Heterogeneity of Effect of Net Ultrafiltration Rate Among Critically Ill Adults Receiving Continuous Renal Replacement Therapy

eMethods
eMethod 1. Multiple imputation procedure
eMethod 2. Cluster process
eMethod 3. Comparison of clusters found after multiple imputation with those found in the complete case analysis

eTables
eTable 1 – Number and Percentage of Missing
eTable 2 – Summary of Posterior Distributions for Heterogeneity of Effect in Each Cluster
eTable 3 – Baseline Patient Characteristics According to Each Clinical Subgroup
eTable 4 – Characteristics of Study Treatment According to Each Clinical Subgroup
eTable 5 – Summary of Posterior Distributions for Heterogeneity of Effect in Each Clinical Subgroup
eTable 6 – Results of the Bayesian Regression Model
eTable 7 – Results of the Bayesian Regression Model

eFigures
eFigure 1. Distributions of Imputed and Unimputed Values
eFigure 2. Low (< 1.01 mL/kg/h), middle (1.01 – 1.75 mL/kg/h) and high (> 1.75 mL/kg/h) groups of NUF rate mortality according to A) baseline characteristics, B) quintiles of fluid balance at day 1, C) quintiles of modified SOFA, D) quintiles of eGFR, E) quintiles of APACHE–III, and F) cardiovascular SOFA
eFigure 3. Optimal number of clusters according to the silhouette method
eFigure 4. Prediction strength according to *kamila* algorithm for different number of simulated clusters in cross-validation
eFigure 5. tSNE Plot
eFigure 6. Probability that the effect size is lower in cluster 2 than in cluster 1
eFigure 7. Bayesian heterogeneity of effect
eFigure 8. Bayesian heterogeneity of effect
eFigure 9. Probability that the effect size is lower in the subgroup of No edema in the subgroup of Edema
eFigure 10. Predicted mortality probability in different scenarios in the clusters
eFigure 11. Predicted mortality probability in different scenarios in the clinical subgroups
eFigure 12. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups
eFigure 13. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clusters further adjusted by the total non–CRRT intravenous fluids
eFigure 14. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups further adjusted by the total non–CRRT intravenous fluids
eFigure 15. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clusters by the total non–CRRT intravenous fluids
eFigure 16. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups by the total non–CRRT intravenous fluids
eFigure 17. Cubic spline plot for predicted mortality according to NUF rate groups for all participants and the clinical subgroups by clusters and edema

eMethod 1. Multiple imputation procedure

For patients with unknown premorbid creatinine and eGFR, source of admission and SOFA score and components, multilevel multiple imputation by chained equation method (MICE) was used to impute it. By leveraging known patient characteristics and accounting for uncertainty in the multiple estimations of missing values, multiple imputation preserves sample size and reduces bias while examining association between variables. Before imputation, the percentage of missing in the variables was assessed (**eTable 1**).

The following variables were considered in the multiple imputation model for premorbid creatinine and eGFR: age, gender, weight, treatment allocation, APACHE–III and 90–day mortality. For the multiple imputation of source of admission, SOFA and its components, the following variables were included: age, gender, weight, treatment allocation, presence of sepsis, use of mechanical ventilation, APACHE–III, and 90–day mortality. Multilevel multiple imputation was conducted using a two–level normal model with homogeneous within group variances (*2l.pan*) for continuous variables, a two–level logistic model (*2l.bin*) for categorical variables, 50 iterations and 5 databases. This multilevel multiple imputation model takes into account the cluster of the data with centers as the cluster variable [1,2].

Since total SOFA and SOFA components are passive variables, the method ‘Just Another Variable’ was used, imputing the source variables (all components) and also the derived variables (total SOFA) separately. It is expected that the ‘Just Another Variable’ approach will make a very bad approximation to the joint density of the variables; however, it can yield valid

inferences for the analysis model [3,4]. Distribution of imputed values are shown in **eFigure 1** in **Online Supplement.**

kamila, as the majority of the cluster algorithms, does not handle multiple datasets from multiple imputation. Thus, in the end, we opted to replace the missing values by the mean of the value from the five datasets after imputation. However, as we now the potential limitations from this strategy, a sensitivity analysis comparing the clusters found after imputation to those found from complete case analysis (711 patients) is shown in **eMethod 3** in **Online Supplement**.

References

1. Drechsler J. (2015) Multiple Imputation of Multilevel Missing Data—Rigor Versus Simplicity. J Educ Behav 40:69-95

2. Taljaard M, Donner A, Klar N (2008) Imputation strategies for missing continuous outcomes in cluster randomized trials. Biom J 50:329-45

3. White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 30:377-99

4. Von Hippel PT (2009) How to impute squares, interactions, and other transformed variables. Sociological Methodology 39:265-91.

eMethod 2. Cluster process

For cluster detection, based on clinical relevance, the following variables were selected a priori: APACHE–III, weight, premorbid eGFR, source of admission, mechanical ventilation, presence of severe sepsis, presence of oliguria, presence of severe organ edema, cardiovascular and respiratory SOFA score, and fluid balance at day 1.

We used the K–means for mixed large data (*kamil*a) method to detect clusters. The best number of clusters was defined by inspecting the prediction strength of clusters after 1,000 cross–validations [1,2]. In addition, we performed a visual display of such clustering method using the Barnes–Hut t–distributed Stochastic Neighbor Embedding (tSNE) method with Gower's distance clustering to confirm and visually display the results [3] and the average silhouette method with Partitioning Around Medoids (PAM) algorithm to confirm and visually display the optimal number of clusters. In addition, we analyzed two clinically relevant subgroups: 'Edema' (patients with baseline clinically significant organ edema) and 'No edema'.

References

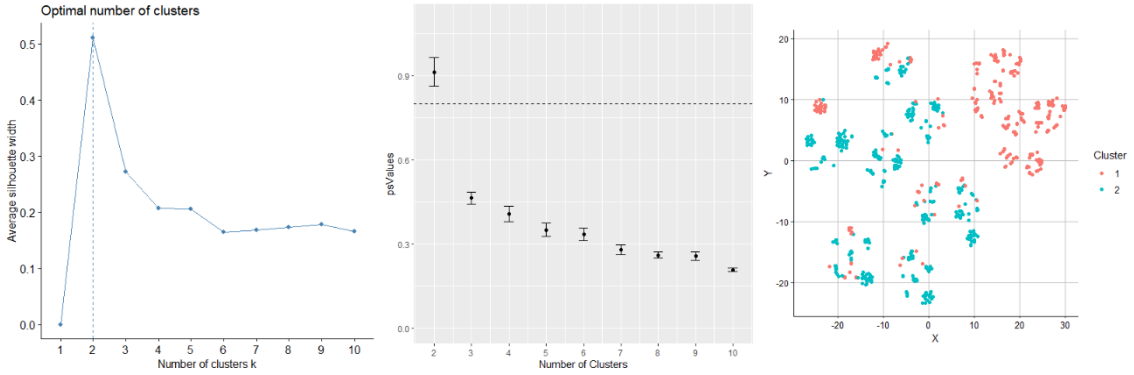
1. Foss AH, Markatou M. kamila (2018) clustering mixed-type data in R and Hadoop. J Stat Softw 13:1e44.

2. Tibshirani R, Walther G (2005) Cluster validation by prediction strength. J Comput Graph Stat 3:511e28.

3. van der Maaten LJP, Hinton GE (2008) Visualizing high dimensional data using t-SNE. J Mach Learn Res 1:2579e605.

eMethod 3. Comparison of clusters found after multiple imputation with those found in the complete case analysis

As with the analysis after imputation, the cluster analysis in the complete case analysis also identified two distinct clusters. The optimal number of clusters was also confirmed to be two by the silhouette method, prediction strength, and the tSNE plot from Gower's distance as shown below.



As shown below, the agreement between the clusters found after imputation and in the complete case analysis is good.

Agreement of the Clusters

	In Complete Case Analysis	
With Multiple Imputation	**1**	**2**
1	400	60
2	1	250

Cohen Kappa: 0.78 (0.82 to 0.86)

As shown in the tables below, the baseline, clinical outcomes, and therapeutic characteristics between the clusters found by the two methods are virtually identical.

eMethod 3 – Characteristics of the Clusters With Multiple Imputation (MI) or complete case analysis (CCA)

	Cluster 1		Cluster 2	
	With MI (*n* = 941)	**In CCA (*n* = 401)**	**With MI (*n* = 493)**	**In CCA (*n* = 310)**
Age, years	64.2 ± 14.9	64.9 ± 14.6	65.4 ± 14.8	66.1 ± 14.0
Female gender	335 (35.6)	137 (34.2)	175 (35.5)	120 (38.7)
Weight, kg	81.2 ± 12.9	80.5 ± 12.8	79.6 ± 12.7	79.9 ± 13.4
Higher–intensity group	461 (49.0)	197 (49.1)	247 (50.1)	154 (49.7)
eGFR	60.1 ± 31.7	59.3 ± 31.9	49.7 ± 29.2	53.4 ± 30.1
Time in ICU before randomization, hours	58.5 ± 133.9	51.8 ± 109.1	40.0 ± 86.7	30.0 ± 51.6
Use of vasopressors*	862 (91.7)	364 (90.8)	171 (34.8)	159 (51.3)
Use of mechanical ventilation	940 (99.9)	401 (100.0)	117 (23.7)	108 (34.8)
Severe sepsis	507 (53.9)	198 (49.4)	202 (41.0)	143 (46.1)
APACHE III score	106.1 ± 27.0	105.3 ± 26.4	94.8 ± 20.9	99.7 ± 23.2
Modified total SOFA score**	11.33 ± 2.3	11.2 ± 2.2	8.2 ± 2.6	8.7 ± 2.7
Cardiovascular	3.6 ± 0.8	3.5 ± 0.9	1.5 ± 1.6	2.0 ± 1.7
Respiratory	3.2 ± 0.6	3.2 ± 0.4	1.8 ± 1.0	1.9 ± 1.1
Coagulation	1.1 ± 1.2	1.0 ± 1.1	0.7 ± 1.0	0.8 ± 1.1
Liver	1.0 ± 1.1	0.9 ± 1.1	0.8 ± 1.2	0.8 ± 1.1
Renal	2.5 ± 1.0	2.4 ± 1.0	3.1 ± 0.9	3.1 ± 1.0
Source of admission				
Emergency department	207 / 877 (23.6)	45 (11.2)	134 / 466 (28.8)	127 (41.0)
Hospital ward	200 / 877 (22.8)	118 (29.4)	178 / 466 (38.2)	105 (33.9)
Transfer from another ICU	84 / 877 (9.6)	38 (9.5)	25 / 466 (5.4)	15 (4.8)
Transfer from another hospital	101 / 877 (11.5)	53 (13.2)	48 / 466 (10.3)	19 (6.1)
OR after emergency surgery	161 / 877 (18.4)	60 (15.0)	43 / 466 (9.2)	16 (5.2)
OR after elective surgery	124 / 877 (14.1)	87 (21.7)	38 / 466 (8.2)	28 (9.0)
final_diagnosis....				
Admission diagnosis				
Nonoperative				
Cardiovascular	367 (39.0)	152 (37.9)	153 (31.0)	110 (35.5)
Genitourinary	52 (5.5)	24 (6.0)	173 (35.1)	100 (32.3)
Respiratory	112 (11.9)	47 (11.7)	33 (6.7)	26 (8.4)
Gastrointestinal	53 (5.6)	9 (2.2)	18 (3.7)	15 (4.8)
Other	36 (3.8)	12 (3.0)	27 (5.5)	12 (3.9)
Operative				
Cardiovascular	214 (22.7)	111 (27.7)	53 (10.8)	31 (10.0)
Gastrointestinal	78 (8.3)	33 (8.2)	19 (3.9)	11 (3.5)
Trauma	13 (1.4)	2 (0.5)	6 (1.2)	1 (0.3)

eMethod 3 – Characteristics of the Clusters With Multiple Imputation (MI) or complete case analysis (CCA)

	Cluster 1		Cluster 2	
	With MI (*n* = 941)	**In CCA (*n* = 401)**	**With MI (*n* = 493)**	**In CCA (*n* = 310)**
Other	16 (1.7)	11 (2.7)	11 (2.2)	4 (1.3)
Criteria for randomization[a]				
Oliguria (urine, < 400 mL/day)	565 (60.0)	236 (58.9)	290 (58.8)	190 (61.3)
Hyperkalemia (K > 6.5 mmol/L)	52 (5.5)	23 (5.7)	59 (12.0)	32 (10.3)
Severe acidemia (pH < 7.20)	393 (41.8)	168 (41.9)	113 (22.9)	99 (31.9)
BUN > 70 mg/dL (plasma urea > 25 mmol/L)	303 (32.2)	120 (29.9)	292 (59.2)	168 (54.2)
Creatinine > 3.4 mg/dL (300 µmol/L)	337 (35.8)	132 (32.9)	342 (69.4)	199 (64.2)
Severe organ edema associated with AKI	439 (46.7)	221 (55.1)	195 (39.6)	101 (32.6)
BUN, mmol/L	20.6 ± 11.0	20.0 ± 10.7	29.2 ± 14.0	27.4 ± 12.9
Creatinine before randomization, µmol/L	280.3 ± 137.2	273.6 ± 128.7	441.1 ± 241.3	414.7 ± 229.4
pH	7.25 ± 0.14	7.24 ± 0.13	7.28 ± 0.11	7.26 ± 0.12
Bicarbonate, mmol/L	18.8 ± 5.7	19.0 ± 5.4	17.5 ± 6.1	16.8 ± 6.0
Base excess, mmol/L	-8.1 ± 6.9	-7.9 ± 6.9	-8.4 ± 7.0	-9.6 ± 7.1
Clinical outcomes				
RRT dependence among survivors at day 28	68 / 536 (12.7)	34 (14.8)	52 / 363 (14.3)	24 (10.9)
90–day mortality	467 / 940 (49.7)	203 (50.7)	167 / 493 (33.9)	116 (37.4)

Data are mean ± standard deviation or No (%)

AKI: acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; BUN: blood urea nitrogen; GFR: estimated glomerular filtration rate; ICU: intensive care unit; OR: operating room; SOFA: Sequential Organ Failure Assessment; MI: multiple imputation; CCA: complete case analysis

* Defined as a cardiovascular SOFA score ≥ 3

** Not considering the neurological component

[a] A given patient may have met more than one of these criteria.

eMethod 3 – Therapeutic Characteristics of the Clusters With and Without Multiple Imputation

	Cluster 1		Cluster 2	
	With MI (*n* = 941)	In CCA (*n* = 401)	With MI (*n* = 493)	In CCA (*n* = 310)
Cumulative net ultrafiltration, mL	12974.8 ± 15521.9	14332.9 ± 16701.8	11111.2 ± 15129.2	9827.2 ± 13188.3
Net ultrafiltration rate, mL/kg/h	1.45 ± 1.01	1.58 ± 1.15	1.39 ± 0.89	1.31 ± 0.92
Net ultrafiltration rate category				
< 1.01 mL/kg/h	297 (31.6)	114 (28.4)	179 (36.3)	126 (40.6)
1.01 – 1.75 mL/kg/h	321 (34.1)	133 (33.2)	156 (31.6)	91 (29.4)
> 1.75 mL/kg/h	323 (34.3)	154 (38.4)	158 (32.0)	93 (30.0)
Duration of study treatment, days	6.4 ± 8.3	6.9 ± 9.6	5.8 ± 8.2	5.2 ± 7.4
Flow rate of effluent, mL/kg/h	26.2 ± 7.34	26.5 ± 7.1	25.4 ± 7.4	26.2 ± 7.4
Dose delivered, %	0.82 ± 0.16	0.83 ± 0.14	0.79 ± 0.16	0.82 ± 0.15
BUN, mmol/L/day	13.4 ± 5.9	12.9 ± 5.4	15.3 ± 7.5	14.4 ± 7.0
Serum creatinine, µmol/L/day	169.7 ± 73.2	162.9 ± 65.7	229.4 ± 134.7	208.1 ± 124.2
Dialysate and replacement fluid, mL/h	2017.6 ± 652.8	2025.4 ± 650.0	1927.0 ± 680.6	1991.3 ± 667.6
Dose of effluent, mL/h/day	2115.0 ± 644.4	2123.6 ± 627.8	2009.9 ± 632.7	2080.5 ± 655.7
Fluid balance excluding NUF volume				
At day 1, mL	1742.9 ± 2359.2	1708.2 ± 2240.8	1010.1 ± 1613.6	1200.9 ± 1902.8
Daily, mL/d*	1753.8 ± 1523.3	1717.9 ± 1424.4	1229.6 ± 1113.6	1390.2 ± 1381.0
Cumulative, mL*	10733.3 ± 14632.8	11462.5 ± 15210.0	8212.7 ± 12359.4	7886.9 ± 12022.6
Fluid balance including NUF volume				
At day 1, mL	942.9 ± 2570.1	813.0 ± 2414.7	219.3 ± 1839.3	446.4 (2166.2)
Daily, mL/d*	-29.2 ± 1909.2	-185.4 ± 1716.5	-385.3 ± 1341.3	-152.2 (1741.2)
Cumulative, mL*	-2253.0 ± 10843.7	-2878.9 ± 9669.4	-2915.9 ± 8871.9	-1961.9 (7722.8)
Total non–CRRT fluids[a]				
At day 1, mL	2465.4 ± 2487.4	2438.3 ± 2407.1	1621.2 ± 1678.6	1816.1 ± 1977.3
Daily, mL/d*	2714.4 ± 1605.4	2640.5 ± 1542.0	2132.9 ± 1174.8	2322.2 ± 1412.2
Cumulative, mL*	16272.3 ± 18775.2	17028.7 ± 18927.1	12723.7 ± 15500.6	12273.4 ± 15538.6
Total non–CRRT IV fluids[b]				
At day 1, mL	2326.6 ± 2419.4	2298.2 ± 2338.9	1579.9 ± 1635.7	1756.8 ± 879.5
Daily, mL/d*	2480.6 ± 1522.1	2415.8 ± 1426.3	2026.4 ± 1092.5	2190.4 ± 1330.1
Cumulative, mL*	14649.7 ± 16537.0	15431.8 ± 16863.1	11843.5 ± 14179.2	11267.3 ± 13877.2
Enteral nutrition				
At day 1, mL	262.8 ± 564.7	262.6 ± 491.4	203.4 ± 466.8	245.1 ± 936.2
Daily, mL/d*	364.8 ± 536.4	334.6 ± 516.7	305.9 ± 533.4	350.4 ± 656.4
Cumulative, mL*	1993.3 ± 3682.1	1940.4 ± 3542.3	1815.6 ± 4665.1	1986.7 ± 5568.4
Urine output				
At day 1, mL	374.8 ± 649.7	357.9 ± 524.1	451.9 ± 701.1	437.5 ± 732.3

eMethod 3 – Therapeutic Characteristics of the Clusters With and Without Multiple Imputation

	Cluster 1		Cluster 2	
	With MI (*n* = 941)	**In CCA (*n* = 401)**	**With MI (*n* = 493)**	**In CCA (*n* = 310)**
Daily, mL/d*	528.8 ± 611.9	508.5 ± 555.6	650.9 ± 748.5	639.1 ± 759.9
Cumulative, mL*	2819.6 ± 3701.3	2925.8 ± 4053.0	2689.7 ± 3112.3	2455.6 ± 2866.2
Blood losses[c]				
At day 1, mL	63.4 ± 269.9	76.4 ± 299.5	14.5 ± 100.9	14.5 ± 112.2
Daily, mL/d*	61.2 ± 267.2	61.9 ± 246.7	36.1 ± 200.3	43.4 ± 230.2
Cumulative, mL*	358.7 ± 1564.1	348.6 ± 1187.5	260.7 ± 1431.4	277.2 ± 1344.3
Other output[d]				
At day 1, mL	285.3 ± 612.4	297.9 ± 636.5	154.6 ± 533.7	176.0 ± 687.6
Daily, mL/d*	369.5 ± 554.1	346.7 ± 555.2	222.7 ± 452.9	256.4 ± 533.4
Cumulative, mL*	2372.3 ± 4558.3	2300.3 ± 4292.4	1578.0 ± 4344.7	1675.3 ± 4778.7
Filters used daily	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.5	0.9 ± 0.5
Patients treated with IHD in ICU	63 (6.7)	37 (9.2)	43 (8.7)	22 (7.1)

Data are mean ± standard deviation or No (%)

BUN: blood urea nitrogen; ICU: intensive care unit; IHD: intermittent hemodialysis; IV: intravenous; MI: multiple imputation; CCA: complete case analysis

* considering only days where continuous renal replacement therapy was used

[a] considering blood, blood products, albumin, enteral nutrition, total parenteral nutrition and other intravenous fluids

[b] considering blood, blood products, albumin, total parenteral nutrition and other intravenous fluids

[c] considering any blood loss in and outside the ICU

[d] other fluid losses (e.g., gastrointestinal losses, drain losses and other)

eTable 1 – Number and Percentage of Missing

	Total (*n* = 1434)	< 1.01 mL/kg/h (*n* = 476)	1.01 – 1.75 mL/kg/h (*n* = 477)	> 1.75 mL/k/h (*n* = 481)
Baseline data	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gender	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Premorbid creatinine	637 (44.4)	203 (42.6)	227 (47.6)	207 (43.0)
Premorbid eGFR	637 (44.4)	203 (42.6)	227 (47.6)	207 (43.0)
Time in ICU before randomization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mechanical ventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Source of admission	91 (6.3)	30 (6.3)	30 (6.3)	31 (6.4)
Nonoperative admission diagnosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Operative admission diagnosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oliguria (< 400 mL/day)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe acidemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BUN > 70 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine > 3.4 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe organ edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BUN before randomization	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Creatinine before randomization	4 (0.3)	1 (0.2)	1 (0.2)	2 (0.4)
pH before randomization	55 (3.8)	31 (6.5)	12 (2.5)	12 (2.5)
Bicarbonate before randomization	9 (0.6)	5 (1.0)	3 (0.6)	1 (0.2)
Base excess before randomization	64 (4.5)	38 (8.0)	13 (2.7)	13 (2.7)
Severity of illness				
APACHE–III	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Total SOFA	97 (6.8)	53 (11.1)	22 (4.6)	22 (4.6)
Cardiovascular SOFA	2 (0.1)	1 (0.2)	0 (0.0)	1 (0.2)
Respiratory SOFA	43 (3.0)	21 (4.4)	12 (2.5)	10 (2.1)
Coagulation SOFA	8 (0.5)	6 (1.2)	0 (0.0)	2 (0.4)
Liver SOFA	59 (4.1)	34 (7.1)	12 (2.5)	13 (2.7)
Renal SOFA	4 (0.3)	4 (0.8)	0 (0.0)	0 (0.0)
Exposure				
NUF rate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NUF volume	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fluid balance at day 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cumulative fluid balance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

eTable 1 – Number and Percentage of Missing

	Total (*n* = 1434)	< 1.01 mL/kg/h (*n* = 476)	1.01 – 1.75 mL/kg/h (*n* = 477)	> 1.75 mL/k/h (*n* = 481)
Outcome				
90–day mortality	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
90–day follow–up	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

eGRF: estimated glomerular filtration rate; ICU: intensive care unit; BUN: blood urea nitrogen; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; NUF: net ultrafiltration

eTable 2 – Summary of Posterior Distributions for Heterogeneity of Effect in Each Cluster

Subgroup	Mean	SD	$Q_{2.5}$	Q_{25}	Median	Q_{75}	$Q_{97.5}$	Prob OR > 1.0	Prob OR > 1.2
	NUF Rate > 1.75 mL/kg/h vs. NUF rate < 1.01 mL/kg/h								
Cluster 1	0.116	0.161	-0.199	0.006	0.116	0.224	0.432	0.762	0.340
Cluster 2	0.138	0.227	-0.306	-0.015	0.136	0.291	0.582	0.729	0.423
All Patients	0.123	0.132	-0.136	0.033	0.122	0.211	0.384	0.824	0.327
	NUF Rate > 1.75 mL/kg/h vs. NUF Rate 1.01 – 1.75 mL/kg/h								
Cluster 1	0.481	0.160	0.168	0.373	0.479	0.588	0.796	0.999	0.969
Cluster 2	0.238	0.240	-0.232	0.075	0.237	0.399	0.705	0.840	0.592
All Patients	0.407	0.133	0.147	0.317	0.407	0.496	0.666	0.999	0.954
	NUF Rate 1.01 – 1.75 mL/kg/h vs. NUF Rate < 1.01 mL/kg/h								
Cluster 1	-0.370	0.163	-0.693	-0.479	-0.370	-0.260	-0.050	0.011	0.000
Cluster 2	-0.097	0.234	-0.554	-0.256	-0.098	0.062	0.361	0.340	0.116
All Patients	-0.280	0.133	-0.541	-0.369	-0.280	-0.191	-0.019	0.018	0.000

SD: standard deviation

eTable 3 – Baseline Characteristics of the Patients According to Each Clinical Subgroup

	Edema (*n* = 634)	No Edema (*n* = 800)	*p* value
Age, years	64.4 ± 14.7	64.8 ± 14.9	0.639
Female gender	242 (38.2)	268 (33.5)	0.075
Weight at enrollment, kg	81.2 ± 12.7	80.2 ± 13.0	0.164
Higher–intensity group	319 (50.3)	389 (48.6)	0.560
eGFR prior to hospital admission	55.9 ± 29.9	56.6 ± 32.2	0.748
Time in ICU before randomization, hours	66.1 ± 156.5	41.1 ± 78.6	< 0.001
Use of vasopressors at enrollment*	462 (73.0)	571 (71.5)	0.563
Use of mechanical ventilation at enrollment	489 (77.1)	568 (71.0)	0.011
Severe sepsis at enrollment	311 (49.1)	398 (49.8)	0.835
APACHE III score	100.8 ± 26.1	103.2 ± 25.2	0.075
Modified total SOFA score at enrollment**	10.3 ± 2.7	10.3 ± 2.8	0.991
Cardiovascular	2.9 ± 1.5	2.8 ± 1.5	0.467
Respiratory	2.9 ± 0.9	2.6 ± 1.0	< 0.001
Coagulation	0.9 ± 1.1	1.0 ± 1.1	0.321
Liver	1.0 ± 1.2	0.9 ± 1.1	0.325
Renal	2.6 ± 1.1	2.8 ± 1.0	< 0.001
Source of admission			0.036
Emergency department	133 (22.9)	208 (27.3)	
Hospital ward	175 (30.1)	203 (26.7)	
Transfer from another ICU	56 (9.6)	53 (7.0)	
Transfer from another hospital	57 (9.8)	92 (12.1)	
OR after emergency surgery	81 (13.9)	123 (16.2)	
OR after elective surgery	80 (13.7)	82 (10.8)	
Admission diagnosis			0.158
Nonoperative			
Cardiovascular	225 (35.5)	295 (36.9)	
Genitourinary	96 (15.1)	129 (16.1)	
Respiratory	74 (11.7)	71 (8.9)	
Gastrointestinal	32 (5.0)	39 (4.9)	
Other	21 (3.3)	42 (5.2)	
Operative			
Cardiovascular	124 (19.6)	143 (17.9)	
Gastrointestinal	42 (6.6)	55 (6.9)	
Trauma	12 (1.9)	7 (0.9)	
Other	8 (1.3)	19 (2.4)	
Criteria for randomization[a]			

eTable 3 – Baseline Characteristics of the Patients According to Each Clinical Subgroup

	Edema (*n* = 634)	**No Edema (*n* = 800)**	***p* value**
Oliguria (urine, < 400 mL/day)	340 (53.6)	515 (64.4)	< 0.001
Hyperkalemia (K > 6.5 mmol/L)	48 (7.6)	63 (7.9)	0.909
Severe acidemia (pH < 7.20)	200 (31.5)	306 (38.2)	0.010
BUN > 70 mg/dL (plasma urea > 25 mmol/L)	267 (42.1)	328 (41.0)	0.711
Creatinine > 3.4 mg/dL (300 µmol/L)	261 (41.2)	418 (52.2)	< 0.001
Severe organ edema associated with AKI	634 (100.0)	0 (0.0)	< 0.001
BUN before randomization, mmol/L	23.4 ± 12.3	23.7 ± 13.1	0.723
Creatinine before randomization, µmol/L	312.0 ± 177.8	353.7 ± 206.2	< 0.001
pH before randomization	7.27 ± 0.13	7.25 ± 0.13	0.012
Bicarbonate before randomization, mmol/L	19.1 ± 5.5	17.8 ± 6.0	< 0.001
Base excess before randomization, mmol/L	-7.4 ± 6.7	-8.8 ± 7.1	< 0.001
Clinical outcomes			
RRT dependence among survivors at day 28	58 (14.9)	62 (12.1)	0.258
90–day mortality	290 (45.7)	344 (43.1)	0.335

Data are mean ± standard deviation or No (%)

AKI: acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; BUN: blood urea nitrogen; GFR: estimated glomerular filtration rate; ICU: intensive care unit; OR: operating room; SOFA: Sequential Organ Failure Assessment

* Defined as a cardiovascular SOFA score ≥ 3

** Not considering the neurological component

[a] A given patient may have met more than one of these criteria.

eTable 4 – Characteristics of Study Treatment According to Each Clinical Subgroup

	Edema (*n* = 634)	No Edema (*n* = 800)	*p* value
Cumulative net ultrafiltration at the end of treatment days, mL	13763.6 ± 15479.7	11201.2 ± (15266.1	0.002
Net ultrafiltration rate, mL/kg/h	1.61 ± 1.07	1.29 ± 0.87	< 0.001
Net ultrafiltration rate category			< 0.001
< 1.01 mL/kg/h	171 (27.0)	305 (38.1)	
1.01 – 1.75 mL/kg/h	207 (32.6)	270 (33.8)	
> 1.75 mL/kg/h	256 (40.4)	225 (28.1)	
Duration of study treatment, days	6.3 ± 8.3	6.1 ± 8.3	0.733
Flow rate of effluent, mL/kg/h	26.1 ± 7.3	25.8 ± 7.4	0.521
Dose delivered, %	0.81 ± 0.16	0.81 ± 0.16	0.637
BUN, mmol/L/day	13.5 ± 6.1	14.4 ± 6.8	0.028
Serum creatinine, µmol/L/day	172.9 ± 84.9	203.0 ± 112.3	< 0.001
Dialysate and replacement fluid, mL/h	1991.8 ± 649.2	1983.3 ± 674.7	0.828
Dose of effluent, mL/h/day	2097.6 ± 634.0	2065.5 ± 648.5	0.399
Fluid balance excluding NUF volume			
At day 1, mL	1233.2 ± 1756.4	1695.3 ± 2414.6	< 0.001
Daily, mL/d*	1525.3 ± 1343.3	1611.8 ± 1473.7	0.251
Cumulative at the end of treatment days, mL*	9936.7 ± 13924.5	9811.3 ± 13961.5	0.866
Fluid balance including NUF volume			
At day 1, mL	272.7 ± 2038.9	1028.0 ± 2553.4	< 0.001
Daily, mL/d*	-417.5 ± 1693.5	59.0 ± 1753.5	< 0.001
Cumulative at the end of treatment days, mL*	-3842.3 ± 11481.7	-1402.0 ± 8939.0	< 0.001
Total non–CRRT fluids[a]			
At day 1, mL	1924.8 ± 1863.5	2372.8 ± 2541.6	< 0.001
Daily, mL/d*	2420.4 ± 1423.8	2589.1 ± 1549.2	0.034
Cumulative at the end of treatment days, mL*	15044.6 ± 17796.0	15058.4 ± 17800.6	0.988
Total non–CRRT IV fluids[b]			
At day 1, mL	1811.7 ± 1779.1	2273.8 ± 2480.8	< 0.001
Daily, mL/d*	2228.8 ± 1316.9	2400.3 ± 1468.7	0.022
Cumulative at the end of treatment days, mL*	13573.6 ± 15572.3	13773.1 ± 16018.3	0.813
Enteral nutrition			
At day 1, mL	255.6 ± 508.3	250.3 ± 584.5	0.906
Daily, mL/d*	331.5 ± 511.4	366.8 ± 555.6	0.299
Cumulative at the end of treatment days, mL*	2040.7 ± 4522.9	1876.3 ± 3372.7	0.510
Urine output			
At day 1, mL	406.8 ± 649.9	396.9 ± 683.5	0.780
Daily, mL/d*	533.2 ± 611.1	600.5 ± 702.7	0.057

eTable 4 – Characteristics of Study Treatment According to Each Clinical Subgroup

	Edema (*n* = 634)	No Edema (*n* = 800)	*p* value
Cumulative at the end of treatment days, mL*	2681.9 ± 3244.5	2848.6 ± 3706.3	0.372
Blood losses[c]			
At day 1, mL	50.3 ± 225.2	43.6 ± 229.5	0.582
Daily, mL/d*	61.5 ± 276.5	45.5 ± 219.7	0.221
Cumulative at the end of treatment days, mL*	339.8 ± 1589.8	313.2 ± 1463.2	0.742
Other output[d]			
At day 1, mL	241.1 ± 556.8	239.9 ± 614.8	0.970
Daily, mL/d*	302.8 ± 499.4	331.8 ± 546.1	0.300
Cumulative at the end of treatment days, mL*	2101.5 ± 4606.6	2097.4 ± 4417.2	0.986
Filters used daily	0.9 ± 0.5	0.9 ± 0.5	0.892
Patients treated with IHD in ICU	52 (8.2)	54 (6.8)	0.346

Data are mean ± standard deviation or No (%)
BUN: blood urea nitrogen; ICU: intensive care unit; IHD: intermittent hemodialysis; IV: intravenous
* considering only days where continuous renal replacement therapy was used
[a] considering blood, blood products, albumin, enteral nutrition, total parenteral nutrition and other intravenous fluids
[b] considering blood, blood products, albumin, total parenteral nutrition and other intravenous fluids
[c] considering any blood loss in and outside the ICU
[d] other fluid losses (e.g., gastrointestinal losses, drain losses and other)

eTable 5 – Summary of Posterior Distributions for Heterogeneity of Effect in Each Clinical Subgroup

Subgroup	Mean	SD	$Q_{2.5}$	Q_{25}	Median	Q_{75}	$Q_{97.5}$	Prob OR > 1.0	Prob OR > 1.2
	NUF Rate > 1.75 mL/kg/h vs. NUF rate < 1.01 mL/kg/h								
Edema	0.042	0.196	-0.343	-0.091	0.042	0.175	0.424	0.854	0.237
No edema	0.193	0.176	-0.152	0.074	0.194	0.313	0.537	0.863	0.524
	NUF Rate > 1.75 mL/kg/h vs. NUF Rate 1.01 – 1.75 mL/kg/h								
Edema	0.447	0.188	0.075	0.322	0.447	0.574	0.816	0.991	0.920
No edema	0.347	0.182	-0.013	0.226	0.348	0.469	0.705	0.971	0.817
	NUF Rate 1.01 – 1.75 mL/kg/h vs. NUF Rate < 1.01 mL/kg/h								
Edema	-0.403	0.209	-0.816	-0.544	-0.402	-0.261	0.001	0.025	0.003
No edema	-0.152	0.168	-0.482	-0.265	-0.153	-0.038	0.179	0.185	0.023

SD: standard deviation

eTable 6 – Results of the Bayesian Regression Model

	Estimate	SE	Lower 95% CrI	Upper 95% CrI	Rhat*
Intercept	-2.222	0.493	-3.203	-1.265	1.000
Cluster 2	-0.121	0.413	-0.935	0.689	1.000
Cardiovascular SOFA	0.101	0.114	-0.124	0.325	1.000
NUF rate group					
Middle	-0.162	0.488	-1.123	0.790	1.000
High	0.114	0.460	-0.792	1.021	1.000
APACHE–III	0.017	0.002	0.012	0.022	1.000
Higher–intensity group	0.033	0.113	-0.187	0.255	1.000
Cluster 2 : Cardiovascular SOFA	-0.166	0.104	-0.369	0.037	1.000
Cardiovascular SOFA : Middle group	-0.075	0.127	-0.324	0.173	1.000
Cardiovascular SOFA : High group	-0.013	0.119	-0.246	0.221	1.000
Cluster 2 : Middle group	0.054	0.405	-0.748	0.842	1.000
Cluster 2 : High group	-0.076	0.386	-0.839	0.677	1.000

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; SE: standard error; CrI: credible interval

* Gelman Rubin statistic to check Markov chains for convergence

eTable 7 – Results of the Bayesian Regression Model

	Estimate	SE	Lower 95% CrI	Upper 95% CrI	Rhat*
Intercept	-2.476	0.339	-3.149	-1.817	1.000
Edema	-0.003	0.300	-0.597	0.583	1.000
Cardiovascular SOFA	0.076	0.072	-0.063	0.218	1.000
NUF rate group					
Middle	-0.006	0.321	-0.636	0.625	1.000
High	0.118	0.318	-0.502	0.736	1.000
APACHE–III	0.018	0.002	0.013	0.023	1.000
Higher–intensity group	0.028	0.112	-0.192	0.248	1.000
Edema : Cardiovascular SOFA	0.081	0.075	-0.065	0.230	1.000
Cardiovascular SOFA : Middle group	-0.081	0.093	-0.262	0.102	1.000
Cardiovascular SOFA : High group	-0.015	0.090	-0.191	0.161	1.000
Edema : Middle group	-0.258	0.285	-0.815	0.297	1.000
Edema : High group	-0.059	0.280	-0.607	0.486	1.000

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; SE: standard error; CrI: credible interval

* Gelman Rubin statistic to check Markov chains for convergence

eFigure 1. Distributions of Imputed and Unimputed Values

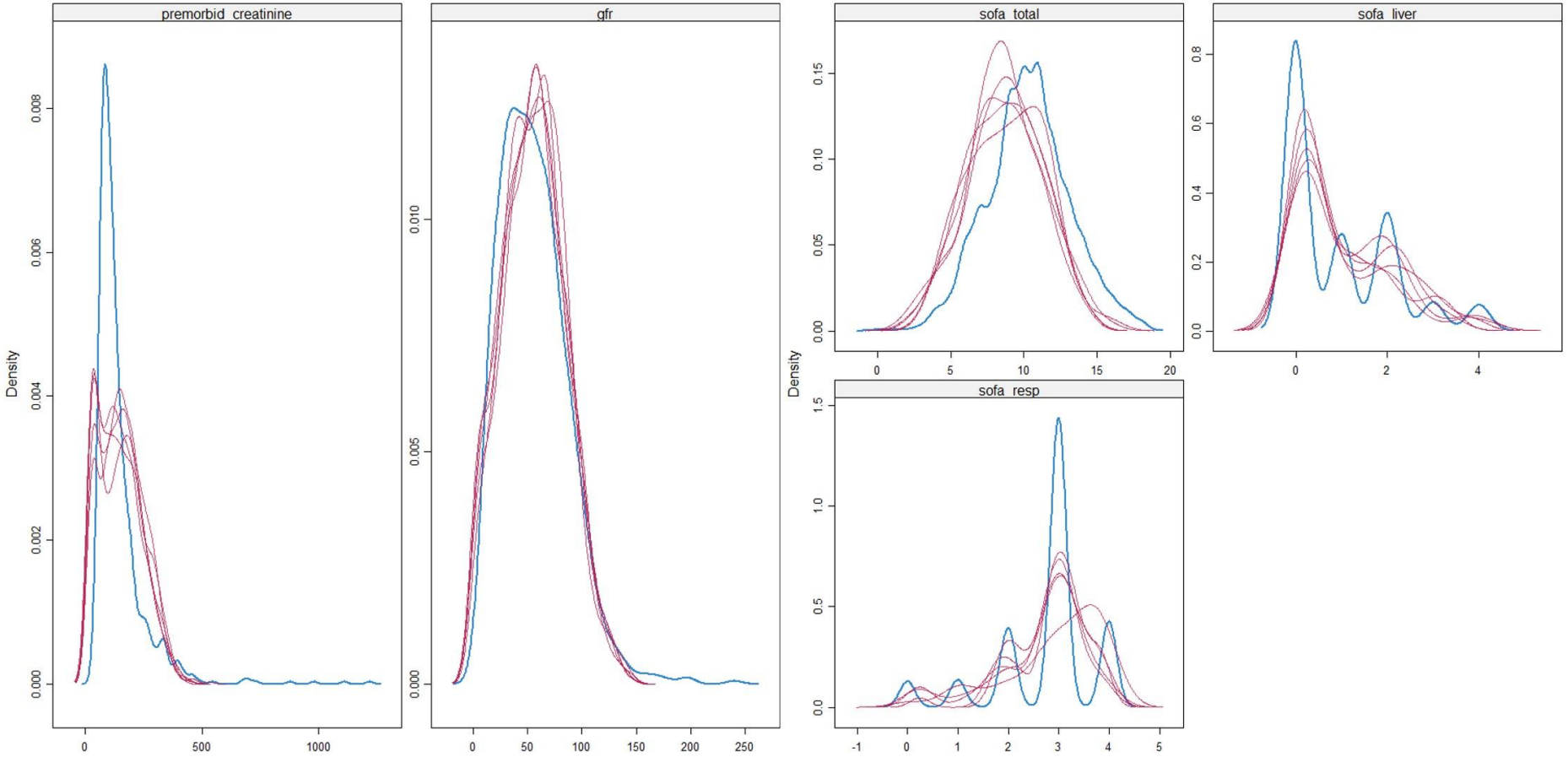
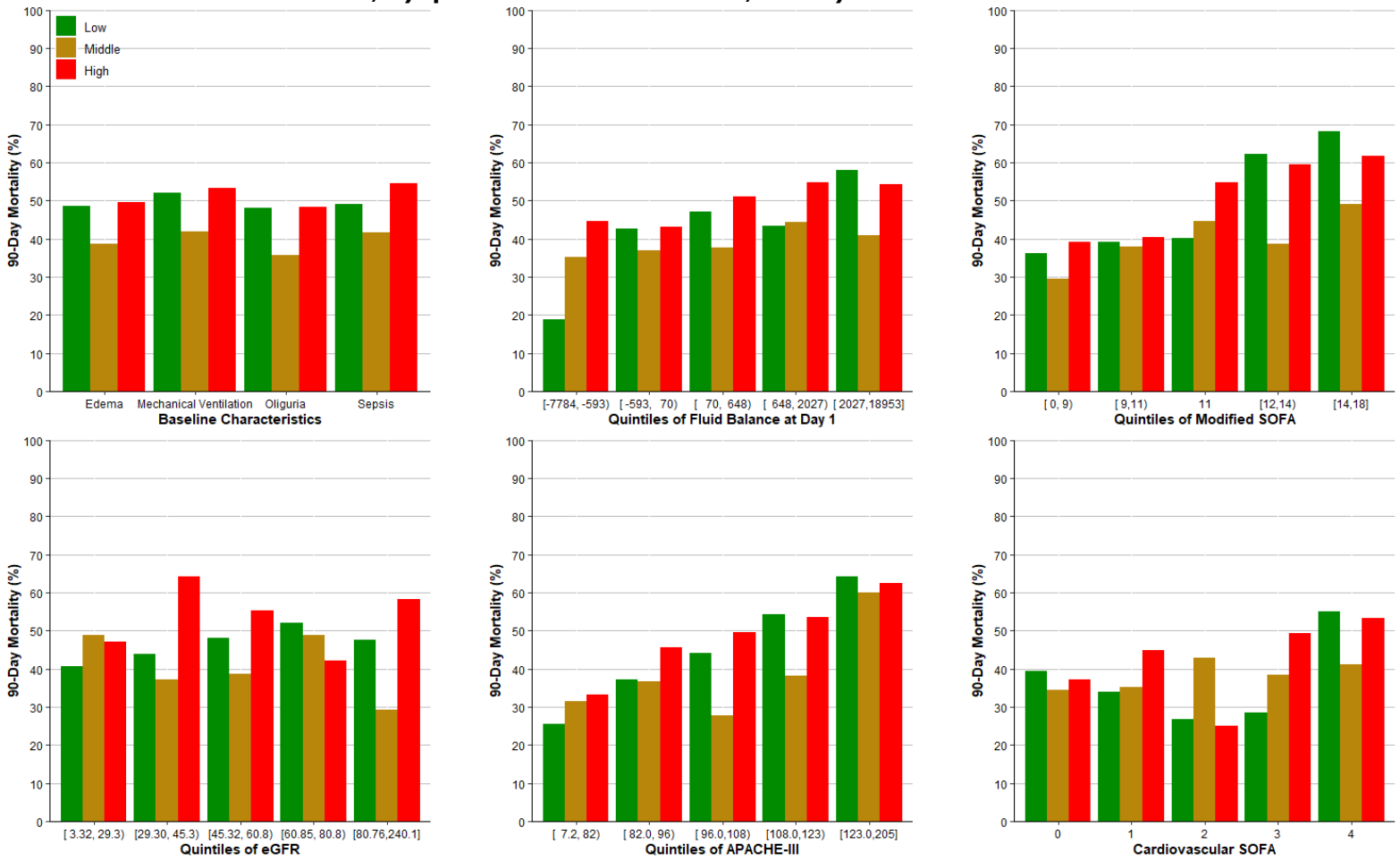


Figure showing distribution of imputed (red) and unimputed (blue) values.

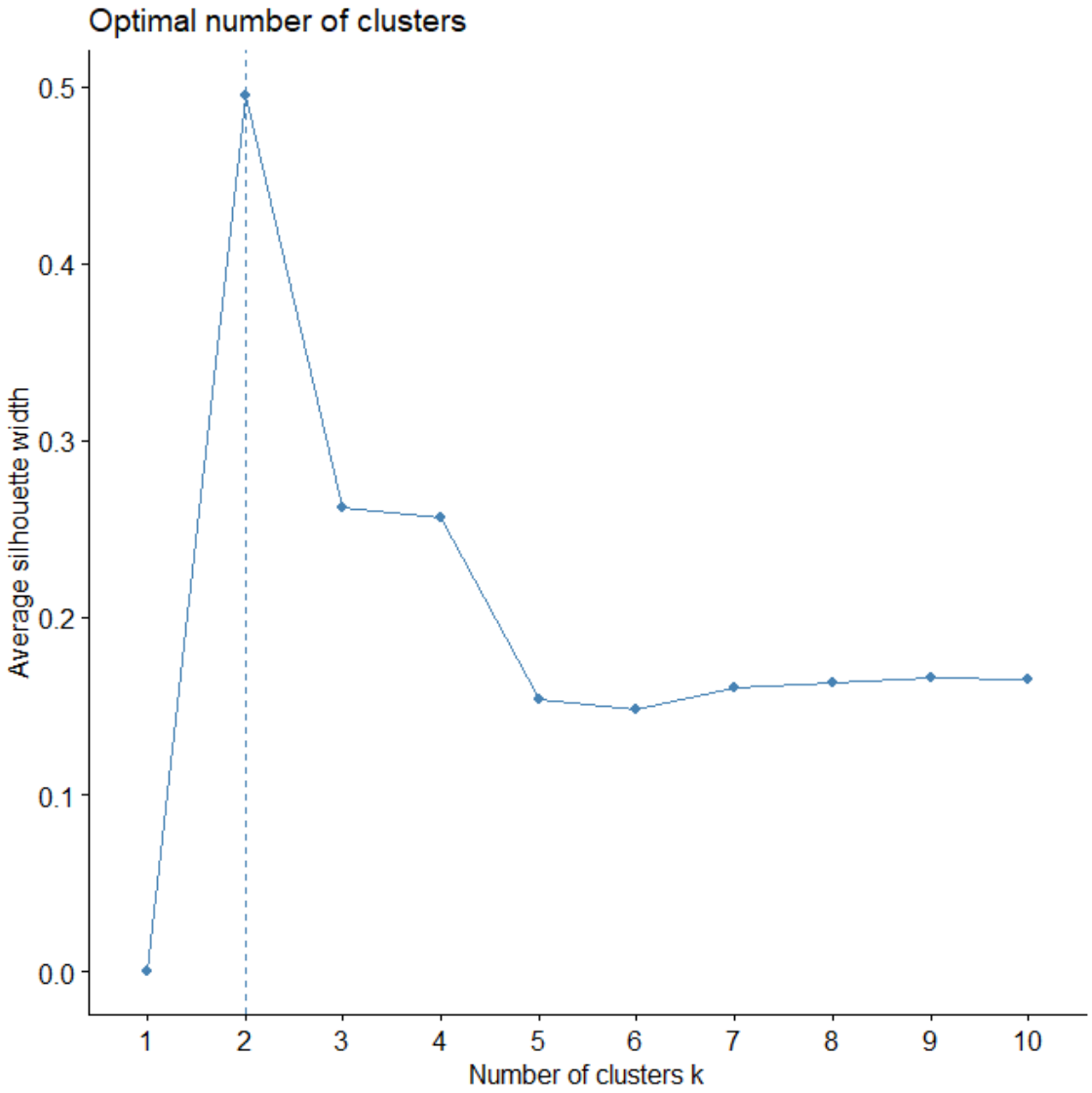
eFigure 2. Low (< 1.01 mL/kg/h), middle (1.01 – 1.75 mL/kg/h) and high (> 1.75 mL/kg/h) groups of NUF rate mortality according to A) baseline characteristics, B) quintiles of fluid balance at day 1, C) quintiles of modified SOFA, D) quintiles of eGFR, E) quintiles of APACHE–III, and F) cardiovascular SOFA



Modified SOFA calculated not considering the neurological component

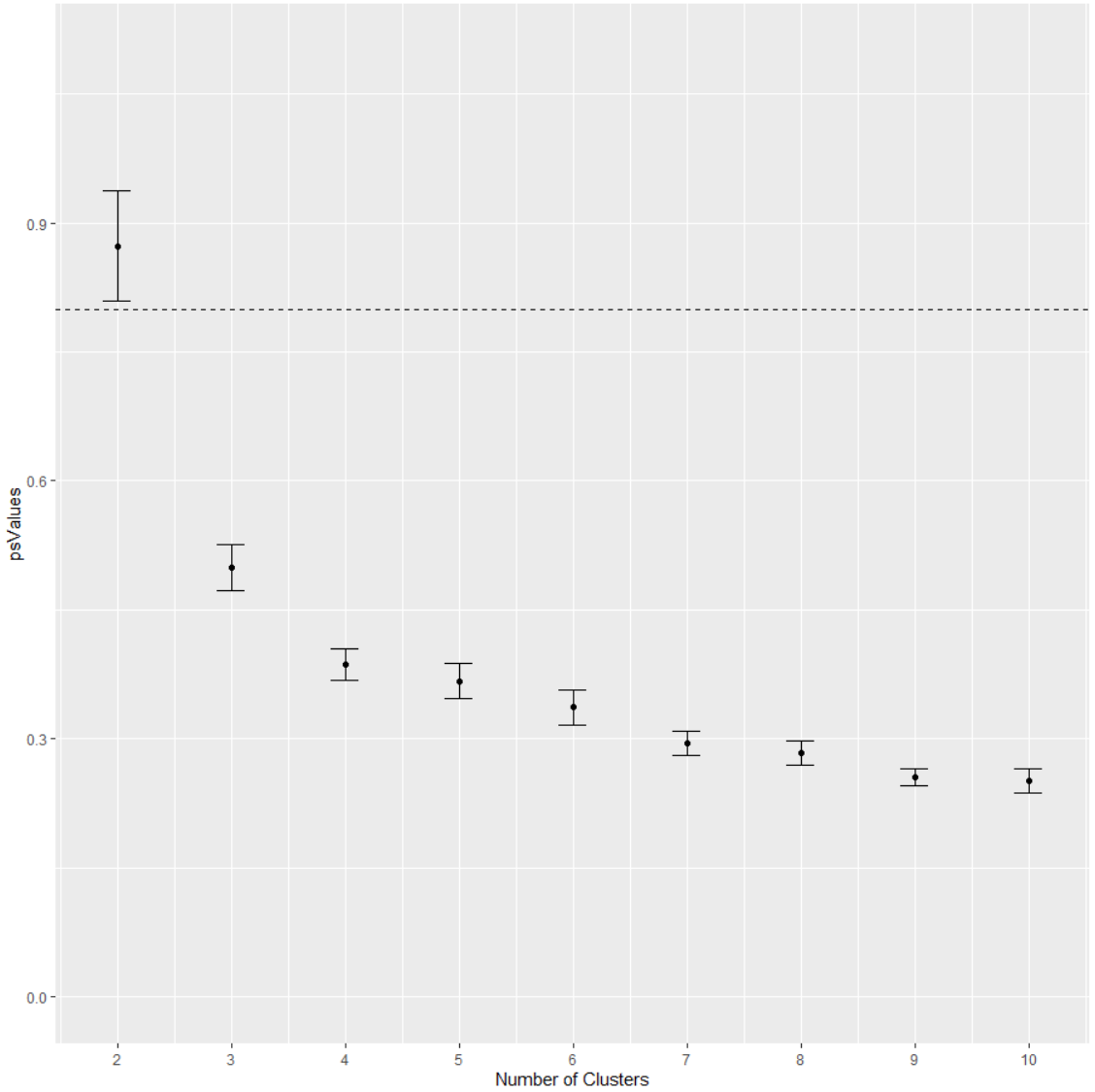
SOFA: Sequential Organ Failure Assessment; eGFR: estimated glomerular filtration rate; APACHE: Acute Physiology and Chronic Health Evaluation

eFigure 3. Optimal number of clusters according to the silhouette method



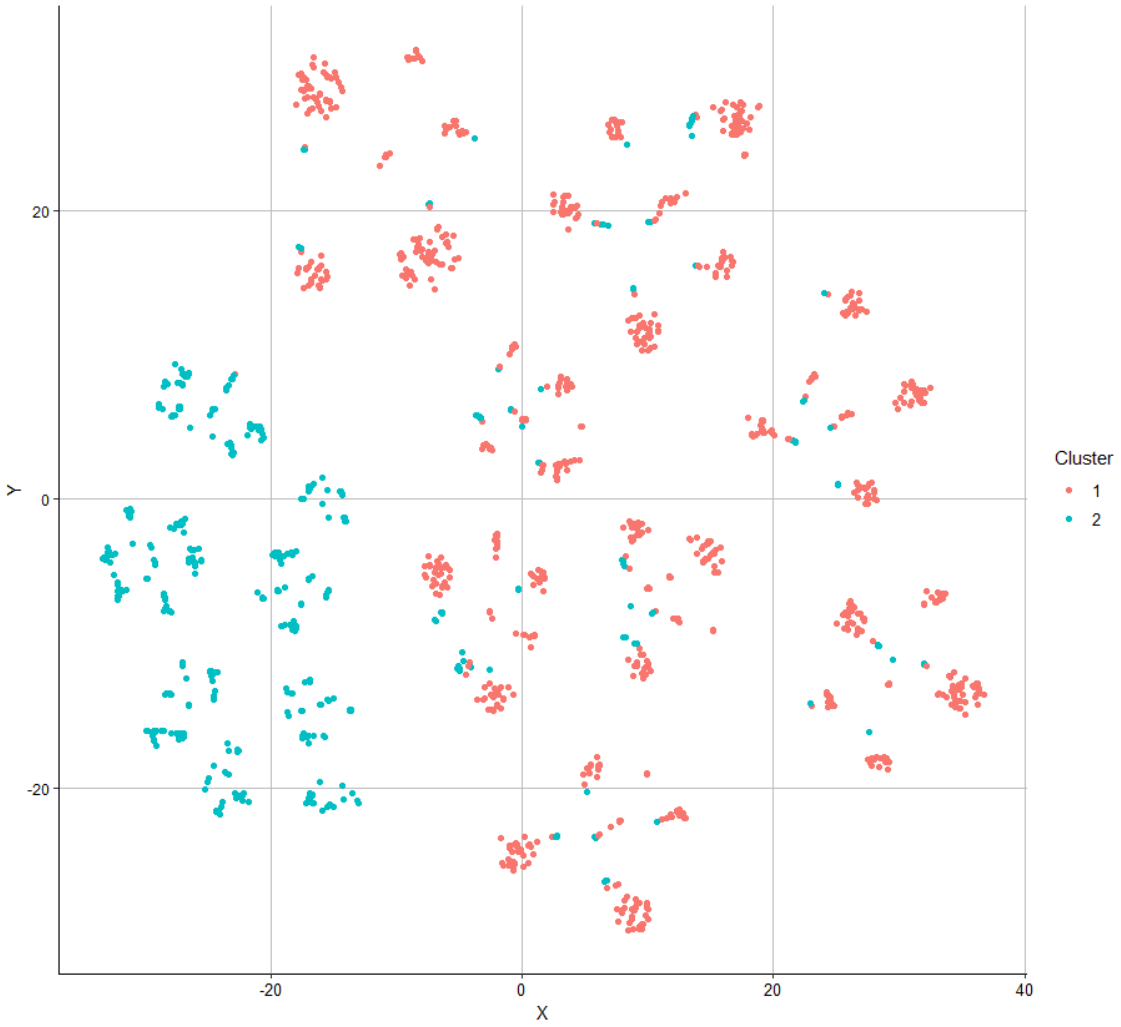
This method computes partitioning around medoids (PAM) algorithm using different values of clusters k. Next, the average clusters silhouette is drawn according to the number of clusters. The average silhouette measures the quality of a clustering. A high average silhouette width indicates a good clustering. The optimal number of clusters k is the one that maximize the average silhouette over a range of possible values for k.

eFigure 4. Prediction strength according to *kamila* algorithm for different number of simulated clusters after cross–validation



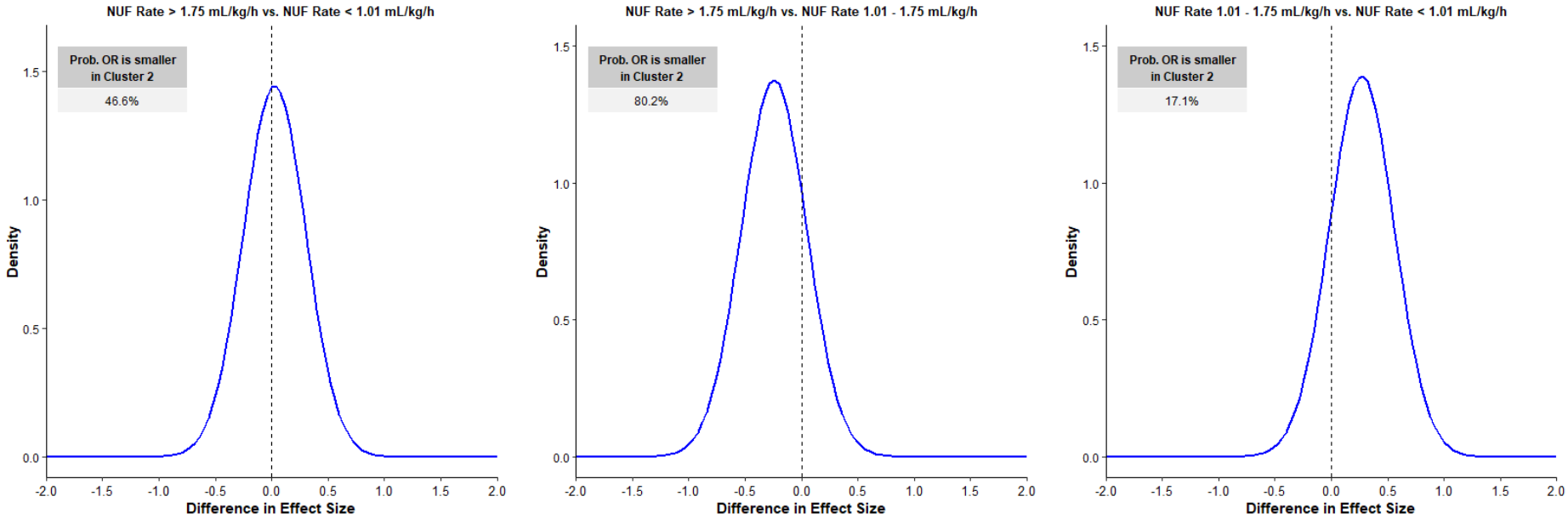
Two clusters provided the highest prediction strength values (psValues) and this value is higher than the prediction strength threshold.

eFigure 5. tSNE Plot



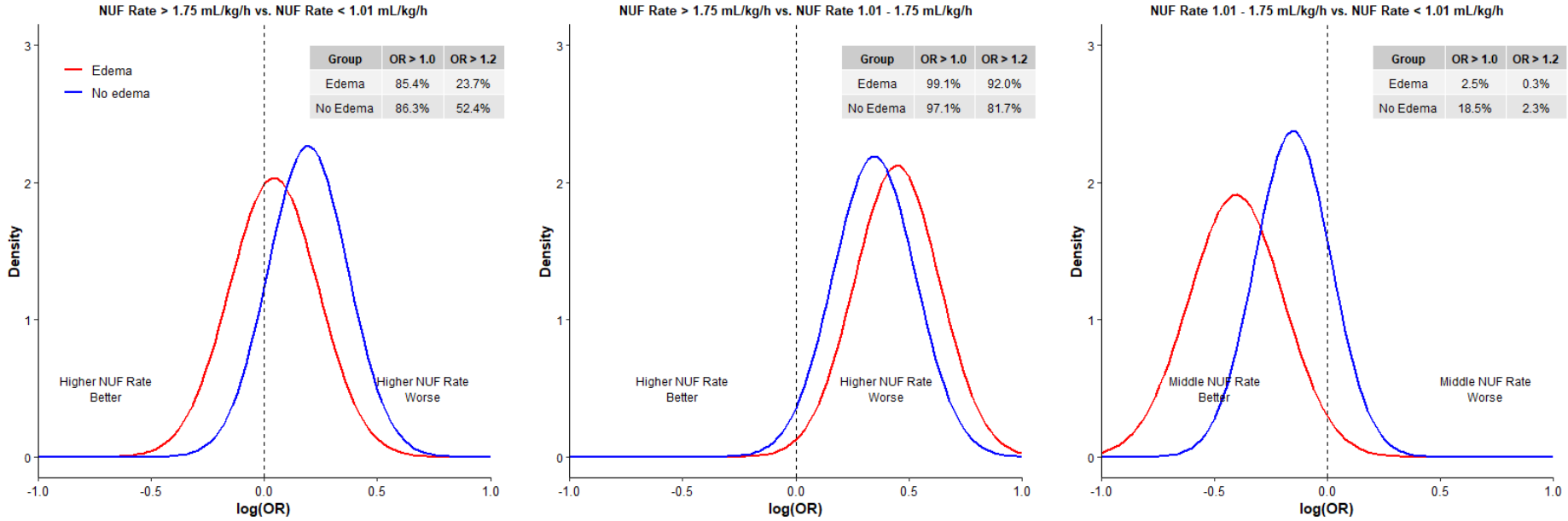
tSNE plot using Gower's distance with colors based on clusters found by *kamila* algorithm. Although some overlap between clusters based on Gower's distance is seen, there is a considerable difference between the two clusters found by *kamila*.
kamila is an iterative clustering method that equitably balances the contribution of continuous and categorical variables. Gower Distance is a distance measure that can be used to calculate the distance between two entities whose attributes have a mix of categorical and numerical values.

eFigure 6. Probability that the effect size is lower in cluster 2 than in cluster 1



This is the probability that the odds ratio is lower in cluster 2 compared to cluster 1. It is calculated from the difference in the odds ratio in cluster 2 *minus* the odds ratio in cluster 1
OR: odds ratio

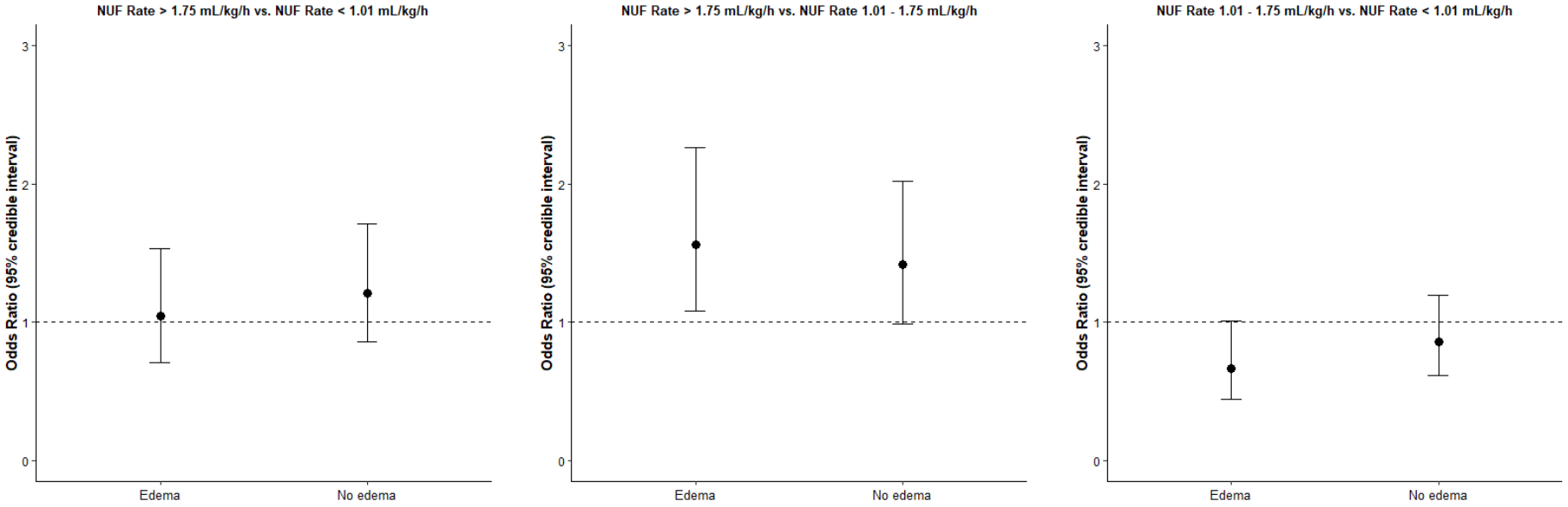
eFigure 7. Bayesian heterogeneity of effect in the pairwise comparisons of A) high vs. low, B) high vs. middle, and C) middle vs. low NUF rate tertiles



Posterior probability distribution of the NUF rate groups treatment effect (log(OR)) in each cluster. The tables contain the probability that the odds ratio for 90–day mortality in the high NUF group (plot A and B) or in the middle NUF group (plot C) is above 1.0 or 1.2 for each cluster found.

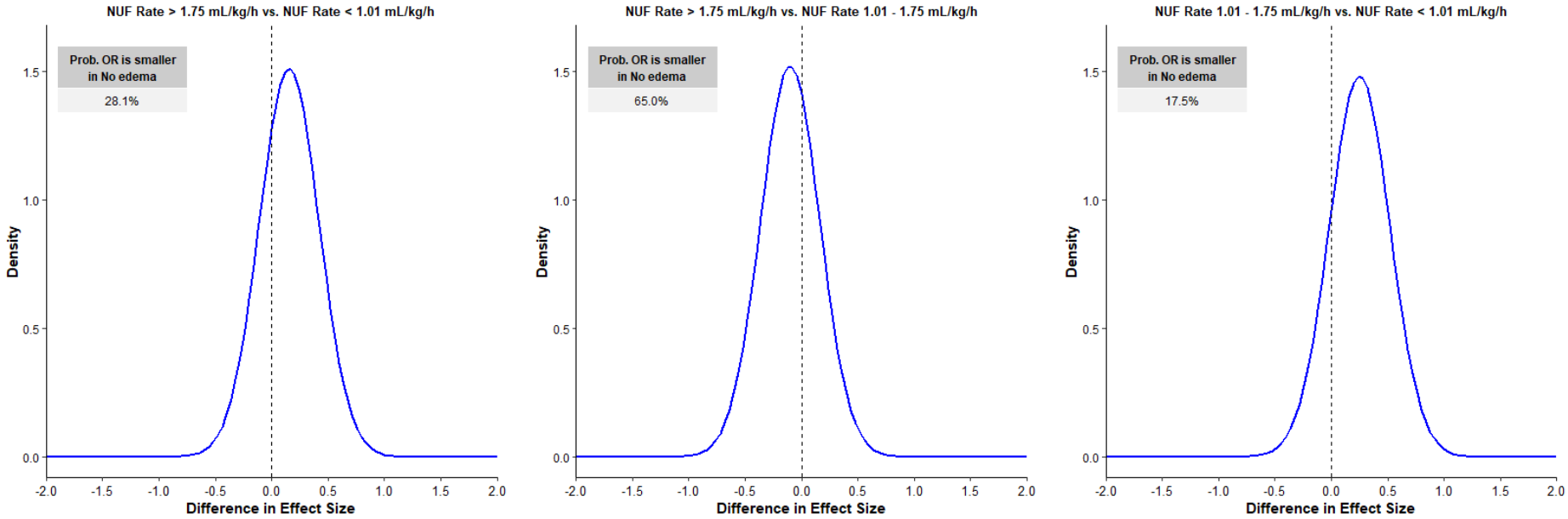
NUF: net ultrafiltration; OR: odds ratio

eFigure 8. Bayesian heterogeneity of effect in the pairwise comparisons of A) high vs. low, B) high vs. middle, and C) middle vs. low NUF rate tertiles



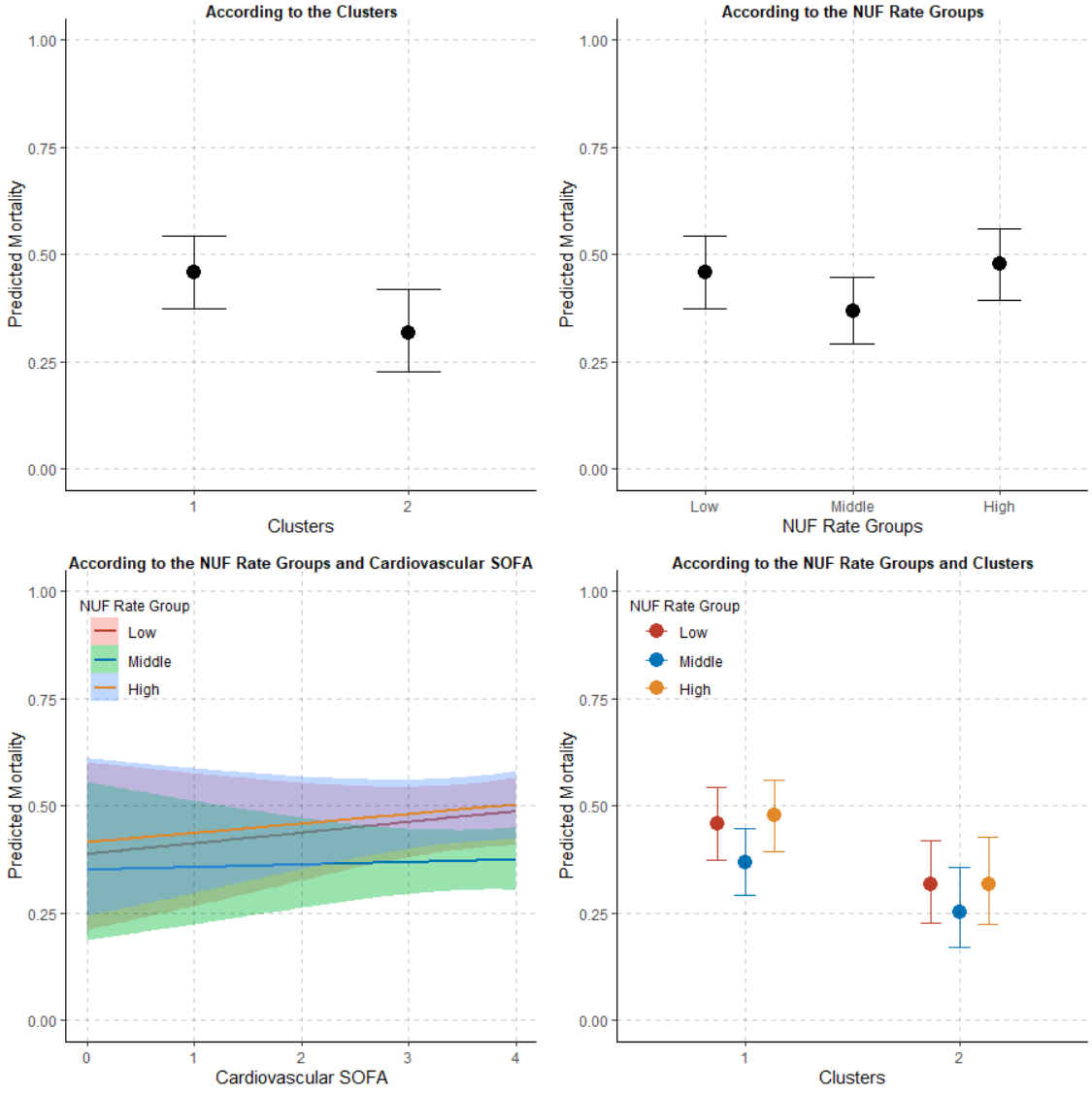
Odds ratio (95% credible intervals) for the association between the high NUF group (plot A and B) or the middle NUF group (plot C) and 90–day mortality according to the clusters found.
NUF: net ultrafiltration

eFigure 9. Probability that the effect size is lower in the subgroup of No edema in the subgroup of Edema



This is the probability that the odds ratio is lower in ‘No edema’ compared to ‘Edema’. It is calculated from the difference in the odds ratio in ‘No edema’ *minus* the odds ratio in ‘Edema;
OR: odds ratio

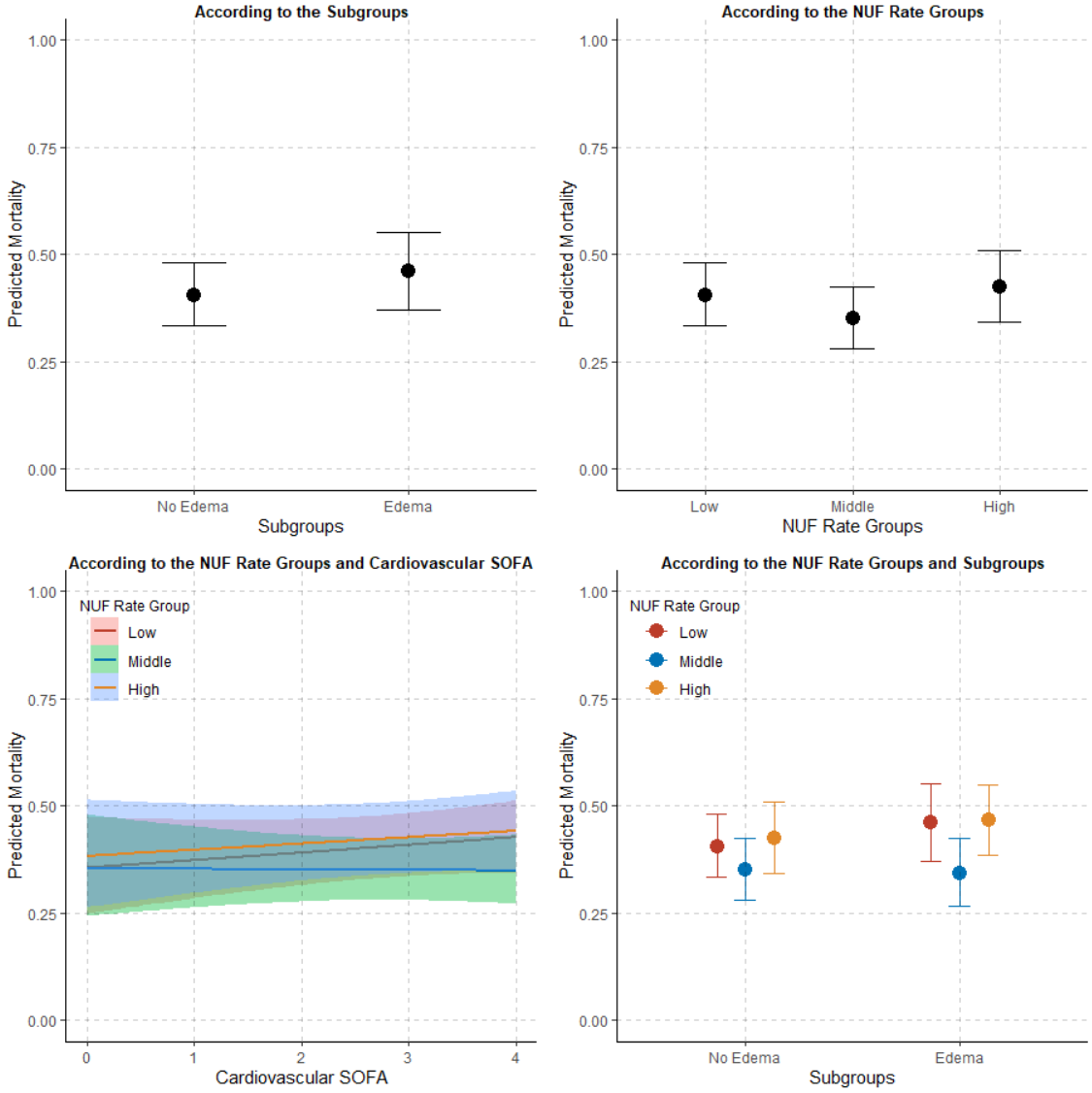
eFigure 10. Predicted mortality probability in different scenarios in the clusters



Predicted mortality extracted from a Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III and treatment allocation in the original trial and considered interactions between cardiovascular SOFA and NUF rate groups, cluster and NUF rate groups, and cluster and cardiovascular SOFA.

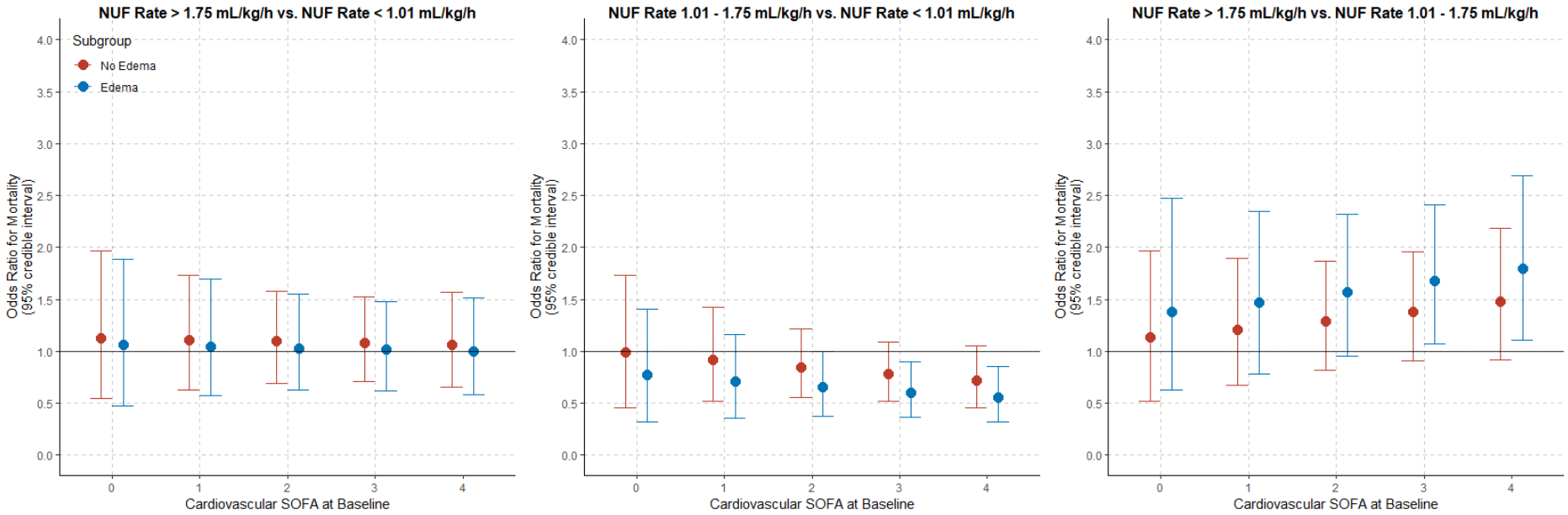
NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

eFigure 11. Predicted mortality probability in different scenarios in the clinical subgroups



Predicted mortality extracted from a Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III and treatment allocation in the original trial and considered interactions between cardiovascular SOFA and NUF rate groups, clinical subgroups and NUF rate groups, and clinical subgroups and cardiovascular SOFA.
NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

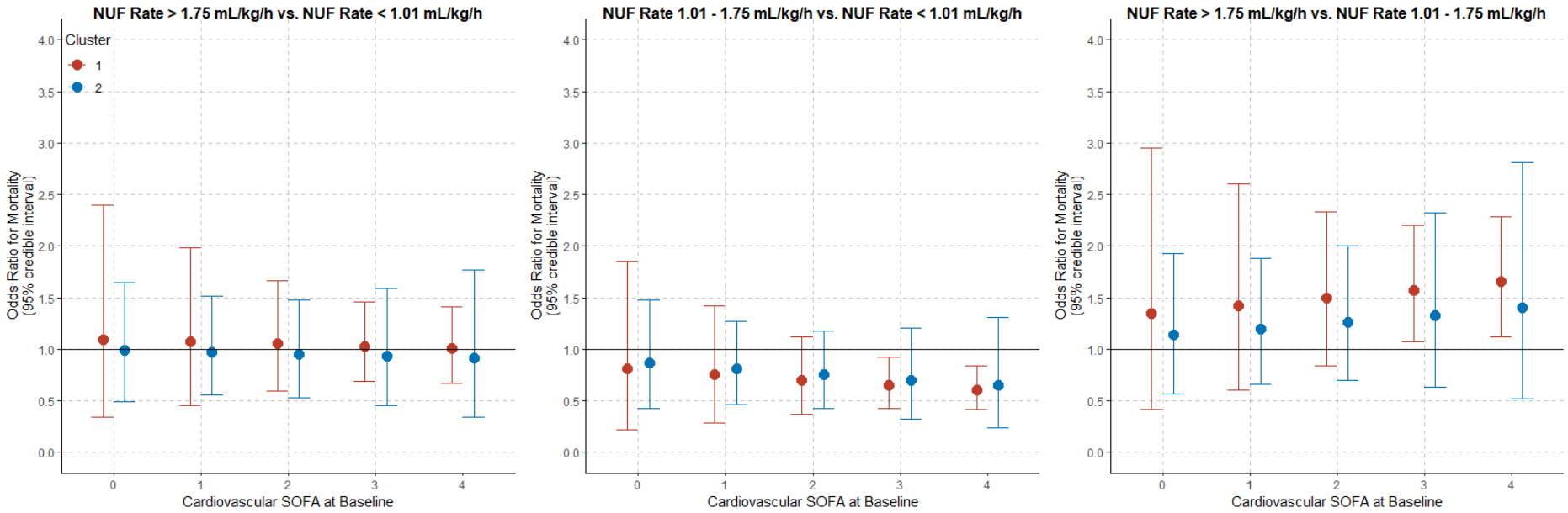
eFigure 12. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups



Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III and treatment allocation in the original trial and considered interactions between cardiovascular SOFA and NUF rate groups, clinical subgroups and NUF rate groups, and clinical subgroups and cardiovascular SOFA. Odds ratio extracted from the median of the posterior distribution and 95% credible intervals calculated as the highest posterior density.

NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

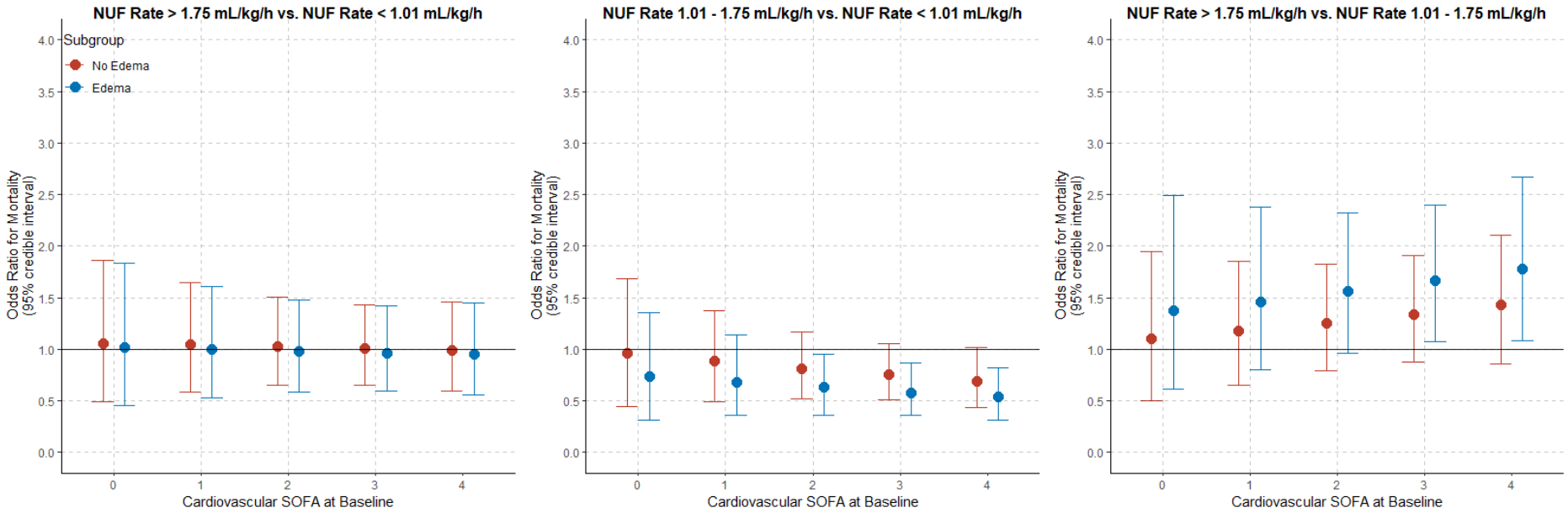
eFigure 13. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clusters further adjusted by total non–CRRT intravenous fluids



Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III, total non–CRRT intravenous fluids (defined as blood, blood products, albumin, total parenteral nutrition and other intravenous fluids) and treatment allocation in the original trial and considered interactions between cardiovascular SOFA and NUF rate groups, cluster and NUF rate groups, and cluster and cardiovascular SOFA. Odds ratio extracted from the median of the posterior distribution and 95% credible intervals calculated as the highest posterior density.

NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

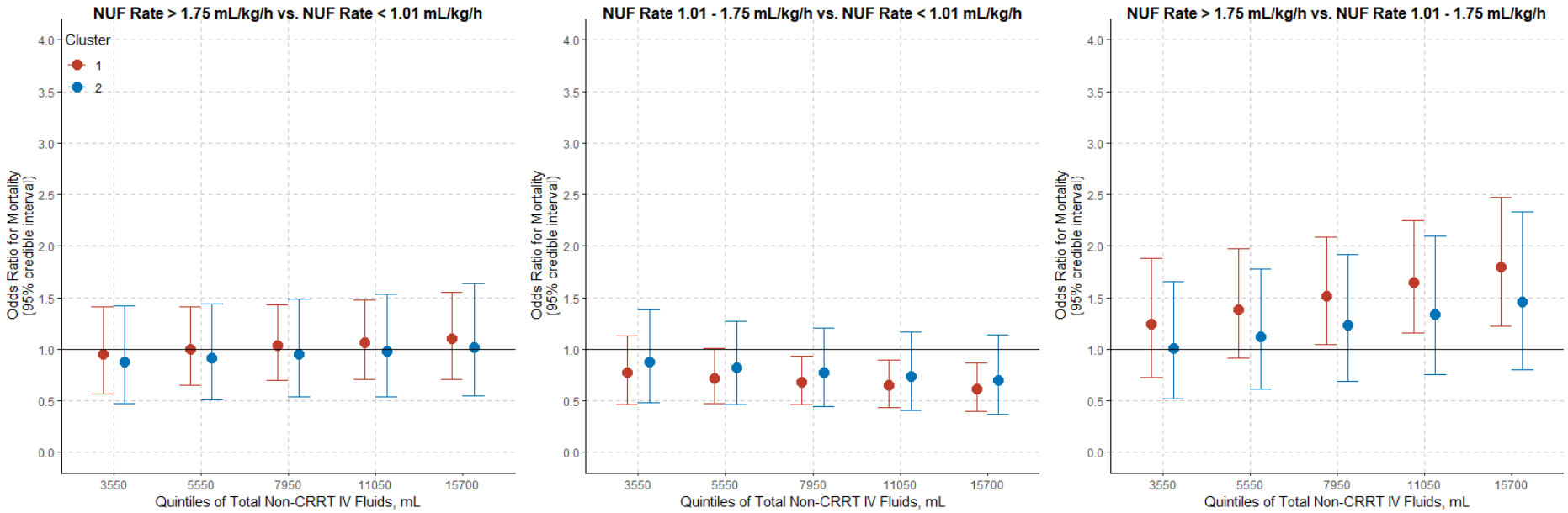
eFigure 14. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups further adjusted by total non–CRRT intravenous fluids



Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III, total non–CRRT intravenous fluids (defined as blood, blood products, albumin, total parenteral nutrition and other intravenous fluids) and treatment allocation in the original trial and considered interactions between cardiovascular SOFA and NUF rate groups, clinical subgroups and NUF rate groups, and clinical subgroups and cardiovascular SOFA. Odds ratio extracted from the median of the posterior distribution and 95% credible intervals calculated as the highest posterior density.

NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

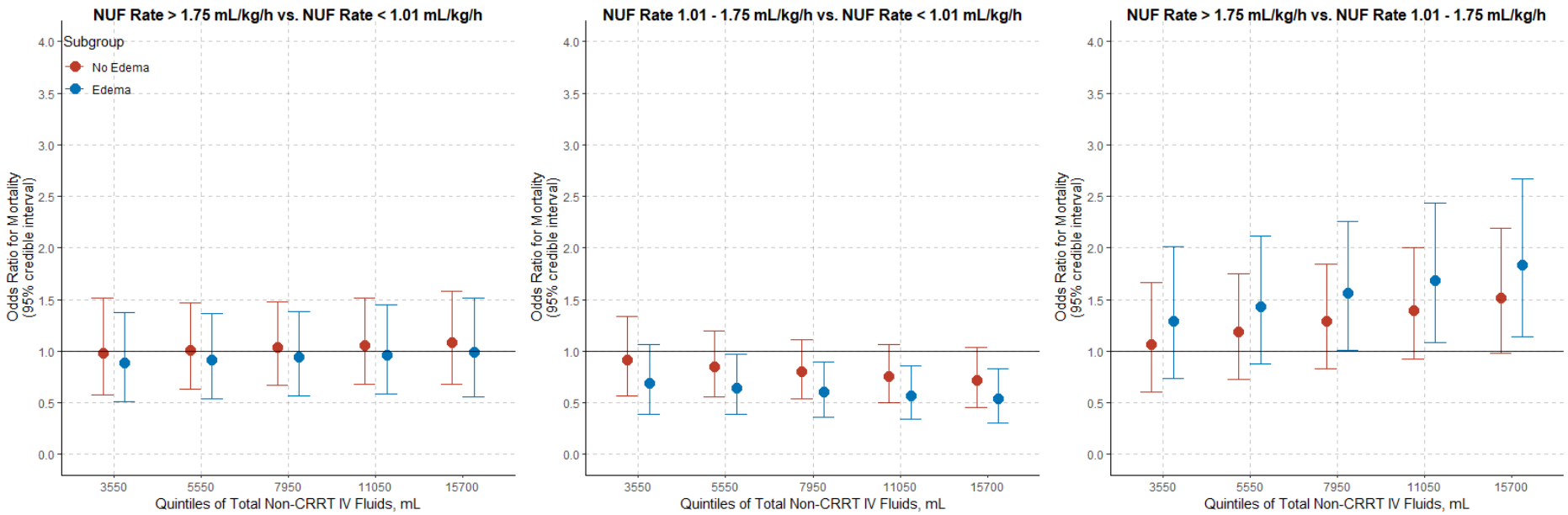
eFigure 15. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clusters further adjusted by total non–CRRT intravenous fluids



Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III and treatment allocation in the original trial and considered interactions between quintiles of total non–CRRT intravenous fluids (defined as blood, blood products, albumin, total parenteral nutrition and other intravenous fluids) and NUF rate groups, cluster and NUF rate groups, and cluster and quintiles of total non–CRRT intravenous fluids. Odds ratio extracted from the median of the posterior distribution and 95% credible intervals calculated as the highest posterior density.

NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

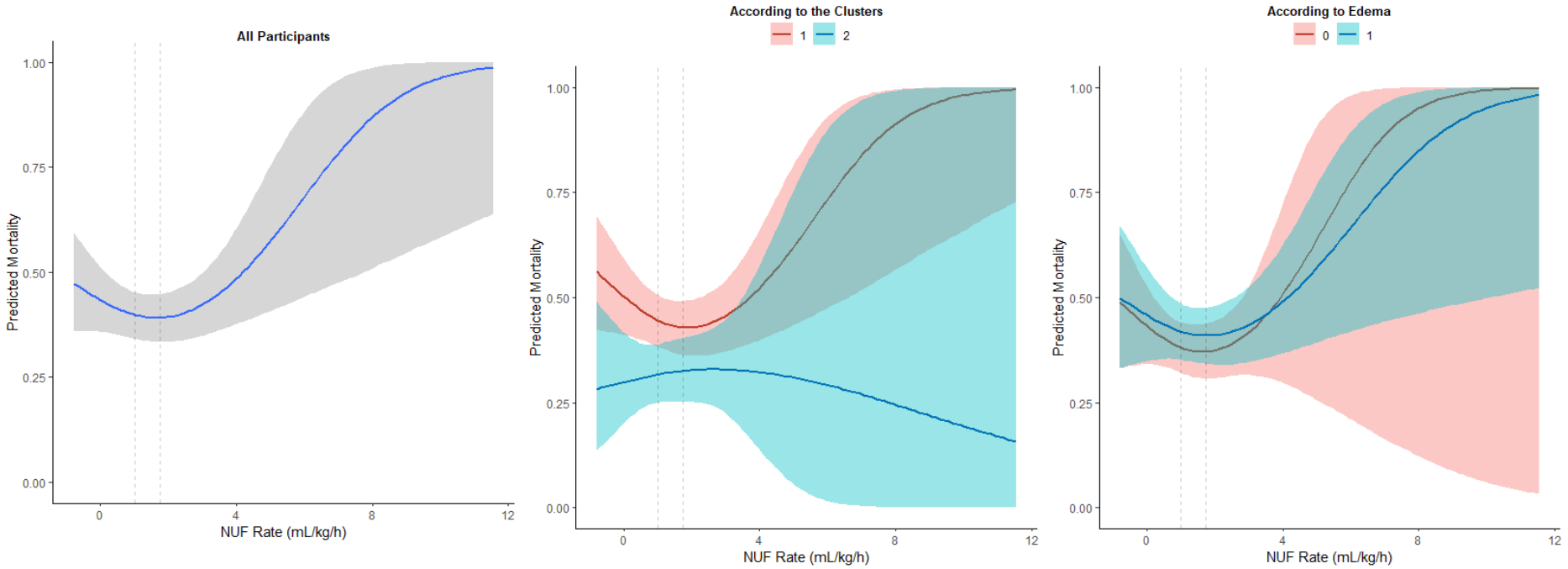
eFigure 16. Odds ratio for 90–day mortality with 95% credible interval according to NUF rate groups and the clinical subgroups by total non–CRRT intravenous fluids



Bayesian multi–level model with a Bernoulli distribution, with centres as random effect and considering non–informative priors. All models were adjusted by APACHE-III and treatment allocation in the original trial and considered interactions between quintiles of total non–CRRT intravenous fluids (defined as blood, blood products, albumin, total parenteral nutrition and other intravenous fluids) and NUF rate groups, clinical subgroups and NUF rate groups, and clinical subgroups and quintiles of total non–CRRT intravenous fluids. Odds ratio extracted from the median of the posterior distribution and 95% credible intervals calculated as the highest posterior density.

NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment

eFigure 17. Cubic spline plot for predicted mortality according to NUF rate groups for all participants and the clinical subgroups by clusters and edema



Cubic spline plot- NUF treated as continuous variable and was adjusted by cardiovascular SOFA, non-CRRT IV fluid, APACHE-III score and randomization group. Results are presented as marginal effect plots for the whole population, according to the cluster (from an interaction between cluster and NUF rate), and according to the presence of edema (from an interaction between presence of edema and NUF rate). *NUF: net ultrafiltration; SOFA: Sequential Organ Failure Assessment;*