Supplementary appendix

The effect of intermittent or continuous feeding and amino acid concentration on urea-to-creatinine ratio in critical illness

Luke Flower MBChB[1,2]*, Ryan W. Haines MBBS[2,3]*, Angela McNelly PhD[3,4,5], Danielle E. Bear PhD [6,7,8] Kiran Koelfat MD[9], Steven Olde Damink PhD[9,10], Nicholas Hart PhD [8,11], Hugh Montgomery MD[4,5], John R. Prowle PhD[3,12,13], Zudin Puthucheary PhD[3,13]

These authors contributed equally to this work.

[1]*Honorary Fellow, William Harvey Research Institute, Queen Mary University of London, London, UK* [2]*Department of Anaesthesia, University College Hospital, 235 Euston Road, London, UK* [3]*William Harvey Research Institute, Queen Mary University of London, London, UK* [4]*University College London (UCL),* [5]*UCL Hospitals NHS Foundation Trust (UCLH), National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), London,* [6]*Department of Nutrition and Dietetics St Thomas' NHS Foundation Trust ,* [7]*Department of Critical Care, Guy's and St. Thomas' NHS Foundation & King's College London (KCL) NIHR BRC, London,* [8] *Centre for Human and Applied Physiological Sciences, Kings College London,* [9]*Department of Surgery and School of Nutrition and Translational Research in Metabolism (NUTRIM), University of Maastricht, Maastricht, The Netherlands,* [10]*Department of General, Visceral and Transplantation Surgery, RWTH University Hospital Aachen, Germany,* [11]*Lane Fox Clinical Respiratory Physiology Research Centre Guy's and St. Thomas' NHS Foundation & King's College London (KCL) NIHR BRC, London,* [12]*Department of Renal Medicine and Transplantation, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, E1 1BB, UK,* [13]*Adult Critical Care Unit, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London, UK.*

Detailed methods

Study design

This study was not a pre-specified analysis of the initial IVC trial. The hypothesis that a raised urea-to-creatinine ratio (UCR) builds on previously published work in this area.[1,2] The incorporation of two methods (an unsupervised machine learning technique and a prespecified modelling approach) strengthened causal investigations and allowed mechanistic inferences to be made.

Trajectory clustering method

Data management first involved inspection of data completeness using base R functions and the *tidyverse* packages. UCR values were inspected for missingness. Over 99% of patients had 2 or more UCR values. Using an unsupervised machine learning technique, we performed k-means trajectory clustering based on repeated UCRs using the *kml* package.

Supplementary tables

Table S1

Cluster	A	B	C	p-value
Continuous Feed (%)	18 (40)	14 (35.9)	12 (70.1)	0.004
RRT (%)	6 (14.3)	28 (71.8)	3 (17.6)	<0.001
Age (mean (SD))	59.51 (14.51)	56.54 (14.59)	55.47 (18.12)	0.001
Apache (mean (SD))	22.05 (11.53)	22.34 (8.39)	19.00 (7.02)	<0.001
Total Patients	45	39	17	
Supplementary table 1. Breakdown of k-means cluster demographics. *The p values here test the null hypothesis that there is no difference in the number of patients receiving continuous feed or renal replacement therapy between the clusters, and that there is no difference in patient age, and Apache score between clusters. RRT – renal replacement therapy*				

Table S2

Secondary analysis linear mixed effects model results of total amino acid, essential amino acid, and individual amino acid plasma concentration against log urea-to-creatinine ratio for day 1 and day 7. LME (n = 84).

AA – amino acid concentration; EAA – essential amino acid concentration.

Variable	Coefficient	Standard error	t-value	p-value	95% CI	
Day 1 logUCR						
AA	0.000	0.000	-1.988	0.051	0.000	0.000
EAA	0.000	0.000	-1.800	0.076	-0.001	0.000
Glutamine	-0.002	0.001	-1.851	0.068	-0.003	0.000
Asparagine	-0.004	0.002	-2.097	0.039	-0.008	0.000
Citrulline	-0.002	0.003	-0.469	0.640	-0.008	0.005
Arginine	0.000	0.000	0.433	0.666	-0.001	0.000
Leucine	-0.001	0.001	-0.776	0.440	-0.003	0.001
Day 7 logUCR						
AA	0.000	0.000	0.851	0.399	0.000	0.000
EAA	0.000	0.000	1.574	0.122	0.000	0.001
Glutamine	0.000	0.001	0.130	0.897	-0.002	0.002
Asparagine	0.002	0.003	0.770	0.445	-0.004	0.008
Citrulline	0.001	0.004	0.187	0.852	-0.007	0.008
Arginine	0.000	0.000	0.123	0.903	-0.001	0.000
Leucine	0.002	0.001	1.199	0.236	-0.001	0.004

Supplementary figures

Figure S1
Patient flow chart.

Note due to practical issues associated with amino acid collection, storage, and transport not all patients included in the trial were able to have these levels analysed.

Figure S2 – Urea-to-creatinine ratio vs day boxplot from day 0 through to day 10 split by feeding regimen. The median is represented by the line dividing the box into two parts. The box represents the interquartile range, and the whiskers represent the range.
CF – continuous feed; IF – intermittent feed; UCR – urea-to-creatinine ratio

Number of patient's data available per day: 0 – 81, 1 – 104, 2 – 101, 3 – 97, 4 – 91, 5 – 88, 6 – 74, 7 – 67, 8 – 73, 9 – 69, 10 – 67
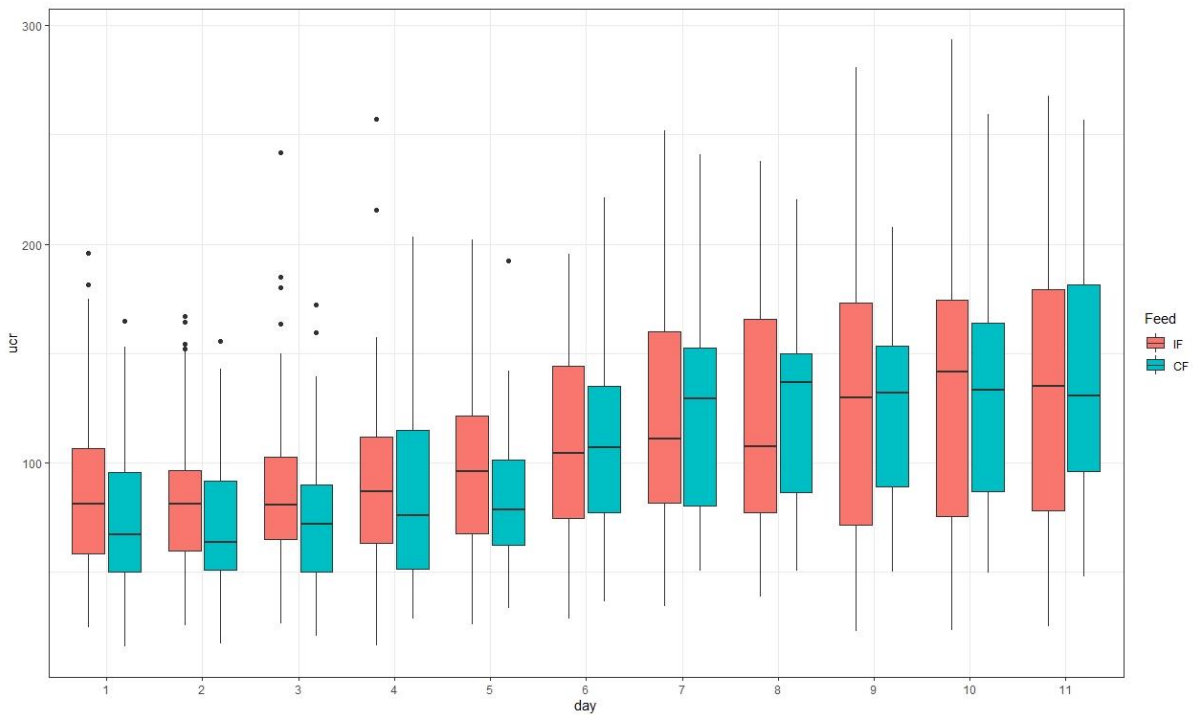

Figure S3 - Histograms of urea and creatinine measurements for each feeding regimen throughout the study.