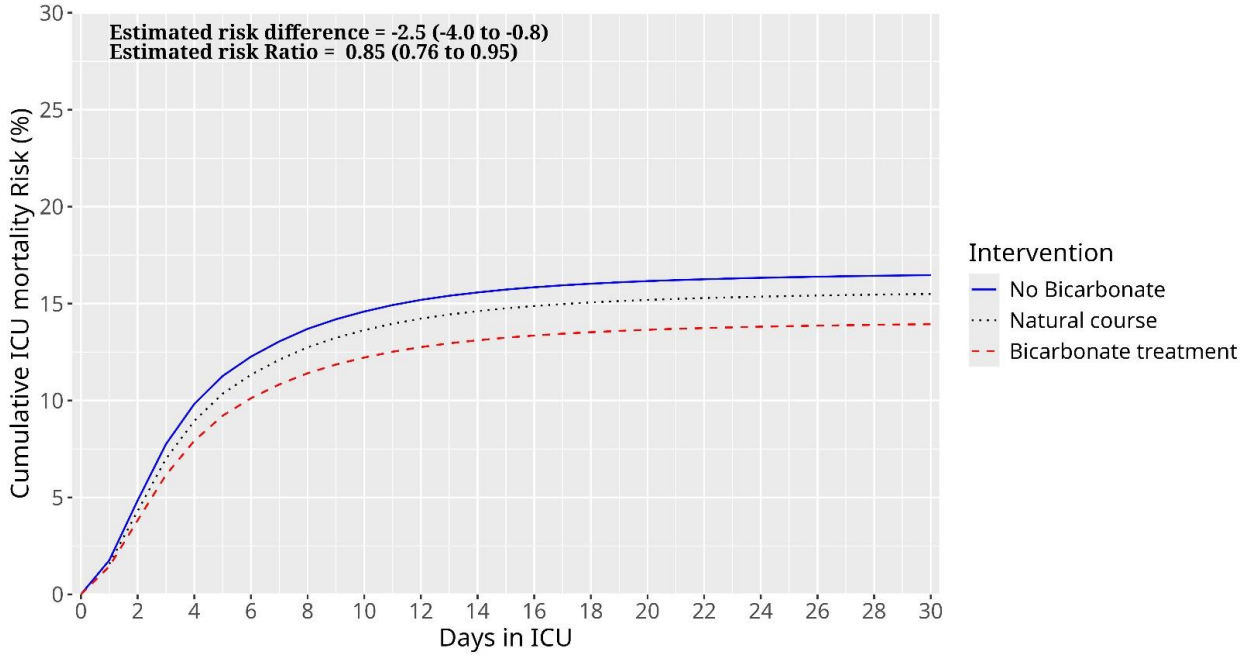


Fig S8 – Cumulative risk curves for subgroup analysis pH<7.3 with AKI



AKI defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage ≥2

Fig S9 – Covariate plot for subgroup analysis pH<7.3 plus requirement for vasoactive support

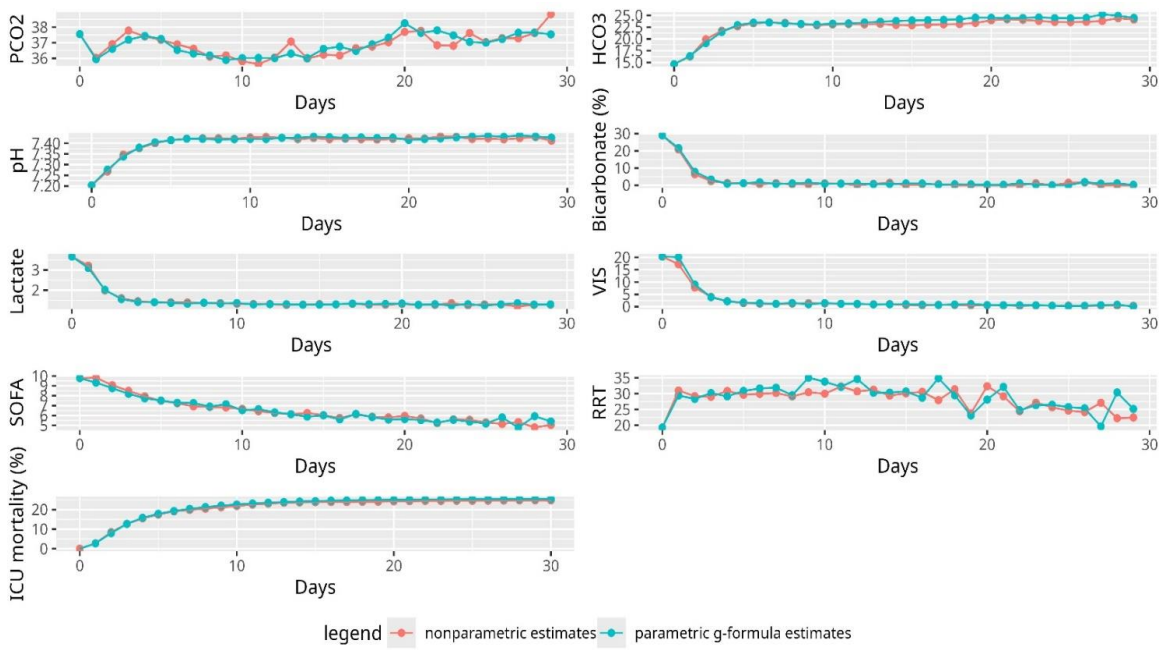
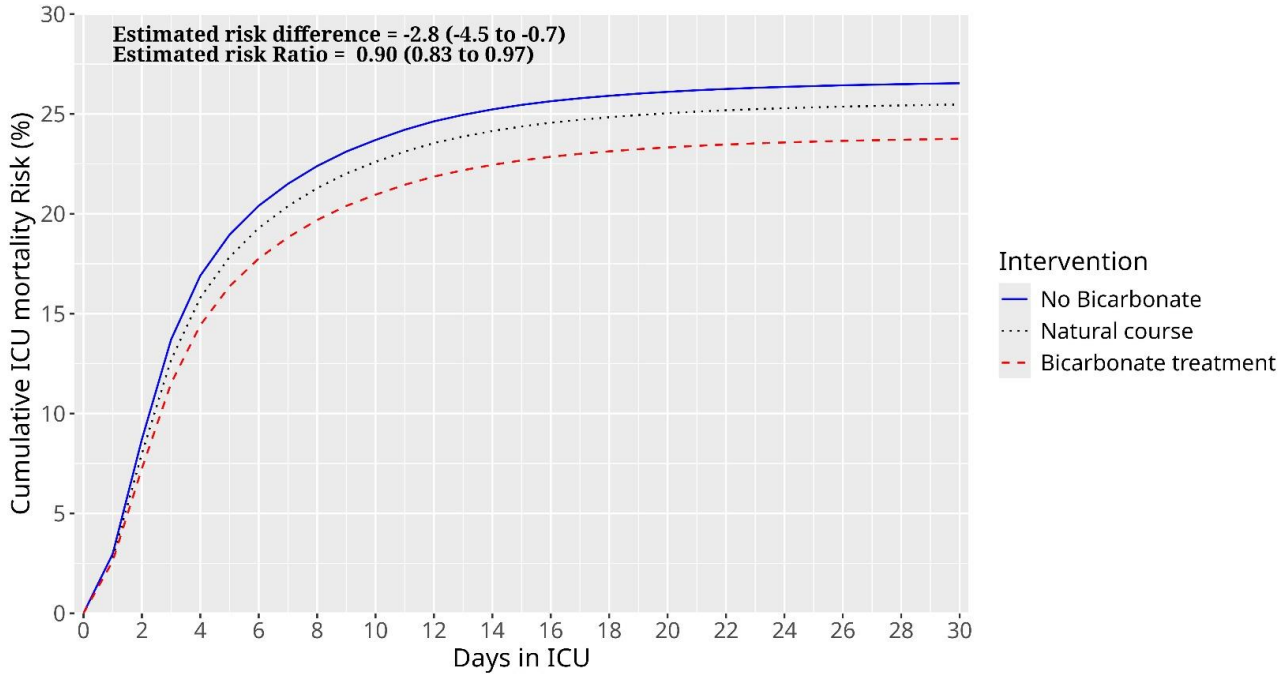


Fig S10 – Cumulative risk curves for subgroup analysis pH<7.3 plus vasoactive support



Vasoactive support defined as vasoactive-inotropic score of ≥10, equivalent to 0.1mcg/kg/min noradrenaline

Fig S11 – Covariate plot for subgroup analysis severe acidosis pH<7.2

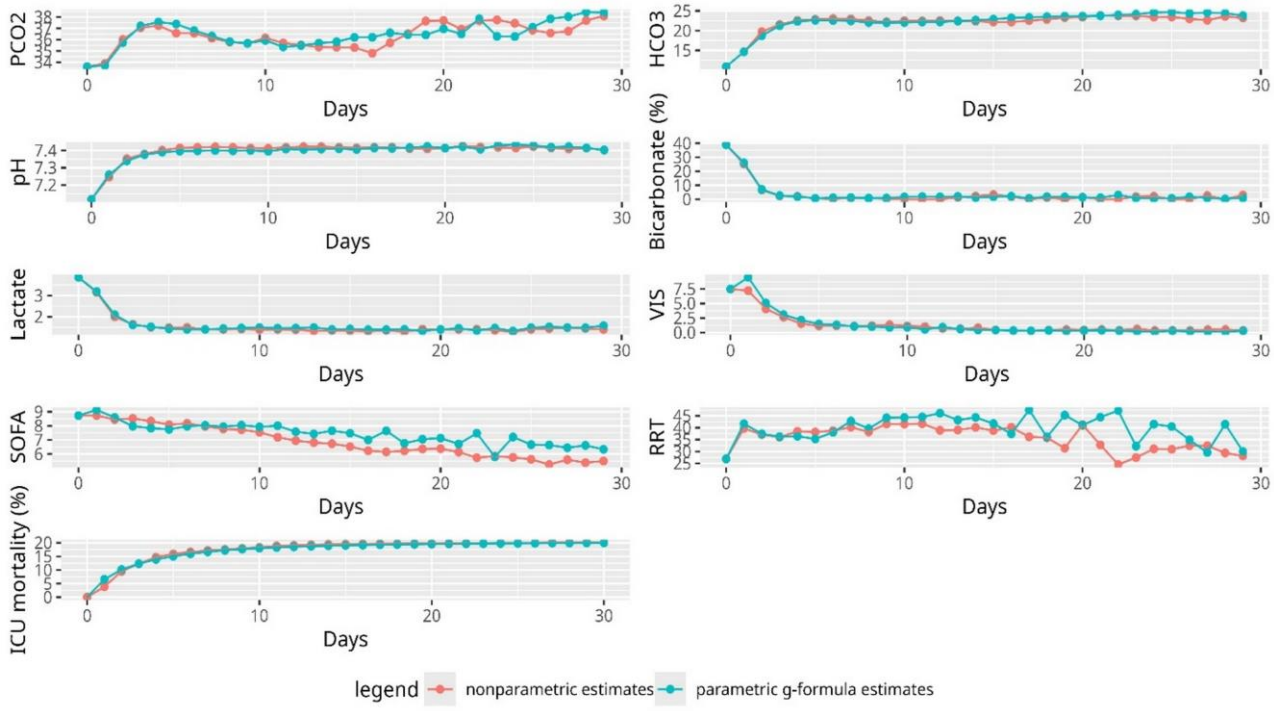


Fig S12 – Cumulative risk curves for subgroup analysis severe acidosis pH<7.2

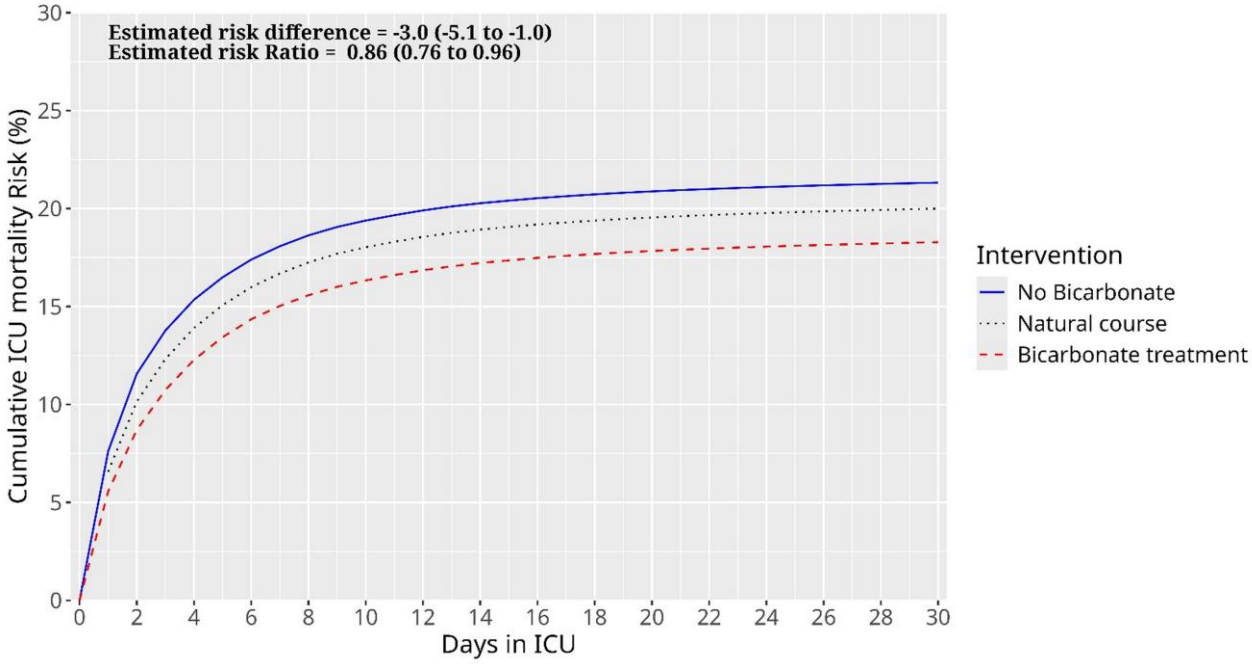


Fig S13 – Covariate plot for subgroup analysis 7.2 ≤ pH <7.3, no AKI or vasoactive support

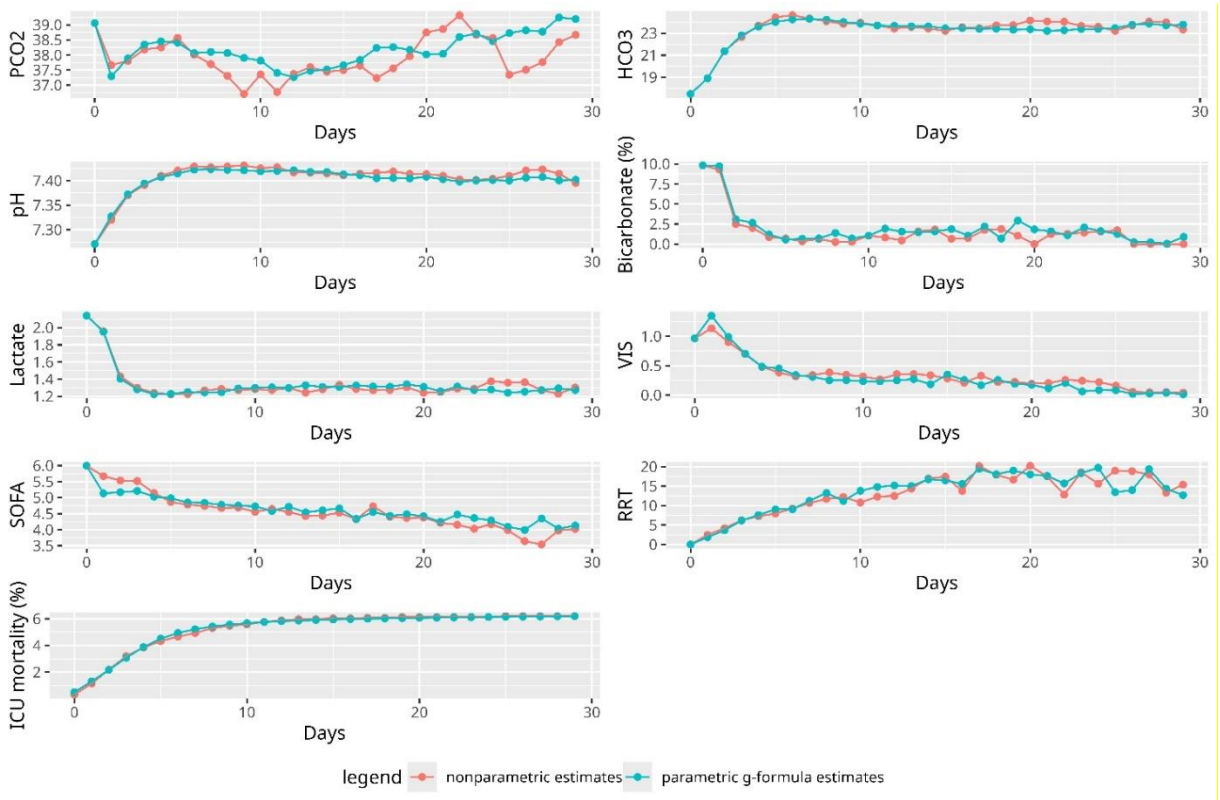
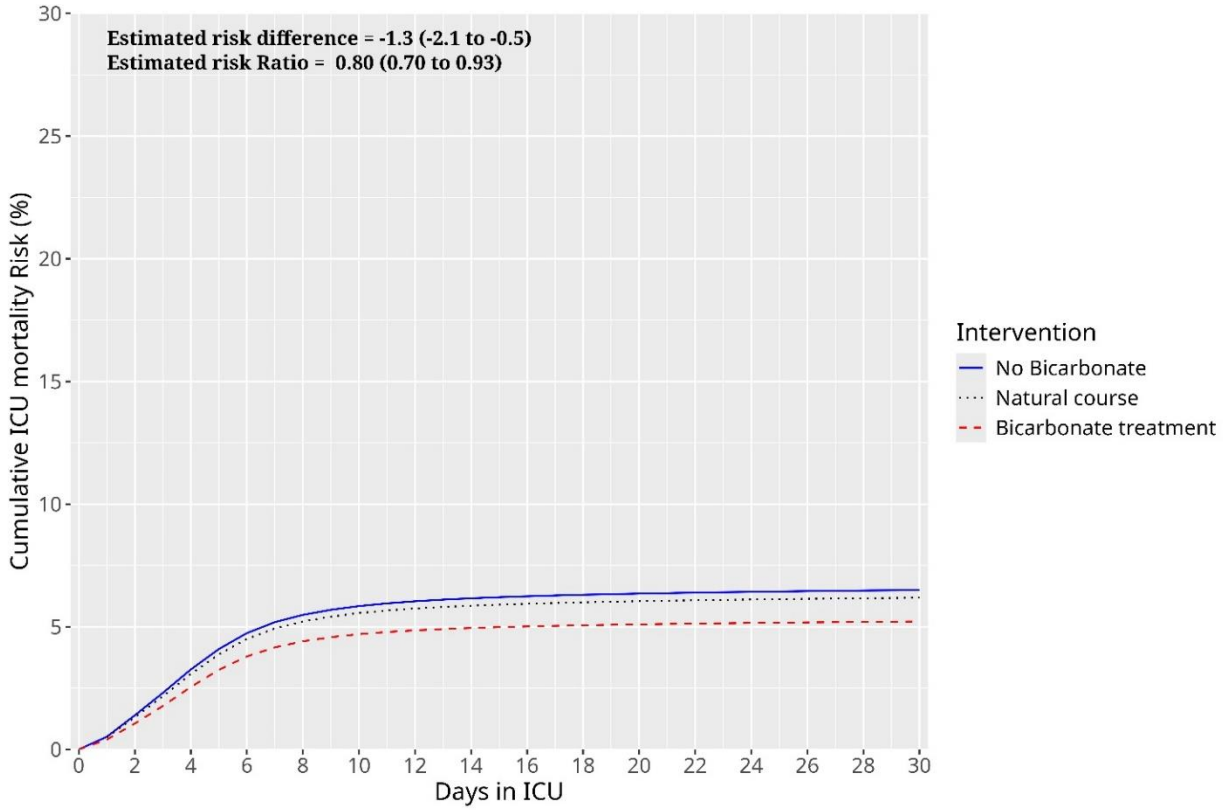
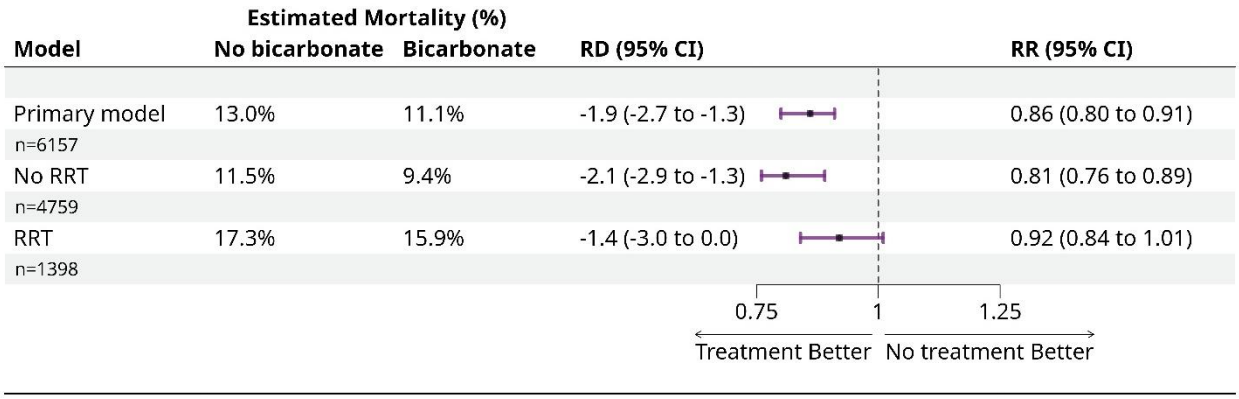


Fig S14 – Cumulative risk curves for subgroup analysis 7.2 ≤ pH <7.3, no AKI or vasoactive support



7.2 ≤ pH <7.3, KDIGO stage≤1 and VIS<10

Fig S15: Sensitivity analyses with patients stratified by use of renal replacement therapy



Mortality estimated based on g-computation as per primary model
RD = absolute risk difference
RR = risk ratio
95% CI = 95% confidence interval
RRT = renal replacement therapy

Rolling Entry Matching – balance assessments

Rolling Entry Matching (REM) controls for time varying confounding and immortal time bias by creating a pool of control patients with a propensity scores calculated based on covariates levels from the same point in time. Patients in the treatment group can start treatment on any of the first 3 days, so for each control patient, data from up to 3 potential match days are retained. This leads to an inflated control group which is likely to affect the accuracy of the unadjusted balance. For this reason, the following graphs only retain the covariate data from the day with the lowest base excess.

Fig S16 – Rolling Entry Matching – Little Observed Variable Estimate plot (LOVE plot)

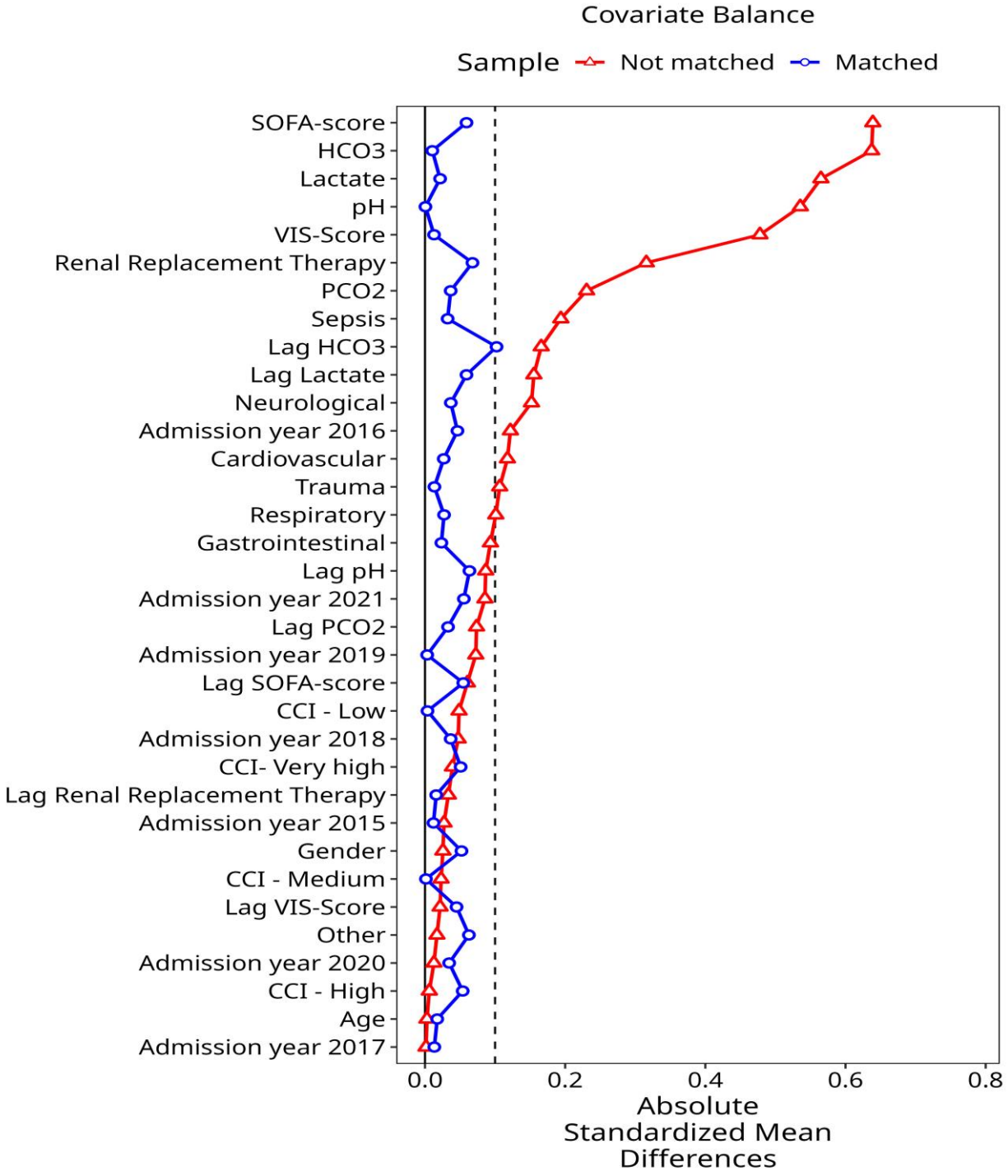
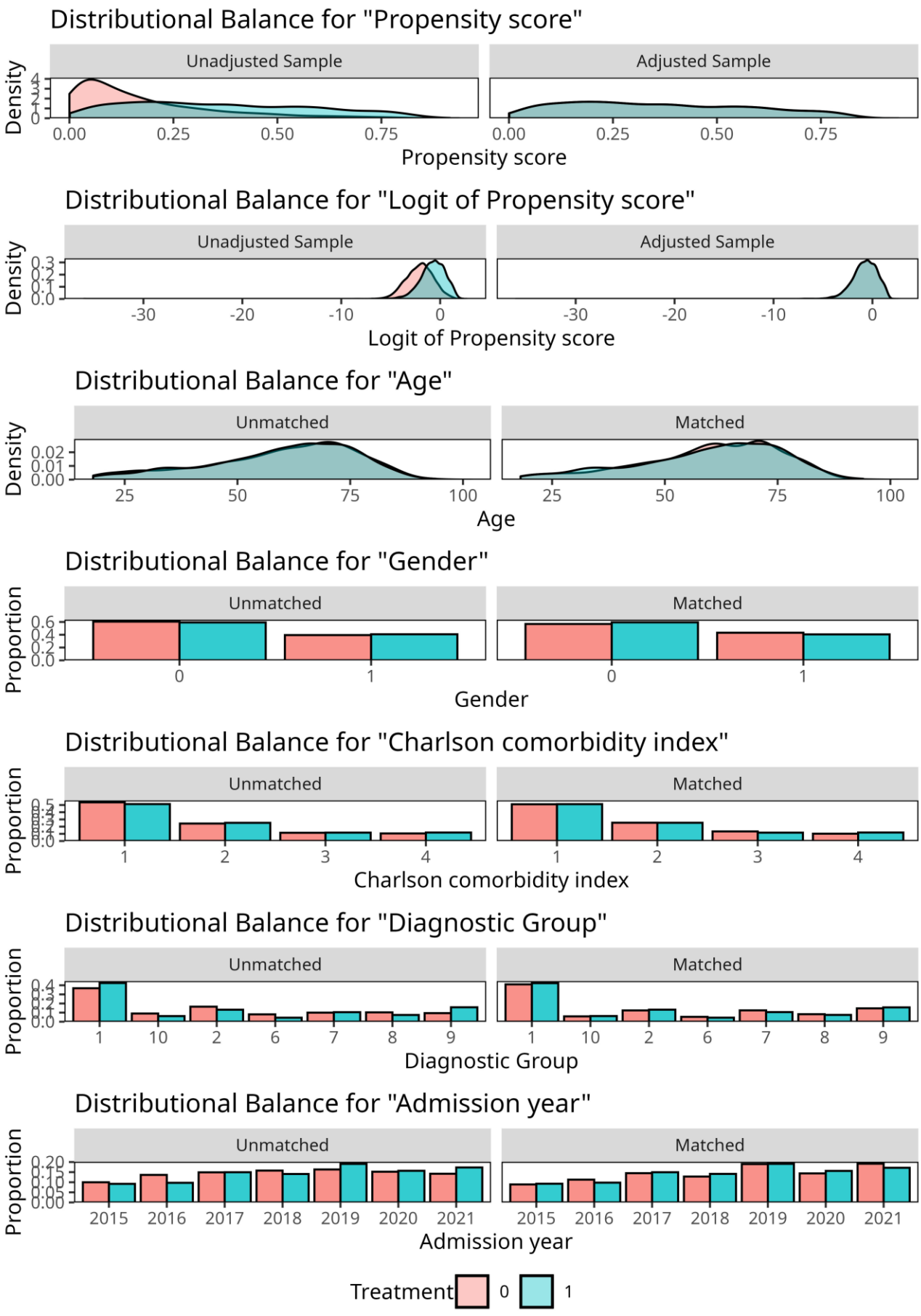
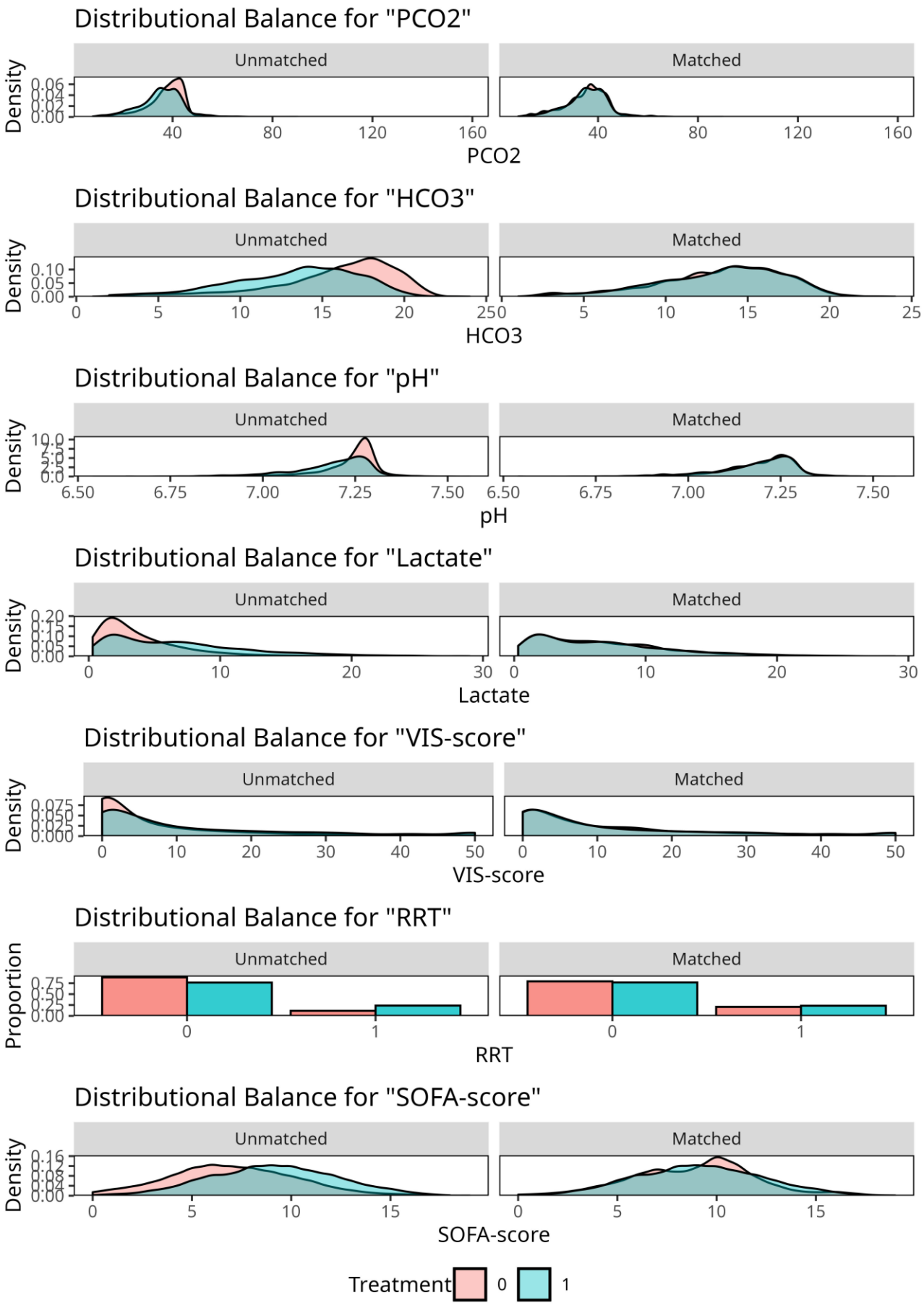


Fig S17 – Rolling Entry Matching – Distributional balances




Distributional Balance for "PCO2"
Unmatched
Matched
Density
PCO2
Distributional Balance for "HCO3"
HCO3
Distributional Balance for "pH"
pH
Distributional Balance for "Lactate"
Lactate
Distributional Balance for "VIS-score"
VIS-score
Distributional Balance for "RRT"
Proportion
RRT
Distributional Balance for "SOFA-score"
SOFA-score
Treatment
0
1

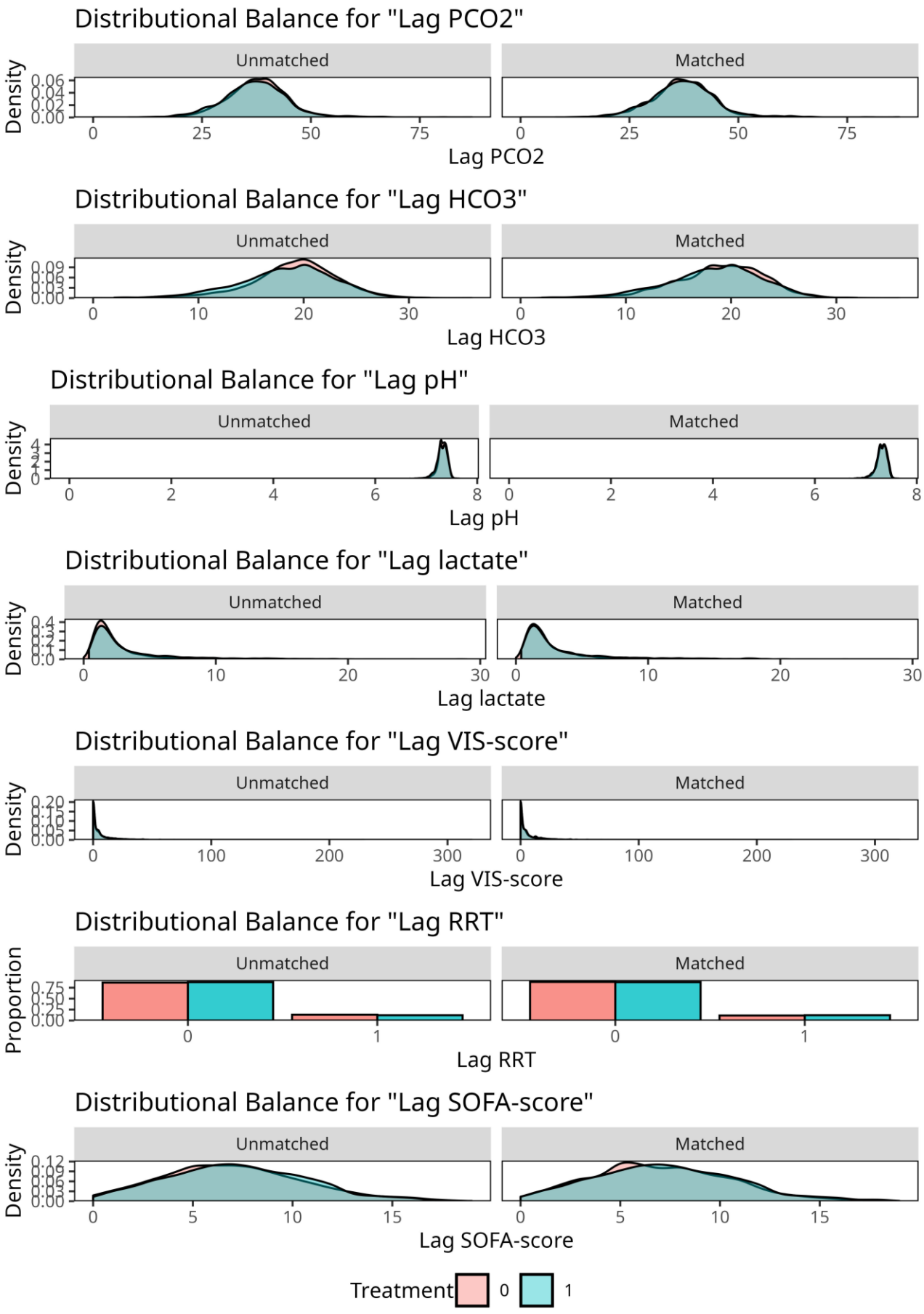

Distributional Balance for "Lag PCO2"
Unmatched
Matched
Density
Lag PCO2
Distributional Balance for "Lag HCO3"
Lag HCO3
Distributional Balance for "Lag pH"
Lag pH
Distributional Balance for "Lag lactate"
Lag lactate
Distributional Balance for "Lag VIS-score"
Lag VIS-score
Distributional Balance for "Lag RRT"
Proportion
Lag RRT
Distributional Balance for "Lag SOFA-score"
Lag SOFA-score
Treatment
0
1

Fig S18 – Rolling Entry Matching – Schoenfeld residuals plot for multi-event Cox regression

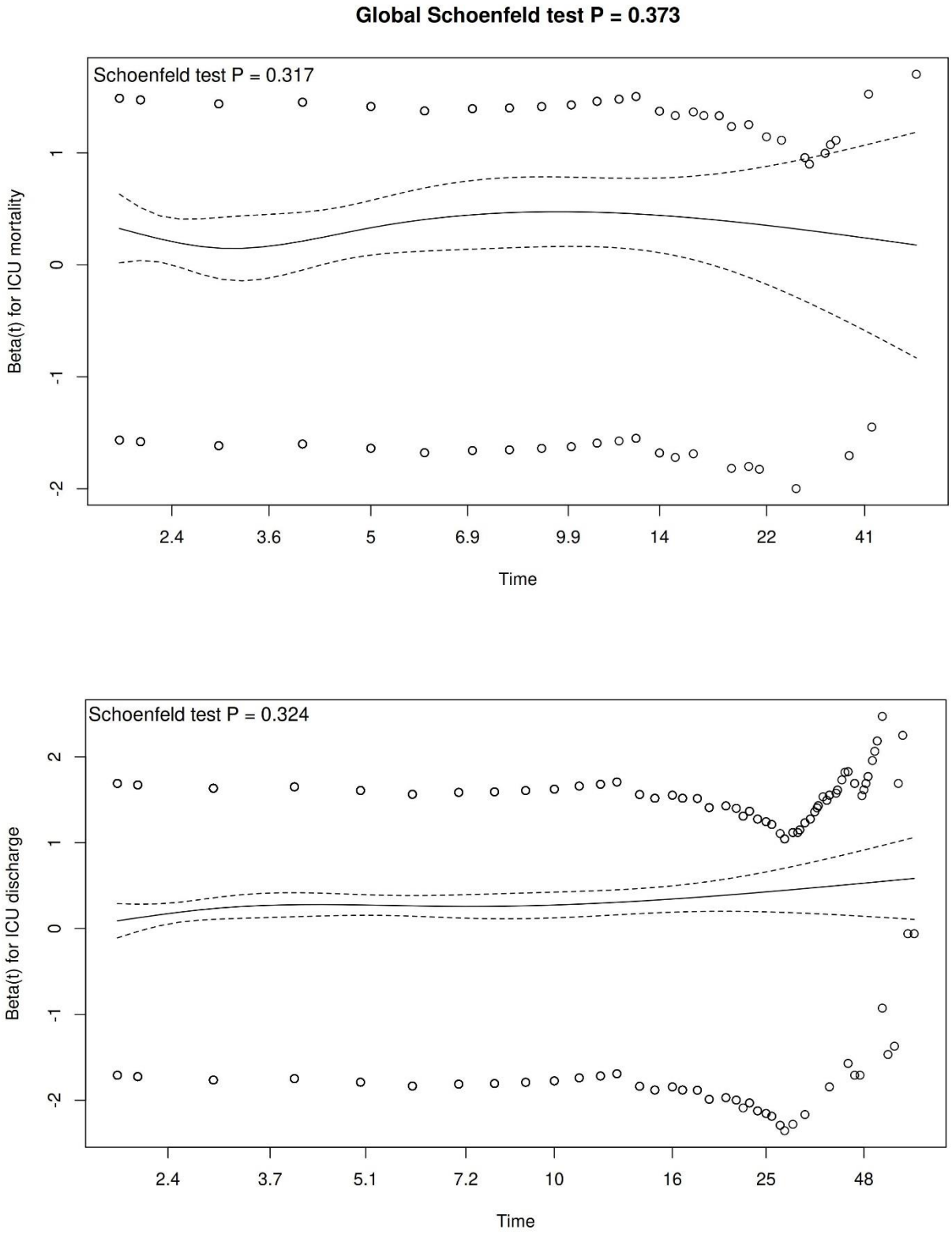


Fig S19 Rolling Entry Matching – Schoenfeld residuals plot for Cox regression 30-day mortality

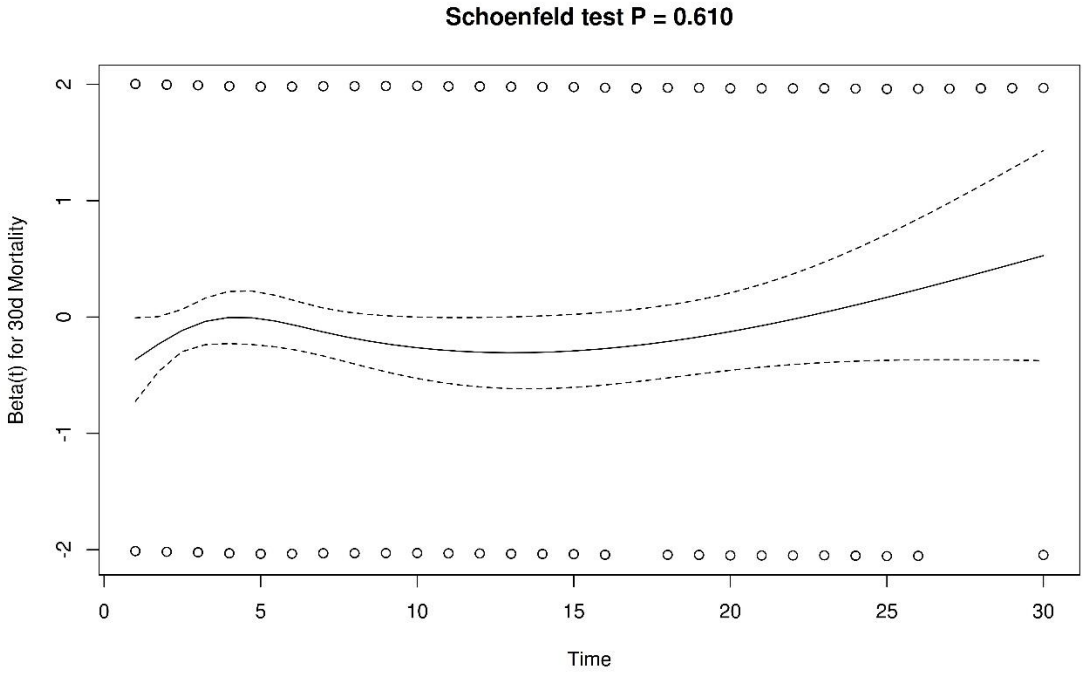
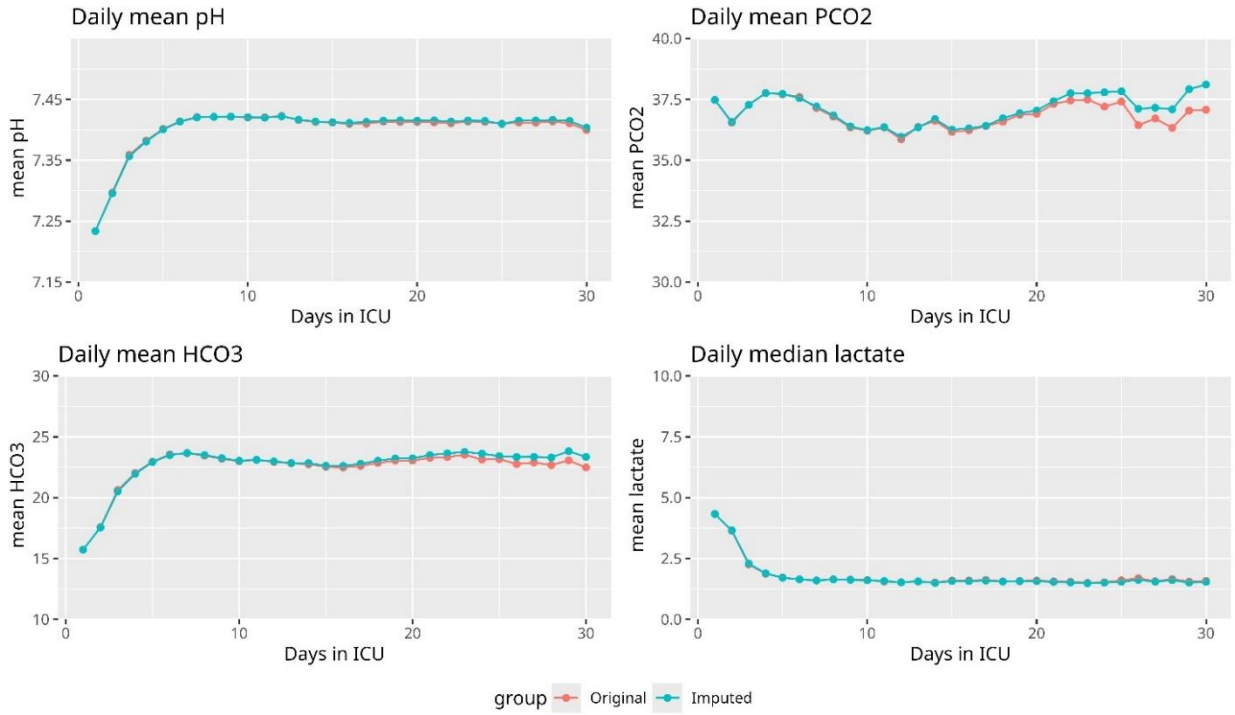


Fig S20 Missing data imputations plot – compares mean daily values with and without imputations.



Missing values for time-varying covariates were imputed by bringing forward previous values from the same patient.