

ADDITIONAL FILE 1

Increased ureagenesis revealing metabolic intolerance to enhanced nutrition in the PICU: a secondary analysis of the PEPaNIC RCT

Ilse Vanhorebeek,^{1*} Nazlı Umman Serin,^{1*} Sascha C.A.T. Verbruggen,² Koen F.M. Joosten,²

Greet Van den Berghe,^{1**} Jan Gunst^{1**}

¹ Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium; ² Division of Pediatric Intensive Care Unit, Department of Neonatal and Pediatric ICU, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands.

* Contributed equally, ** Contributed equally

TABLE OF CONTENTS

Table S1: Age-dependent reference values for creatinine

Table S2: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome

Table S3: Increased ureagenesis as a (partial) explanation of the increased risk of new infections with early-PN vs late-PN, penalizing for death

Table S4: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, including RRT patients

Table S5: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, excluding neonates

Table S6: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, infants vs older children

Table S7: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, boys vs girls

Table S8: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, patients with vs without day 2 hypophosphatemia

Table S9: Increased ureagenesis vs protein dose as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome

Figure S1: Directed acyclic graph for the multivariable models.

Figure S2: ROC curves for plasma urea and the plasma urea/creatinine ratio

Table S1: Age-dependent reference values for creatinine

Age	Reference range ($\mu\text{mol/L}$)	Mean of reference range ($\mu\text{mol/L}$)	Mean of reference range (mg/dL)
1 day	37-81	59.0	0.67
2 days	32-69	50.5	0.57
3 days	29-62	45.5	0.51
4 days	27-58	42.5	0.48
5 days	25-55	40.0	0.45
6 days	24-53	38.5	0.44
7 - 13 days	23-51	37.0	0.42
14 - 20 days	21-46	33.5	0.38
21 - 27 days	19-41	30.0	0.34
28 days - <2 months	17-37	27.0	0.31
2 - <3 months	15-33	24.0	0.27
3 - <4 months	15-30	22.5	0.25
4 - $\leq$ 12 months	14-32	23.0	0.26
>1 - $\leq$ 4 years	18-35	26.5	0.30
>4 - $\leq$ 13 years	31-68	49.5	0.56
>13 - <18 years	37-88	62.5	0.71

Reference value ranges for serum creatinine according to age were obtained from the *Erasmus MC Laboratory Diagnostics reference guide, Erasmus University Medical Center, Rotterdam, the Netherlands* (<https://www.erasmusmc.nl/nl-nl/laboratoriumdiagnostiek/bepalingenwijzer>). Mean creatinine values were calculated from those reference ranges. Concentrations in $\mu\text{mol/L}$ were divided by 88.4 for conversion to concentrations in mg/dL .

Table S2: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome

		aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.654 (1.148-2.383)	0.0063
	Model B. Randomization to early-PN versus late-PN	1.538 (1.063-2.227)	0.021
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.328 (1.117-1.588)	0.0011
UCR	Model A. Randomization to early-PN versus late-PN	1.716 (1.176-2.504)	0.0046
	Model B. Randomization to early-PN versus late-PN	1.378 (0.929-2.042)	0.10
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.746 (1.353-2.265)	<0.0001
Time to new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.582 (1.133-2.210)	0.0065
	Model B. Randomization to early-PN versus late-PN	1.502 (1.071-2.108)	0.017
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.153 (1.038-1.259)	0.010
UCR	Model A. Randomization to early-PN versus late-PN	1.647 (1.162-2.336)	0.0045
	Model B. Randomization to early-PN versus late-PN	1.362 (0.945-1.962)	0.095
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.498 (1.233-1.800)	<0.0001
Likelihood of earlier live PICU discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.856 (0.765-0.958)	0.0068
	Model B. Randomization to early-PN versus late-PN	0.936 (0.835-1.048)	0.25
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.590 (0.531-0.652)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.856 (0.765-0.958)	0.0068
	Model B. Randomization to early-PN versus late-PN	0.955 (0.849-1.075)	0.44
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.745 (0.671-0.824)	<0.0001
Likelihood of earlier live hospital discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.877 (0.782-0.982)	0.023
	Model B. Randomization to early-PN versus late-PN	0.946 (0.843-1.061)	0.33
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.618 (0.557-0.685)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.877 (0.782-0.982)	0.023
	Model B. Randomization to early-PN versus late-PN	0.947 (0.841-1.065)	0.36
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.778 (0.703-0.860)	<0.0001
90-day mortality			
Urea	Model A. Randomization to early-PN versus late-PN	1.419 (0.800-2.517)	0.22
	Model B. Randomization to early-PN versus late-PN	1.113 (0.612-2.025)	0.72
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.745 (1.384-2.219)	<0.0001

UCR	Model A. Randomization to early-PN versus late-PN	1.419 (0.800-2.517)	0.22
	Model B. Randomization to early-PN versus late-PN	1.187 (0.653-2.156)	0.57
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.432 (1.029-1.993)	0.033

Model A assessed the independent impact of early-PN (n=665) vs late-PN (n=663) on the respective outcomes in patients with urea and creatinine data available and not receiving RRT in the first week, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

Table S3: Increased ureagenesis as a (partial) explanation of the increased risk of new infections with early-PN vs late-PN

		aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.579 (1.115-2.236)	0.0094
	Model B. Randomization to early-PN versus late-PN	1.406 (0.984-2.007)	0.059
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.697 (1.413-2.057)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	1.607 (1.123-2.301)	0.0089
	Model B. Randomization to early-PN versus late-PN	1.309 (0.902-1.901)	0.15
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.710 (1.326-2.220)	<0.0001
Time to new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.446 (1.082-1.933)	0.012
	Model B. Randomization to early-PN versus late-PN	1.335 (0.994-1.793)	0.053
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.186 (1.099-1.270)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	1.469 (1.088-1.984)	0.011
	Model B. Randomization to early-PN versus late-PN	1.259 (0.917-1.728)	0.15
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.335 (1.121-1.573)	0.0016

Model A assessed the independent impact of early-PN (n=665) vs late-PN (n=663) on the respective outcomes in patients with urea and creatinine data available and not receiving RRT in the first week, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. In addition, however, we penalized for risk of death in the PICU, assigning a new infection on the day of death if the patient was not scored as having a new infection before. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

Table S4: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, including RRT patients

		aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.777 (1.243-2.541)	0.0014
	Model B. Randomization to early-PN versus late-PN	1.619 (1.126-2.328)	0.0087
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.326 (1.142-1.547)	0.0002
UCR	Model A. Randomization to early-PN versus late-PN	1.781 (1.234-2.570)	0.0018
	Model B. Randomization to early-PN versus late-PN	1.464 (1.001-2.143)	0.048
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.656 (1.299-2.126)	<0.0001
Time to new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.675 (1.210-2.320)	0.0016
	Model B. Randomization to early-PN versus late-PN	1.564 (1.123-2.177)	0.0074
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.164 (1.058-1.263)	0.0030
UCR	Model A. Randomization to early-PN versus late-PN	1.679 (1.200-2.349)	0.0021
	Model B. Randomization to early-PN versus late-PN	1.418 (0.999-2.014)	0.048
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.424 (1.192-1.681)	0.0002
Likelihood of earlier live PICU discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.838 (0.749-0.937)	0.0019
	Model B. Randomization to early-PN versus late-PN	0.915 (0.817-1.025)	0.12
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.640 (0.583-0.701)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.838 (0.749-0.937)	0.0019
	Model B. Randomization to early-PN versus late-PN	0.916 (0.815-1.030)	0.14
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.778 (0.703-0.859)	<0.0001
Likelihood of earlier live hospital discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.859 (0.767-0.963)	0.0088
	Model B. Randomization to early-PN versus late-PN	0.933 (0.832-1.046)	0.23
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.653 (0.594-0.715)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.859 (0.767-0.963)	0.0088
	Model B. Randomization to early-PN versus late-PN	0.913 (0.812-1.026)	0.12
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.815 (0.738-0.897)	<0.0001
90-day mortality			
Urea	Model A. Randomization to early-PN versus late-PN	1.586 (0.925-2.721)	0.090
	Model B. Randomization to early-PN versus late-PN	1.236 (0.706-2.164)	0.45
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.524 (1.254-1.862)	<0.0001

UCR	Model A. Randomization to early-PN versus late-PN	1.586 (0.925-2.721)	0.090
	Model B. Randomization to early-PN versus late-PN	1.455 (0.831-2.545)	0.18
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.201 (0.876-1.630)	0.24

Model A assessed the independent impact of early-PN (n=681) vs late-PN (n=675) on the respective outcomes in patients with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

Table S5: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, excluding neonates

		aOR/aHR (95% CI)	P
Risk of new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.629 (1.071-2.476)	0.021
	Model B. Randomization to early-PN versus late-PN	1.551 (1.016-2.367)	0.040
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.299 (1.080-1.577)	0.0050
UCR	Model A. Randomization to early-PN versus late-PN	1.717 (1.106-2.668)	0.014
	Model B. Randomization to early-PN versus late-PN	1.459 (0.930-2.290)	0.097
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.748 (1.314-2.345)	0.0001
Time to new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.584 (1.075-2.335)	0.018
	Model B. Randomization to early-PN versus late-PN	1.522 (1.030-2.251)	0.033
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.135 (1.012-1.248)	0.032
UCR	Model A. Randomization to early-PN versus late-PN	1.678 (1.112-2.532)	0.012
	Model B. Randomization to early-PN versus late-PN	1.443 (0.947-2.199)	0.085
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.500 (1.208-1.835)	0.0004
Likelihood of earlier live PICU discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.884 (0.783-0.998)	0.046
	Model B. Randomization to early-PN versus late-PN	0.939 (0.831-1.062)	0.31
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.580 (0.518-0.646)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.884 (0.783-0.998)	0.046
	Model B. Randomization to early-PN versus late-PN	0.968 (0.854-1.098)	0.61
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.751 (0.671-0.837)	<0.0001
Likelihood of earlier live hospital discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.879 (0.777-0.993)	0.038
	Model B. Randomization to early-PN versus late-PN	0.922 (0.816-1.043)	0.19
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.613 (0.547-0.684)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.879 (0.777-0.993)	0.038
	Model B. Randomization to early-PN versus late-PN	0.941 (0.830-1.067)	0.34
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.773 (0.693-0.860)	<0.0001
90-day mortality			
Urea	Model A. Randomization to early-PN versus late-PN	1.147 (0.608-2.162)	0.67
	Model B. Randomization to early-PN versus late-PN	0.908 (0.467-1.767)	0.77
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.663 (1.302-2.152)	<0.0001

UCR	Model A. Randomization to early-PN versus late-PN	1.147 (0.608-2.162)	0.67
	Model B. Randomization to early-PN versus late-PN	0.988 (0.513-1.904)	0.97
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.407 (0.975-2.019)	0.067

Model A assessed the independent impact of early-PN (n=575) vs late-PN (563) on the respective outcomes in patients older than 28 days not receiving RRT in the first week with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

Table S6: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, infants vs older children

		Infants		Children	
		aOR/aHR (95% CI)	P	aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	1.746 (1.066-2.860)	0.025	1.615 (0.913-2.855)	0.096
	Model B. Randomization to early-PN versus late-PN	1.416 (0.849-2.362)	0.18	1.580 (0.891-2.800)	0.11
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.964 (1.408-2.775)	<0.0001	1.120 (0.919-1.376)	0.25
UCR	Model A. Randomization to early-PN versus late-PN	1.752 (1.055-2.909)	0.028	1.823 (0.997-3.332)	0.047
	Model B. Randomization to early-PN versus late-PN	1.261 (0.712-2.233)	0.42	1.575 (0.851-2.914)	0.14
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.913 (1.165-3.195)	0.010	1.632 (1.193-2.261)	0.0022
Time to new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	1.611 (1.033-2.512)	0.033	1.534 (0.907-2.596)	0.10
	Model B. Randomization to early-PN versus late-PN	1.362 (0.863-2.150)	0.18	1.518 (0.896-2.574)	0.11
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.559 (1.232-1.938)	0.0004	1.064 (0.906-1.200)	0.40
UCR	Model A. Randomization to early-PN versus late-PN	1.629 (1.030-2.578)	0.034	1.750 (1.000-3.064)	0.047
	Model B. Randomization to early-PN versus late-PN	1.286 (0.774-2.137)	0.33	1.518 (0.855-2.695)	0.15
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.534 (1.058-2.177)	0.024	1.410 (1.111-1.756)	0.0059
Likelihood of earlier live PICU discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.772 (0.652-0.914)	0.0027	0.878 (0.753-1.024)	0.097
	Model B. Randomization to early-PN versus late-PN	0.904 (0.759-1.077)	0.25	0.909 (0.780-1.061)	0.22
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.565 (0.478-0.662)	<0.0001	0.608 (0.529-0.694)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.772 (0.652-0.914)	0.0027	0.878 (0.753-1.024)	0.097
	Model B. Randomization to early-PN versus late-PN	0.895 (0.741-1.080)	0.24	0.952 (0.814-1.114)	0.54
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.708 (0.577-0.862)	0.0005	0.746 (0.658-0.841)	<0.0001
Likelihood of earlier live hospital discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.810 (0.682-0.961)	0.015	0.918 (0.786-1.072)	0.28
	Model B. Randomization to early-PN versus late-PN	0.946 (0.791-1.130)	0.53	0.949 (0.813-1.107)	0.50
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.552 (0.465-0.650)	<0.0001	0.660 (0.576-0.749)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.810 (0.682-0.961)	0.015	0.918 (0.786-1.072)	0.28
	Model B. Randomization to early-PN versus late-PN	0.919 (0.760-1.111)	0.38	0.976 (0.834-1.142)	0.76
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.726 (0.587-0.892)	0.0021	0.766 (0.680-0.860)	<0.0001
90-day mortality					
Urea	Model A. Randomization to early-PN versus late-PN	2.236 (0.893-5.598)	0.076	1.073 (0.487-2.365)	0.86
	Model B. Randomization to early-PN versus late-PN	1.688(0.659-4.328)	0.26	0.854 (0.371-1.967)	0.71
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	2.375 (1.452-3.970)	0.0006	1.538 (1.178-2.063)	0.0008
UCR	Model A. Randomization to early-PN versus late-PN	2.236 (0.893-5.598)	0.076	1.073 (0.487-2.365)	0.86
	Model B. Randomization to early-PN versus late-PN	2.140 (0.800-5.726)	0.12	0.884 (0.388-2.013)	0.76
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.091 (0.542-2.286)	0.80	1.421 (0.958-2.116)	0.079

Model A assessed the independent impact of early-PN vs late-PN on the respective outcomes in patients not receiving RRT in the first week with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). Analyses were split up for infants (<1 year, 305 early-PN, 299 late-PN) versus older children (<1 year, 360 early-PN, 364 late-PN). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

Table S7: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, boys versus girls

		Boys		Girls	
		aOR/aHR (95% CI)	P	aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	1.290 (0.804-2.068)	0.28	2.695 (1.445-5.025)	0.0012
	Model B. Randomization to early-PN versus late-PN	1.218 (0.755-1.965)	0.41	2.378 (1.263-4.479)	0.0057
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.286 (1.045-1.626)	0.017	1.500 (1.127-1.990)	0.0062
UCR	Model A. Randomization to early-PN versus late-PN	1.164 (0.714-1.897)	0.54	3.380 (1.747-6.540)	0.0001
	Model B. Randomization to early-PN versus late-PN	0.995 (0.599-1.654)	0.98	2.086 (1.037-4.195)	0.034
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.523 (1.101-2.109)	0.011	3.086 (1.846-5.343)	<0.0001
Time to new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	1.287 (0.836-1.982)	0.25	2.334 (1.335-4.078)	0.0020
	Model B. Randomization to early-PN versus late-PN	1.229 (0.794-1.904)	0.35	2.088 (1.184-3.681)	0.0087
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.155 (1.002-1.295)	0.046	1.404 (1.111-1.726)	0.0061
UCR	Model A. Randomization to early-PN versus late-PN	1.168 (0.745-1.831)	0.49	3.018 (1.648-5.526)	0.0001
	Model B. Randomization to early-PN versus late-PN	1.011 (0.632-1.617)	0.96	1.968 (1.032-3.751)	0.034
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.412 (1.074-1.817)	0.014	2.275 (1.562-3.280)	<0.0001
Likelihood of earlier live PICU discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.833 (0.717-0.967)	0.016	0.873 (0.733-1.040)	0.12
	Model B. Randomization to early-PN versus late-PN	0.889 (0.764-1.035)	0.12	0.994 (0.833-1.186)	0.94
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.608 (0.528-0.695)	<0.0001	0.556 (0.471-0.649)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.833 (0.717-0.967)	0.016	0.873 (0.733-1.040)	0.12
	Model B. Randomization to early-PN versus late-PN	0.909 (0.778-1.062)	0.22	1.029 (0.852-1.242)	0.76
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.765 (0.669-0.869)	<0.0001	0.672 (0.563-0.798)	<0.0001
Likelihood of earlier live hospital discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.895 (0.769-1.041)	0.15	0.852 (0.714-1.016)	0.075
	Model B. Randomization to early-PN versus late-PN	0.957 (0.821-1.115)	0.57	0.933 (0.781-1.114)	0.44
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.603 (0.521-0.694)	<0.0001	0.636 (0.544-0.735)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.895 (0.769-1.041)	0.15	0.852 (0.714-1.016)	0.075
	Model B. Randomization to early-PN versus late-PN	0.962 (0.824-1.124)	0.62	0.928 (0.769-1.119)	0.43
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.753 (0.658-0.858)	<0.0001	0.809 (0.686-0.948)	0.0083
90-day mortality					
Urea	Model A. Randomization to early-PN versus late-PN	1.268 (0.565-2.847)	0.56	1.641 (0.690-3.902)	0.25
	Model B. Randomization to early-PN versus late-PN	0.998 (0.430-2.315)	0.99	1.202 (0.474-3.049)	0.69
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.416 (1.082-1.949)	0.0091	2.352 (1.643-3.530)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	1.268 (0.565-2.847)	0.56	1.641 (0.690-3.902)	0.25
	Model B. Randomization to early-PN versus late-PN	0.988 (0.424-2.305)	0.97	1.545 (0.620-3.850)	0.34
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.557 (1.044-2.375)	0.030	1.162 (0.548-2.337)	0.68

Model A assessed the independent impact of early-PN vs late-PN on the respective outcomes in patients not receiving RRT in the first week with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). Analyses were split up for boys (376 early-PN, 382 late-PN) versus girls (289 early-PN, 281 late-PN). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection.^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values.^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT, renal replacement therapy, UCR: urea/creatinine ratio.

Table S8: Increased ureagenesis as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome, patients with vs without day 2 hypophosphatemia

		Hypophosphatemia on day 2		No hypophosphatemia on day 2	
		aOR/aHR (95% CI)	P	aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	3.090 (1.084-8.807)	0.022	1.496 (0.972-2.302)	0.066
	Model B. Randomization to early-PN versus late-PN	2.824 (0.979-8.149)	0.039	1.383 (0.893-2.142)	0.14
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.352 (0.826-2.163)	0.21	1.278 (1.051-1.574)	0.012
UCR	Model A. Randomization to early-PN versus late-PN	2.841 (1.004-8.041)	0.034	1.530 (0.980-2.391)	0.060
	Model B. Randomization to early-PN versus late-PN	2.538 (0.887-7.258)	0.064	1.266 (0.789-2.030)	0.32
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	2.062 (1.123-3.904)	0.019	1.510 (1.099-2.094)	0.011
Time to new infection in the PICU					
Urea	Model A. Randomization to early-PN versus late-PN	2.572 (0.966-6.850)	0.039	1.530 (1.019-2.298)	0.039
	Model B. Randomization to early-PN versus late-PN	2.404 (0.893-6.472)	0.060	1.426 (0.943-2.156)	0.091
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.241 (0.785-1.791)	0.32	1.136 (1.004-1.259)	0.043
UCR	Model A. Randomization to early-PN versus late-PN	2.507 (0.942-6.673)	0.044	1.526 (1.016-2.293)	0.040
	Model B. Randomization to early-PN versus late-PN	2.248 (0.843-5.992)	0.080	1.310 (0.851-2.015)	0.21
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.779 (1.081-2.933)	0.024	1.335 (1.041-1.681)	0.024
Likelihood of earlier live PICU discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.621 (0.473-0.815)	0.0007	0.902 (0.778-1.046)	0.17
	Model B. Randomization to early-PN versus late-PN	0.703 (0.530-0.932)	0.015	1.012 (0.870-1.176)	0.88
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.641 (0.490-0.815)	0.0001	0.609 (0.537-0.686)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.621 (0.473-0.815)	0.0007	0.902 (0.778-1.046)	0.17
	Model B. Randomization to early-PN versus late-PN	0.669 (0.504-0.888)	0.0060	1.022 (0.874-1.196)	0.78
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.807 (0.651-0.992)	0.041	0.724 (0.628-0.831)	<0.0001
Likelihood of earlier live hospital discharge					
Urea	Model A. Randomization to early-PN versus late-PN	0.816 (0.621-1.070)	0.14	0.888 (0.763-1.033)	0.12
	Model B. Randomization to early-PN versus late-PN	0.907 (0.688-1.197)	0.49	0.972 (0.834-1.133)	0.71
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.554 (0.418-0.714)	<0.0001	0.643 (0.568-0.724)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.816 (0.621-1.070)	0.14	0.888 (0.763-1.033)	0.12
	Model B. Randomization to early-PN versus late-PN	0.854 (0.647-1.126)	0.26	0.963 (0.823-1.128)	0.64
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.806 (0.648-0.990)	0.039	0.785 (0.681-0.900)	0.0004
90-day mortality					
Urea	Model A. Randomization to early-PN versus late-PN	14.761 (1.710-127.434)	0.0022	0.974 (0.484-1.961)	0.94
	Model B. Randomization to early-PN versus late-PN	33.886 (1.654-694.321)	0.0022	0.711 (0.339-1.490)	0.36
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	3.953 (1.863-10.062)	<0.0001	1.618 (1.254-2.132)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	14.761 (1.710-127.434)	0.0022	0.974 (0.484-1.961)	0.94

Model B. Randomization to early-PN versus late-PN	16.394 (1.762-152.522)	0.0020	0.740 (0.347-1.575)	0.43
Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.799 (0.316-1.909)	0.61	1.575 (1.033-2.403)	0.035

Model A assessed the independent impact of early-PN vs late-PN on the respective outcomes in patients not receiving RRT in the first week with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). Analyses were split up for patients with hypophosphatemia on day 2 (188 early-PN, 114 late-PN) versus patients without hypophosphatemia on day 2 (374 early-PN, 431 late-PN). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT, renal replacement therapy, UCR: urea/creatinine ratio.

Table S9: Increased ureagenesis vs protein dose as a (partial) explanation of the harm by early-PN vs late-PN to clinical outcome

		aOR/aHR (95% CI)	P
Risk of acquiring a new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.654 (1.148-2.383)	0.0063
	Model B. Randomization to early-PN versus late-PN	1.538 (1.063-2.227)	0.021
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.328 (1.117-1.588)	0.0011
	Model C. Randomization to early-PN versus late-PN	0.841 (0.510-1.385)	0.49
	Model C. Average daily protein dose up to day max urea (per g added)	1.893 (1.390-2.589)	<0.0001
	Model D. Randomization to early-PN versus late-PN	0.777 (0.467-1.293)	0.33
	Model D. Average daily protein dose up to day max urea (per g added)	1.894 (1.386-2.597)	<0.0001
	Model D. Max plasma urea first week (per 30 mg/dL added) ^a	1.313 (1.111-1.568)	0.0013
UCR	Model A. Randomization to early-PN versus late-PN	1.716 (1.176-2.504)	0.0046
	Model B. Randomization to early-PN versus late-PN	1.378 (0.929-2.042)	0.10
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.746 (1.353-2.265)	<0.0001
	Model C. Randomization to early-PN versus late-PN	0.865 (0.515-1.455)	0.58
	Model C. Average daily protein dose up to day max urea (per g added)	1.850 (1.357-2.531)	0.0001
	Model D. Randomization to early-PN versus late-PN	0.809 (0.477-1.371)	0.42
	Model D. Average daily protein dose up to day max urea (per g added)	1.650 (1.199-2.276)	0.0021
	Model D. Max plasma UCR first week (per 30 mg/dL added) ^a	1.606 (1.239-2.087)	0.0004
Time to new infection in the PICU			
Urea	Model A. Randomization to early-PN versus late-PN	1.582 (1.133-2.210)	0.0065
	Model B. Randomization to early-PN versus late-PN	1.502 (1.071-2.108)	0.017
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.153 (1.038-1.259)	0.010
	Model C. Randomization to early-PN versus late-PN	0.887 (0.567-1.387)	0.59
	Model C. Average daily protein dose up to day max urea (per g added)	1.743 (1.325-2.290)	<0.0001
	Model D. Randomization to early-PN versus late-PN	0.826 (0.525-1.299)	0.40
	Model D. Average daily protein dose up to day max urea (per g added)	1.762 (1.340-2.314)	<0.0001
	Model D. Max plasma urea first week (per 30 mg/dL added) ^a	1.179 (1.051-1.298)	0.0070
UCR	Model A. Randomization to early-PN versus late-PN	1.647 (1.162-2.336)	0.0045
	Model B. Randomization to early-PN versus late-PN	1.362 (0.945-1.962)	0.095
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.498 (1.233-1.800)	<0.0001
	Model C. Randomization to early-PN versus late-PN	0.907 (0.565-1.454)	0.68
	Model C. Average daily protein dose up to day max urea (per g added)	1.720 (1.302-2.272)	0.0001
	Model D. Randomization to early-PN versus late-PN	0.846 (0.525-1.365)	0.49
	Model D. Average daily protein dose up to day max urea (per g added)	1.568 (1.182-2.081)	0.0018

	Model D. Max plasma UCR first week (per 30 mg/dL added) ^a	1.431 (1.160-1.741)	0.0011
Likelihood of earlier live PICU discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.856 (0.765-0.958)	0.0068
	Model B. Randomization to early-PN versus late-PN	0.936 (0.835-1.048)	0.25
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.590 (0.531-0.652)	<0.0001
	Model C. Randomization to early-PN versus late-PN	1.278 (1.091-1.498)	0.0025
	Model C. Average daily protein dose up to day max urea (per g added)	0.695 (0.626-0.771)	<.0001
	Model D. Randomization to early-PN versus late-PN	1.353 (1.154-1.585)	0.0002
	Model D. Average daily protein dose up to day max urea (per g added)	0.712 (0.641-0.789)	<0.0001
	Model D. Max plasma urea first week (per 30 mg/dL added) ^a	0.602 (0.543-0.665)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.856 (0.765-0.958)	0.0068
	Model B. Randomization to early-PN versus late-PN	0.955 (0.849-1.075)	0.44
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.745 (0.671-0.824)	<0.0001
	Model C. Randomization to early-PN versus late-PN	1.280 (1.091-1.501)	0.0025
	Model C. Average daily protein dose up to day max urea (per g added)	0.703 (0.635-0.778)	<0.0001
	Model D. Randomization to early-PN versus late-PN	1.318 (1.123-1.547)	0.0007
	Model D. Average daily protein dose up to day max urea (per g added)	0.738 (0.665-0.818)	<0.0001
	Model D. Max plasma UCR first week (per 30 mg/dL added) ^a	0.796 (0.717-0.881)	<0.0001
Likelihood of earlier live hospital discharge			
Urea	Model A. Randomization to early-PN versus late-PN	0.877 (0.782-0.982)	0.023
	Model B. Randomization to early-PN versus late-PN	0.946 (0.843-1.061)	0.33
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	0.618 (0.557-0.685)	<0.0001
	Model C. Randomization to early-PN versus late-PN	1.211 (1.033-1.421)	0.018
	Model C. Average daily protein dose up to day max urea (per g added)	0.742 (0.667-0.824)	<0.0001
	Model D. Randomization to early-PN versus late-PN	1.236 (1.055-1.449)	0.009
	Model D. Average daily protein dose up to day max urea (per g added)	0.776 (0.698-0.862)	<0.0001
	Model D. Max plasma urea first week (per 30 mg/dL added) ^a	0.633 (0.571-0.700)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	0.877 (0.782-0.982)	0.023
	Model B. Randomization to early-PN versus late-PN	0.947 (0.841-1.065)	0.36
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	0.778 (0.703-0.860)	<0.0001
	Model C. Randomization to early-PN versus late-PN	1.195 (1.019-1.400)	0.028
	Model C. Average daily protein dose up to day max urea (per g added)	0.756 (0.682-0.837)	<0.0001
	Model D. Randomization to early-PN versus late-PN	1.208 (1.031-1.416)	0.019
	Model D. Average daily protein dose up to day max urea (per g added)	0.790 (0.712-0.877)	<0.0001
	Model D. Max plasma UCR first week (per 30 mg/dL added) ^a	0.818 (0.738-0.904)	<0.0001

90-day mortality			
Urea	Model A. Randomization to early-PN versus late-PN	1.419 (0.800-2.517)	0.22
	Model B. Randomization to early-PN versus late-PN	1.113 (0.612-2.025)	0.72
	Model B. Max plasma urea first week (per 30 mg/dL added) ^a	1.745 (1.384-2.219)	<0.0001
	Model C. Randomization to early-PN versus late-PN	1.144 (0.552-2.371)	0.71
	Model C. Average daily protein dose up to day max urea (per g added)	1.247 (0.782-1.962)	0.34
	Model D. Randomization to early-PN versus late-PN	0.883 (0.410-1.905)	0.75
	Model D. Average daily protein dose up to day max urea (per g added)	1.266 (0.774-2.040)	0.34
	Model D. Max plasma urea first week (per 30 mg/dL added) ^a	1.741 (1.381-2.217)	<0.0001
UCR	Model A. Randomization to early-PN versus late-PN	1.419 (0.800-2.517)	0.22
	Model B. Randomization to early-PN versus late-PN	1.187 (0.653-2.156)	0.57
	Model B. Max plasma UCR first week (per 30 units added) ^{a,b}	1.432 (1.029-1.993)	0.033
	Model C. Randomization to early-PN versus late-PN	1.120 (0.535-2.345)	0.76
	Model C. Average daily protein dose up to day max urea (per g added)	1.264 (0.794-1.990)	0.31
	Model D. Randomization to early-PN versus late-PN	1.039 (0.493-2.191)	0.91
	Model D. Average daily protein dose up to day max urea (per g added)	1.150 (0.713-1.829)	0.56
	Model D. Max plasma UCR first week (per 30 mg/dL added) ^a	1.405 (1.001-1.967)	0.049

Model A assessed the independent impact of early-PN (n=665) vs late-PN (n=663) on the respective outcomes in patients not receiving RRT in the first week with urea and creatinine data available, adjusting for center, age, type of illness, severity of illness (PIM3 and PeLOD scores) and severity of malnutrition risk (dichotomized STRONGkids score). In model B, the first week's maximal value of urea or UCR was added to assess potential mediation of any harm by early-PN. For the risk of acquiring a new infection in the PICU, a left-truncation approach was applied, considering patients who acquired a new infection before the day of the maximal urea or UCR in the first week as having no new infection. ^a aOR and aHR are expressed per 30 mg/dL urea or per 30 units UCR increase for better visualization, corresponding to roughly the day 1 values. ^b The UCR was calculated as the ratio of urea over an age-normalized creatinine value (i.e. creatinine concentration divided by the arithmetic mean of the normal range for the age of the patient).

Abbreviations: aHR: adjusted hazard ratio, aOR: adjusted odds ratio, CI: confidence interval, PeLOD: pediatric logistic organ dysfunction score, PICU: pediatric intensive care unit, PIM3: pediatric index of mortality 3 score, PN: parenteral nutrition, STRONGkids: screening tool for risk on nutritional status and growth, RRT: renal replacement therapy, UCR: urea/creatinine ratio.

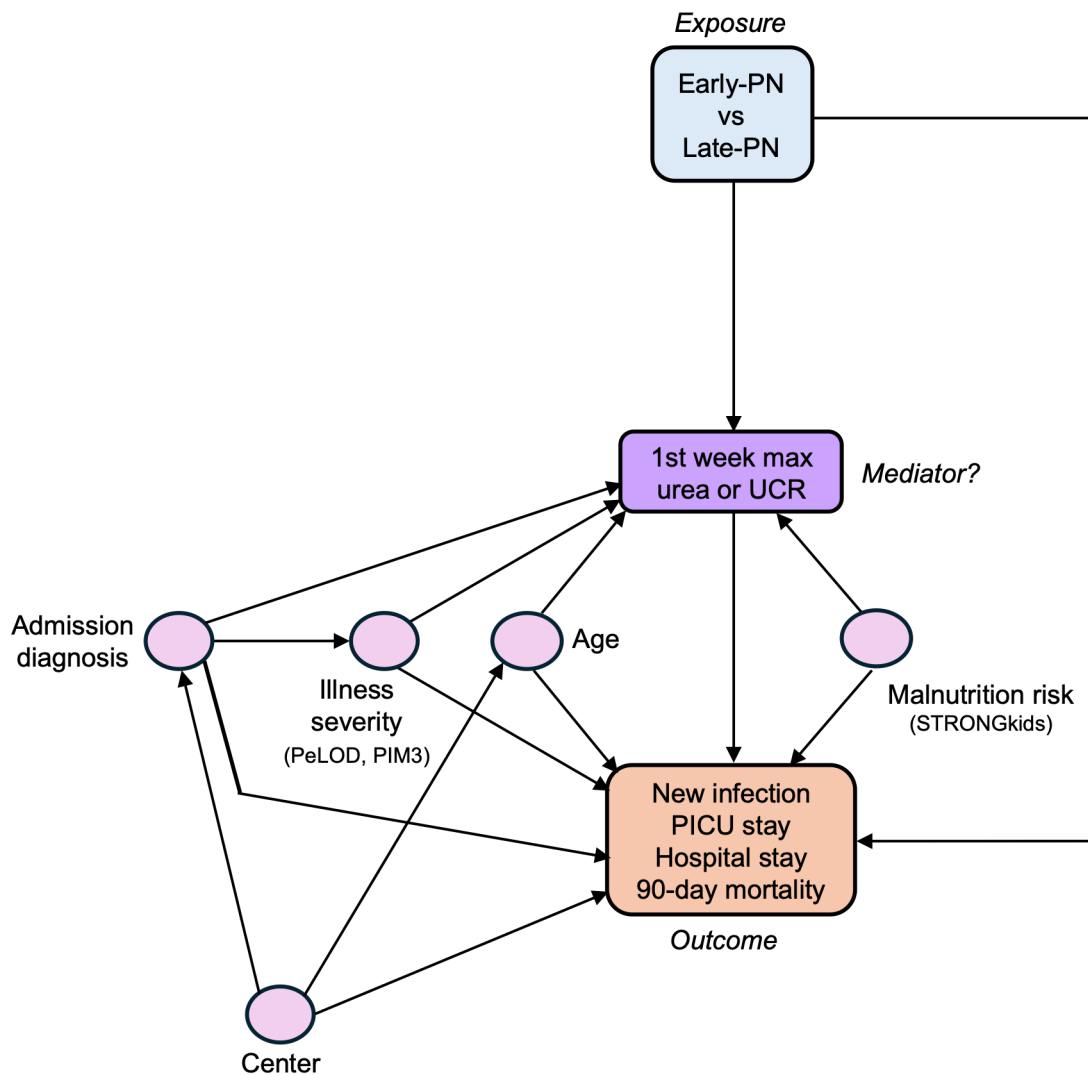


Figure S1: Directed acyclic graph for the multivariable models. The exposure is the randomized intervention early-PN versus late-PN. Investigated outcomes include likelihood of a new infection (studied as risk for the event and time to the event), likelihood of earlier live PICU or hospital discharge and 90-day mortality. Potential confounders are indicated by the pink nodes, and arrows indicate potential causal paths. The maximum urea or UCR in the first week in the PICU was studied as a potential mediator of the harm by early-PN versus late-PN on clinical outcome.

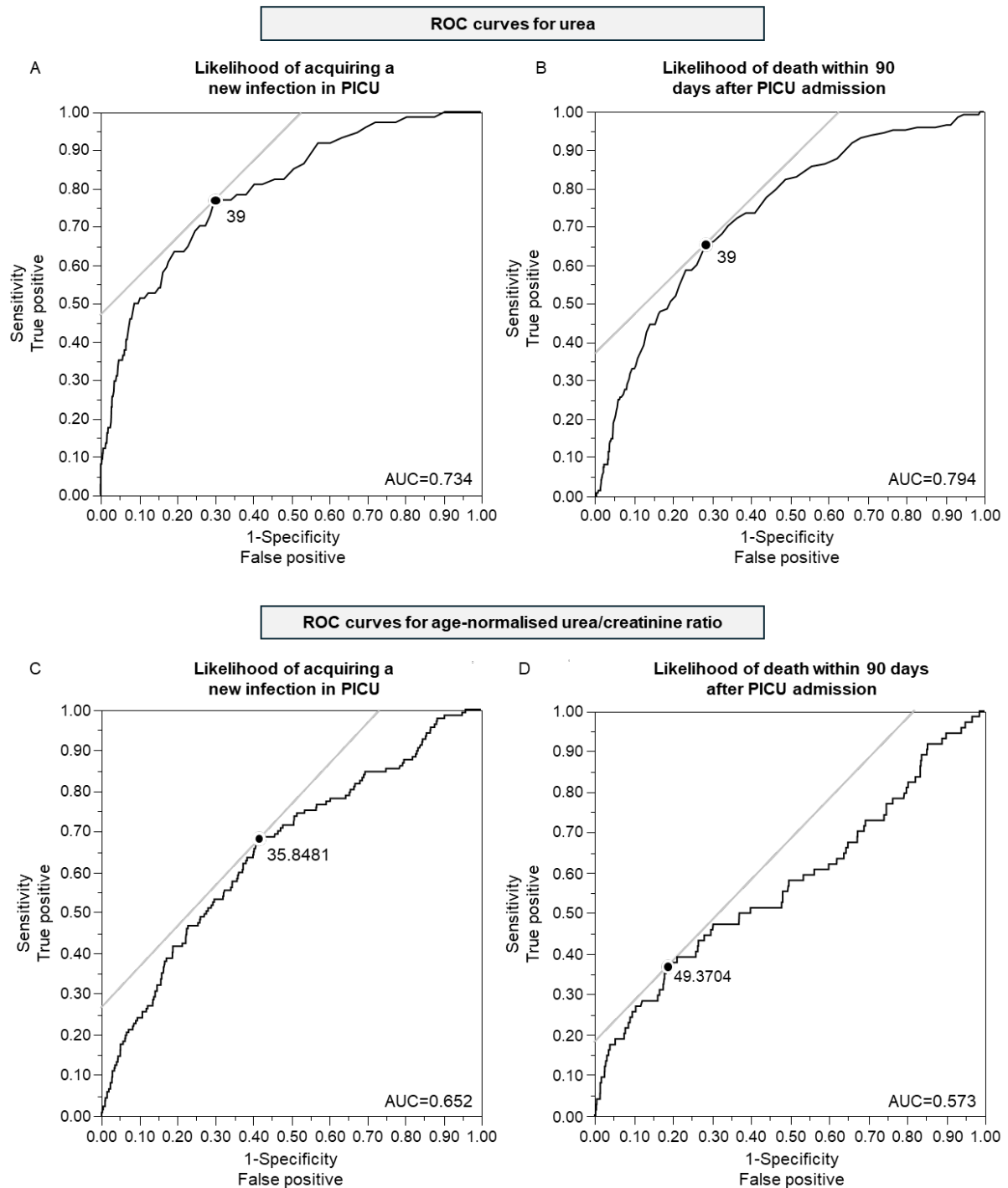


Figure S2: Receiver operating characteristic (ROC) curves for urea and the age-normalized urea/creatinine ratio (UCR) in the first week after PICU admission for prediction of adverse outcomes. (A) ROC curve for maximum urea in the first week predicting likelihood of acquiring a new infection in the PICU. (B) ROC curve for maximum urea in the first week predicting likelihood of death within 90 days after PICU admission. (C) ROC curve for maximum age-normalized UCR in the first week predicting likelihood of acquiring a new infection in the PICU. (D) ROC curve for maximum age-normalized UCR in the first week predicting likelihood of death within 90 days after PICU admission. The dots indicated on the curves represent the optimal cut-off values maximizing sensitivity and specificity.

Abbreviations: AUC: area under the curve, PICU: pediatric intensive care unit, ROC: receiver operating characteristic, UCR: urea/creatinine ratio