

Prevalence and prognostic value of abnormal liver test results in critically ill children and the impact of delaying parenteral nutrition

Supplemental file

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Supplementary Figure 1: Daily plasma total bilirubin concentrations in neonates and patients aged between 28 days and 17 years

Supplementary Figure 2: Propensity score matching consort diagram and matching criteria

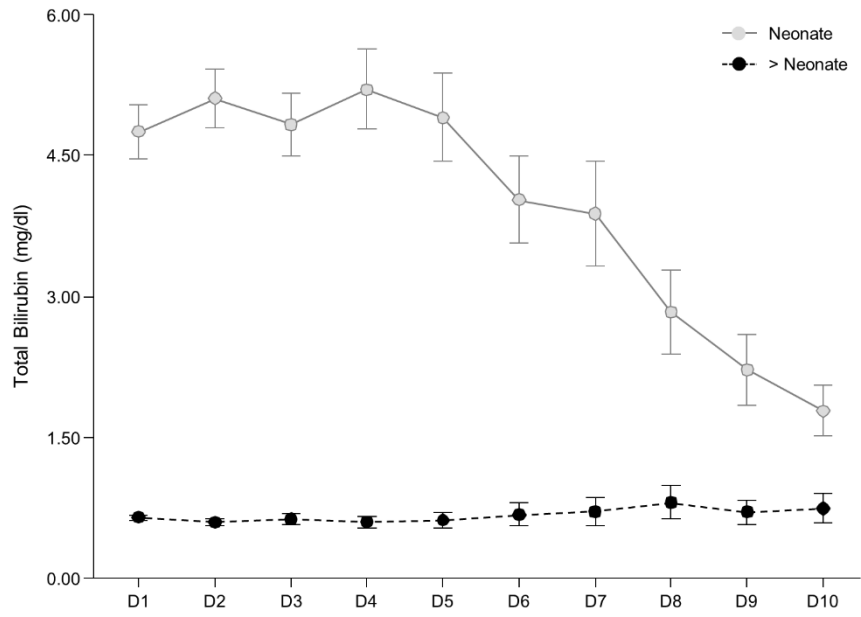
Supplementary Table 1A-N: Baseline characteristics of matched subsets

Supplementary Figure 3: Relation between plasma ALP concentrations and PICU mortality

Supplementary Figure 4: Relation between plasma γ GT concentrations and PICU mortality

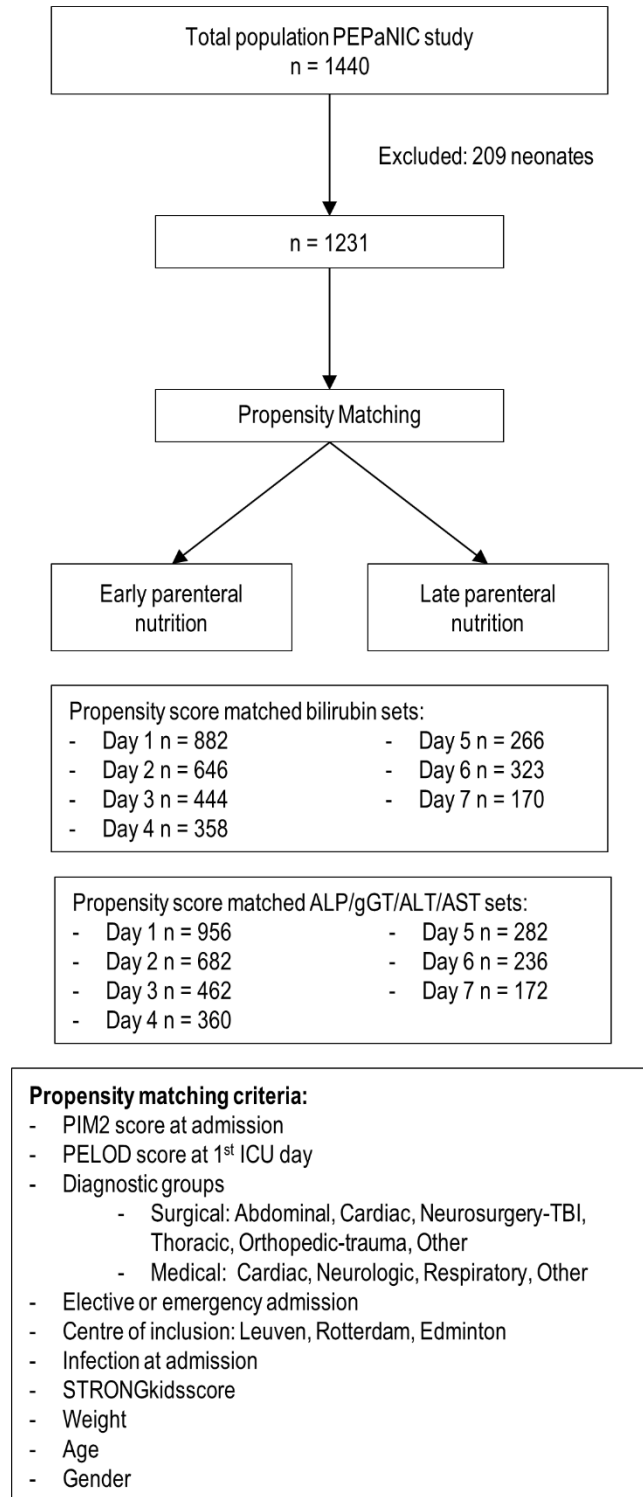
Supplementary Figure 5: Relation between plasma ALT concentrations and PICU mortality

Supplementary Figure 6: Relation between plasma AST concentrations and PICU mortality



Supplemental Figure 1: Daily plasma total bilirubin concentrations of all patients still in the PICU.

Grey dots present 209 neonates (<28 days old), black dots represent 1231 patients aged between 28 days and 17 years. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.



Supplement Figure 2: Propensity score matching diagram and matching criteria.

	Early PN group (n=441)	Late PN group (n=441)	P-value
Baseline characteristics			
Gender - male (n, %)	247 (56%)	250 (56.7%)	0.83
Age - years (median + IQR)	2.8 [0.5-7.6]	2.7 [0.5-8.4]	0.65
Weight - kg (median + IQR)	13.2 [6.8-22.2]	13 [6.4-24.8]	0.70
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.19
Centre			0.69
Leuven (n, %)	327 (74.1%)	330 (74.8%)	
Rotterdam (n, %)	107 (24.3%)	101 (22.9%)	
Edmonton (n, %)	7 (1.6%)	10 (2.3%)	
Emergency admission (n, %)	180 (40.8%)	181 (41%)	0.94
PIM2 probability of death ^b (median + IQR)	0.05 [0.02-0.18]	0.05 [0.02-0.16]	0.65
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	22 [12-32]	0.88
Diagnostic category (n, %)			0.82
Surgical			
Abdominal	14 (3.2%)	15 (3.4%)	
Cardiac	205 (46.5%)	201 (45.6%)	
Neurosurgery-TBI	46 (10.4%)	39 (8.8%)	
Thoracic	19 (4.3%)	17 (3.9%)	
Orthopedic-trauma	26 (5.9%)	22 (5%)	
Other	18 (4.1%)	32 (7.3%)	
Medical			
Cardiac	13 (2.9%)	14 (3.2%)	
Neurologic	30 (6.8%)	30 (6.8%)	
Respiratory	37 (8.4%)	38 (8.6%)	
Other	33 (7.5%)	33 (7.5%)	
Infection at admission (n, %)	152 (34.5%)	145 (32.9%)	0.61
Liver parameters			
Total plasma bilirubin day 1 - mg/dL (mean±SE)	0.62 ± 0.04	0.68 ± 0.04	0.03

Supplemental Table 1A: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 1 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=323)	Late PN group (n=323)	P-value
Baseline characteristics			
Gender - male (n, %)	186 (57.6%)	191 (59.1%)	0.69
Age - years (median + IQR)	1.9 [0.4-6.4]	1.9 [0.4-7.3]	0.62
Weight - kg (median + IQR)	12 [6.5-21.5]	11.5 [5.5-22]	0.69
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.07
Centre			0.96
Leuven (n, %)	225 (69.7%)	228 (70.6%)	
Rotterdam (n, %)	94 (29.1%)	91 (28.2%)	
Edmonton (n, %)	4 (1.2%)	4 (1.2%)	
Emergency admission (n, %)	154 (47.7%)	157 (48.6%)	0.81
PIM2 probability of death ^b (median + IQR)	0.07 [0.03-0.24]	0.07 [0.04-0.19]	0.56
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	13 [12-32]	0.80
Diagnostic category (n, %)			0.58
Surgical			
Abdominal	6 (1.9%)	12 (3.7%)	
Cardiac	146 (45.2%)	150 (46.4%)	
Neurosurgery-TBI	30 (9.3%)	21 (6.5%)	
Thoracic	10 (3.1%)	9 (2.8%)	
Orthopedic-trauma	18 (5.6%)	10 (3.1%)	
Other	12 (3.7%)	18 (5.6%)	
Medical			
Cardiac	13 (4%)	11 (3.4%)	
Neurologic	28 (8.7%)	29 (9%)	
Respiratory	32 (9.9%)	32 (9.9%)	
Other	28 (8.7%)	31 (9.6%)	
Infection at admission (n, %)	135 (41.8%)	131 (40.6%)	0.74
Liver parameters			
Plasma total bilirubin day 2 - mg/dL (mean±SE)	0.49 ± 0.03	0.7 ± 0.07	<0.01

Supplemental Table 1B: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 2 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=222)	Late PN group (n=222)	P-value
Baseline characteristics			
Gender - male (n, %)	122 (55%)	128 (57.7%)	0.56
Age - years (median + IQR)	1.6 [0.3-5.8]	1.5 [0.3-6.1]	0.95
Weight - kg (median + IQR)	10.3 [5.3-19.2]	5 [10.7-20.5]	0.97
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.77
Centre			0.47
Leuven (n, %)	149 (67.1%)	151 (68%)	
Rotterdam (n, %)	71 (32%)	66 (29.7%)	
Edmonton (n, %)	2 (0.9%)	5 (2.3%)	
Emergency admission (n, %)	115 (51.8%)	119 (53.6%)	0.70
PIM2 probability of death ^b (median + IQR)	0.09 [0.37-0.27]	0.1 [0.05-0.23]	0.90
PELOD score ^c 1st ICU day (median + IQR)	22 [13-32]	30 [12-32]	0.74
Diagnostic category (n, %)			0.10
Surgical			
Abdominal	3 (1.4%)	7 (3.2%)	
Cardiac	94 (42.3%)	97 (43.7%)	
Neurosurgery-TBI	25 (11.3%)	14 (6.3%)	
Thoracic	11 (5%)	3 (1.4%)	
Orthopedic-trauma	11 (5%)	7 (3.2%)	
Other	11 (5%)	15 (6.8%)	
Medical			
Cardiac	10 (4.5%)	8 (3.6%)	
Neurologic	12 (5.4%)	21 (9.5%)	
Respiratory	29 (13.1%)	28 (12.6%)	
Other	16 (7.2%)	22 (9.9%)	
Infection at admission (n, %)	104 (46.8%)	106 (47.7%)	0.84
Liver parameters			
Plasma total bilirubin day 3 - mg/dL (mean±SE)	0.48 ± 0.05	0.81 ± 0.12	<0.01

Supplemental Table 1C: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 3 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=179)	Late PN group (n=179)	P-value
Baseline characteristics			
Gender - male (n, %)	97 (54.2%)	102 (57%)	0.59
Age - years (median + IQR)	1.8 [0.4-6.8]	1.6 [0.4-5.7]	0.82
Weight - kg (median + IQR)	11.2 [5.6-22]	11 [5.5-21.7]	0.93
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.63
Centre			0.36
Leuven (n, %)	110 (61.5%)	112 (62.6%)	
Rotterdam (n, %)	68 (38%)	63 (35.2%)	
Edmonton (n, %)	1 (0.6%)	4 (2.2%)	
Emergency admission (n, %)	111 (62%)	117 (65.4%)	0.51
PIM2 probability of death ^b (median + IQR)	0.13 [0.04-0.28]	0.14 [0.06-0.29]	0.64
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	23 [12-32]	0.85
Diagnostic category (n, %)			0.12
Surgical			
Abdominal	0 (0%)	8 (4.5%)	
Cardiac	60 (33.5%)	59 (33%)	
Neurosurgery-TBI	20 (11.2%)	13 (7.3%)	
Thoracic	6 (3.4%)	2 (1.1%)	
Orthopedic-trauma	6 (3.4%)	5 (2.8%)	
Other	13 (7.3%)	14 (7.8%)	
Medical			
Cardiac	13 (7.3%)	11 (6.1%)	
Neurologic	13 (7.3%)	17 (9.5%)	
Respiratory	29 (16.2%)	31 (17.3%)	
Other	19 (10.6%)	19 (10.6%)	
Infection at admission (n, %)	101 (56.4%)	101 (56.4%)	1.00
Liver parameters			
Plasma total bilirubin day 4 - mg/dL (mean±SE)	0.46 ± 0.05	0.7 ± 0.12	0.01

Supplemental Table 1D: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 4 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=133)	Late PN group n=133)	P-value
Baseline characteristics			
Gender - male (n, %)	76 (57.1%)	72 (54.1%)	0.62
Age - years (median + IQR)	1.7 [0.4-6.3]	1.5 [0.3-7.4]	0.89
Weight - kg (median + IQR)	11 [5.8-20]	10 [5.1-24]	0.84
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.81
Centre			0.77
Leuven (n, %)	86 (64.7%)	82 (61.7%)	
Rotterdam (n, %)	46 (34.6%)	49 (36.8%)	
Edmonton (n, %)	1 (0.8%)	2 (1.5%)	
Emergency admission (n, %)	82 (61.7%)	87 (65.4%)	0.52
PIM2 probability of death ^b (median + IQR)	0.16 [0.05-0.35]	0.16 [0.06-0.31]	0.94
PELOD score ^c 1st ICU day (median + IQR)	30 [13-32]	30 [12-32]	0.71
Diagnostic category (n, %)			0.06
Surgical			
Abdominal	1 (0.8%)	7 (5.3%)	
Cardiac	44 (33.1%)	44 (33.1%)	
Neurosurgery-TBI	14 (10.5%)	7 (5.3%)	
Thoracic	5 (3.8%)	1 (0.8%)	
Orthopedic-trauma	6 (4.5%)	2 (1.5%)	
Other	7 (5.3%)	13 (9.8%)	
Medical			
Cardiac	9 (6.8%)	7 (5.3%)	
Neurologic	9 (6.8%)	13 (9.8%)	
Respiratory	23 (17.3%)	29 (21.8%)	
Other	15 (11.3%)	10 (7.5%)	
Infection at admission (n, %)	75 (56.4%)	77 (57.9%)	0.80
Liver parameters			
Plasma total bilirubin day 5 - mg/dL (mean±SE)	0.42 ± 0.05	0.81 ± 0.18	<0.01

Supplemental Table 1E: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 5 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=116)	Late PN group (n=116)	P-value
Baseline characteristics			
Gender - male (n, %)	70 (60.3%)	65 (56%)	0.50
Age - years (median + IQR)	1.8 [0.4-8.4]	1.6 [0.4-7.6]	0.69
Weight - kg (median + IQR)	11.1 [6-21.5]	10.5 [5.1-25]	0.63
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.14
Centre			0.88
Leuven (n, %)	70 (60.3%)	68 (58.6%)	
Rotterdam (n, %)	44 (37.9%)	45 (38.8%)	
Edmonton (n, %)	2 (1.7%)	3 (2.6%)	
Emergency admission (n, %)	77 (66.4%)	80 (69%)	0.67
PIM2 probability of death ^b (median + IQR)	0.16 [0.05-0.37]	0.15 [0.06-0.31]	0.62
PELOD score ^c 1st ICU day (median + IQR)	23 [12-32]	30.5 [12-32]	0.71
Diagnostic category (n, %)			0.77
Surgical			
Abdominal	0 (0%)	1 (0.9%)	
Cardiac	34 (29.3%)	34 (29.3%)	
Neurosurgery-TBI	9 (7.8%)	6 (5.2%)	
Thoracic	3 (2.6%)	2 (1.7%)	
Orthopedic-trauma	5 (4.3%)	4 (3.4%)	
Other	5 (4.3%)	11 (9.5%)	
Medical			
Cardiac	9 (7.8%)	7 (6%)	
Neurologic	9 (7.8%)	13 (11.2%)	
Respiratory	25 (21.6%)	25 (21.6%)	
Other	17 (14.7%)	13 (11.2%)	
Infection at admission (n, %)	70 (60.3%)	68 (58.6%)	0.78
Liver parameters			
Plasma total bilirubin day 6 - mg/dL (mean±SE)	0.42 ± 0.04	0.85 ± 0.25	0.02

Supplemental Table 1F: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 6 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=85)	Late PN group (n=85)	P-value
Baseline characteristics			
Gender - male (n, %)	46 (54.1%)	49 (57.6%)	0.64
Age - years (median + IQR)	1.7 [0.4-9.1]	1.8 [0.3-9.1]	0.90
Weight - kg (median + IQR)	11 [5.2-23.9]	27.4	0.81
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.79
Centre			0.34
Leuven (n, %)	51 (60%)	48 (56.5%)	
Rotterdam (n, %)	34 (40%)	35 (41.2%)	
Edmonton (n, %)	0 (0%)	2 (2.4%)	
Emergency admission (n, %)	60 (70.6%)	59 (69.4%)	0.86
PIM2 probability of death ^b (median + IQR)	0.15 [0.06-0.34]	0.16 [0.07-0.33]	0.72
PELOD score ^c 1st ICU day (median + IQR)	23 [21-32]	22 [12-32]	0.35
Diagnostic category (n, %)			0.80
Surgical			
Abdominal	1 (1.2%)	2 (2.4%)	
Cardiac	23 (27.1%)	26 (30.6%)	
Neurosurgery-TBI	11 (12.9%)	6 (7.1%)	
Thoracic	2 (2.4%)	1 (1.2%)	
Orthopedic-trauma	4 (4.7%)	2 (2.4%)	
Other	4 (4.7%)	8 (9.4%)	
Medical			
Cardiac	4 (4.7%)	4 (4.7%)	
Neurologic	9 (10.6%)	10 (11.8%)	
Respiratory	13 (15.3%)	16 (18.8%)	
Other	14 (16.5%)	10 (11.8%)	
Infection at admission (n, %)	53 (62.4%)	52 (61.2%)	0.87
Liver parameters			
Plasma total bilirubin day 7 - mg/dL (mean±SE)	0.49 ± 0.09	0.96 ± 0.36	0.05

Supplemental Table 1G: Baseline characteristics and the plasma total bilirubin concentration of the propensity matched subset from patients with available plasma total bilirubin concentration on day 7 in the PICU. ^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness. To convert plasma total bilirubin concentrations in mg/dL to $\mu\text{mol/L}$, multiply by 17.1.

	Early PN group (n=487)	Late PN group (n=487)	P-value
Baseline characteristics			
Gender - male (n, %)	271 (56.7%)	277 (57.9%)	0.69
Age - years (median + IQR)	2.7 [0.5-7.3]	2.5 [0.5-8.1]	0.63
Weight - kg (median + IQR)	12.7 [6.6-22]	13 [6.3-23.6]	0.67
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.12
Centre			0.34
Leuven (n, %)	311 (65.1%)	318 (66.5%)	
Rotterdam (n, %)	158 (33.1%)	145 (30.3%)	
Edmonton (n, %)	9 (1.9%)	15 (3.1%)	
Emergency admission (n, %)	211 (44.1%)	212 (44.4%)	0.94
PIM2 probability of death ^b (median + IQR)	0.06 [0.03-0.21]	0.06 [0.03-0.17]	0.45
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	22 [12-32]	0.70
Diagnostic category (n, %)			0.95
Surgical			
Abdominal	13 (2.7%)	18 (3.8%)	
Cardiac	215 (45%)	208 (43.5%)	
Neurosurgery-TBI	45 (9.4%)	44 (9.2%)	
Thoracic	18 (3.8%)	18 (3.8%)	
Orthopedic-trauma	22 (4.6%)	23 (4.8%)	
Other	21 (4.4%)	29 (6.1%)	
Medical			
Cardiac	18 (3.8%)	13 (2.7%)	
Neurologic	38 (7.9%)	36 (7.5%)	
Respiratory	44 (9.2%)	47 (9.8%)	
Other	44 (9.2%)	42 (8.8%)	
Infection at admission (n, %)	182 (38.1%)	168 (35.1%)	0.34
Liver parameters (mean + SE)			
ALP day 1 - U/L	147 ± 4	149 ± 4	0.87
γGT day 1 - U/L	29 ± 5	25 ± 3	0.29
ALT day 1 - U/L	51 ± 8	65 ± 11	0.88
AST day 1 - U/L	137 ± 21	160 ± 21	0.76

Supplemental Table 1H: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 1 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

	Early PN group (n=341)	Late PN group (n=341)	P-value
Baseline characteristics			
Gender - male (n, %)	202 (59.2%)	196 (57.5%)	0.64
Age - years (median + IQR)	1.7 [0.4-6.4]	1.8 [0.4-7]	0.85
Weight - kg (median + IQR)	11 [5.7-20.5]	11 [5.5-21.5]	0.88
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.20
Centre			0.93
Leuven (n, %)	219 (64.2%)	216 (63.3%)	
Rotterdam (n, %)	117 (34.3%)	119 (34.9%)	
Edmonton (n, %)	5 (1.5%)	6 (1.8%)	
Emergency admission (n, %)	163 (47.8%)	176 (51.6%)	0.31
PIM2 probability of death ^b (median + IQR)	0.08 [0.03-0.24]	0.09 [0.04-0.21]	0.46
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	22 [12-32]	0.93
Diagnostic category (n, %)			0.28
Surgical			
Abdominal	9 (2.6%)	13 (3.8%)	
Cardiac	151 (44.3%)	155 (45.5%)	
Neurosurgery-TBI	33 (9.7%)	21 (6.2%)	
Thoracic	13 (3.8%)	8 (2.3%)	
Orthopedic-trauma	15 (4.4%)	7 (2.1%)	
Other	14 (4.1%)	18 (5.3%)	
Medical			
Cardiac	17 (5%)	12 (3.5%)	
Neurologic	23 (6.7%)	31 (9.1%)	
Respiratory	34 (10%)	40 (11.7%)	
Other	32 (9.4%)	36 (10.6%)	
Infection at admission (n, %)	138 (40.5%)	145 (42.5%)	0.58
Liver parameters (mean + SE)			
ALP day 2 - U/L	143 ± 4	147 ± 5	0.80
γGT day 2 - U/L	33 ± 9	24 ± 3	0.75
ALT day 2 - U/L	57 ± 8	103 ± 24	0.40
AST day 2 - U/L	154 ± 38	279 ± 77	0.15

Supplemental Table 11: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 2 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

	Early PN group (n=231)	Late PN group (n=231)	P-value
Baseline characteristics			
Gender - male (n, %)	128 (55.4%)	133 (57.6%)	0.63
Age - years (median + IQR)	1.8 [0.3-6.3]	2 [0.3-7.4]	0.97
Weight - kg (median + IQR)	12 [5.3-20]	11.6 [5.1-21.7]	0.95
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.62
Centre			0.52
Leuven (n, %)	140 (60.6%)	138 (59.7%)	
Rotterdam (n, %)	89 (38.5%)	88 (38.1%)	
Edmonton (n, %)	2 (0.9%)	5 (2.2%)	
Emergency admission (n, %)	130 (56.3%)	129 (55.8%)	0.92
PIM2 probability of death ^b (median + IQR)	0.11 [0.05-0.27]	0.1 [0.05-0.26]	0.59
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	22 [12-32]	0.87
Diagnostic category (n, %)			0.05
Surgical			
Abdominal	3 (1.3%)	11 (4.8%)	
Cardiac	89 (38.5%)	96 (41.6%)	
Neurosurgery-TBI	25 (10.8%)	15 (6.5%)	
Thoracic	8 (3.5%)	3 (1.3%)	
Orthopedic-trauma	13 (5.6%)	5 (2.2%)	
Other	12 (5.2%)	14 (6.1%)	
Medical			
Cardiac	14 (6.1%)	7 (3%)	
Neurologic	15 (6.5%)	20 (8.7%)	
Respiratory	31 (13.4%)	35 (15.2%)	
Other	21 (9.1%)	25 (10.8%)	
Infection at admission (n, %)	110 (47.6%)	114 (49.4%)	0.71
Liver parameters (mean + SE)			
ALP day 3 - U/L	147 ± 6	149 ± 7	0.7
γGT day 3 - U/L	30 ± 4	31 ± 5	0.52
ALT day 3 - U/L	56 ± 9	119 ± 36	0.11
AST day 3 - U/L	102 ± 13	260 ± 67	0.1

Supplemental Table 1J: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 3 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

	Early PN group (n=180)	Late PN group (n=180)	P-value
Baseline characteristics			
Gender - male (n, %)	101 (56.1%)	102 (56.7%)	0.91
Age - years (median + IQR)	1.7 [0.4-5.1]	2.2 [0.4-7]	0.37
Weight - kg (median + IQR)	11 [5.6-20]	11.8 [5.8-22]	0.36
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.44
Centre			0.74
Leuven (n, %)	109 (60.6%)	104 (57.8%)	
Rotterdam (n, %)	67 (37.2%)	70 (38.9%)	
Edmonton (n, %)	4 (2.2%)	6 (3.3%)	
Emergency admission (n, %)	112 (62.2%)	118 (65.6%)	0.51
PIM2 probability of death ^b (median + IQR)	0.16 [0.06-0.31]	0.15 [0.06-0.3]	0.78
PELOD score ^c 1st ICU day (median + IQR)	26.5 [12-32]	22 [12-32]	0.27
Diagnostic category (n, %)			0.17
Surgical			
Abdominal	1 (0.6%)	10 (5.6%)	
Cardiac	67 (37.2%)	61 (33.9%)	
Neurosurgery-TBI	18 (10%)	13 (7.2%)	
Thoracic	5 (2.8%)	2 (1.1%)	
Orthopedic-trauma	4 (2.2%)	5 (2.8%)	
Other	9 (5%)	14 (7.8%)	
Medical			
Cardiac	14 (7.8%)	9 (5%)	
Neurologic	14 (7.8%)	18 (10%)	
Respiratory	29 (16.1%)	31 (17.2%)	
Other	19 (10.6%)	17 (9.4%)	
Infection at admission (n, %)	99 (55%)	102 (56.7%)	0.75
Liver parameters (mean + SE)			
ALP day 4 - U/L	154 ± 7	141 ± 5	0.16
γGT day 4 - U/L	33 ± 3	33 ± 4	0.28
ALT day 4 - U/L	59 ± 10	129 ± 36	0.05
AST day 4 - U/L	86 ± 11	230 ± 62	0.07

Supplemental Table 1K: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 4 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

	Early PN group (n=141)	Late PN group (n=141)	P-value
Baseline characteristics			
Gender - male (n, %)	73 (51.8%)	79 (56%)	0.47
Age - years (median + IQR)	1.8 [0.4-5.9]	1.6 [0.4-7.5]	0.79
Weight - kg (median + IQR)	11.2 [5.5-20]	11 [5.4-24.5]	0.81
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.50
Centre			0.69
Leuven (n, %)	79 (56%)	76 (53.9%)	
Rotterdam (n, %)	60 (42.6%)	61 (43.3%)	
Edmonton (n, %)	2 (1.4%)	4 (2.8%)	
Emergency admission (n, %)	90 (63.8%)	94 (66.7%)	0.61
PIM2 probability of death ^b (median + IQR)	0.17 [0.06-0.34]	0.16 [0.06-0.31]	0.92
PELOD score ^c 1st ICU day (median + IQR)	22 [12.5-32]	22 [12-32]	0.62
Diagnostic category (n, %)			0.01
Surgical			
Abdominal	0 (0%)	7 (5%)	
Cardiac	44 (31.2%)	48 (34%)	
Neurosurgery-TBI	17 (12.1%)	9 (6.4%)	
Thoracic	5 (3.5%)	0 (0%)	
Orthopedic-trauma	6 (4.3%)	4 (2.8%)	
Other	8 (5.7%)	12 (8.5%)	
Medical			
Cardiac	9 (6.4%)	6 (4.3%)	
Neurologic	8 (5.7%)	16 (11.3%)	
Respiratory	25 (17.7%)	26 (18.4%)	
Other	19 (13.5%)	13 (9.2%)	
Infection at admission (n, %)	80 (56.7%)	80 (56.7%)	1.00
Liver parameters (mean + SE)			
ALP day 5 - U/L	160 ± 7	142 ± 6	0.04
γGT day 5 - U/L	49 ± 9	39 ± 5	0.22
ALT day 5 - U/L	60 ± 10	150 ± 39	0.21
AST day 5 - U/L	75 ± 11	244 ± 85	0.08

Supplemental Table 1L: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 5 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

	Early PN group (n=118)	Late PN group (n=118)	P-value
Baseline characteristics			
Gender - male (n, %)	63 (53.4%)	65 (55.1%)	0.79
Age - years (median + IQR)	2 [0.4-5.9]	1.6 [0.4-8.4]	0.95
Weight - kg (median + IQR)	11.6 [6-20]	10.5 [5.1-25.5]	0.79
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.46
Centre			0.33
Leuven (n, %)	63 (53.4%)	57 (48.3%)	
Rotterdam (n, %)	54 (45.8%)	57 (48.3%)	
Edmonton (n, %)	4 (3.4%)	4 (3.4%)	
Emergency admission (n, %)	79 (66.9%)	81 (68.6%)	0.78
PIM2 probability of death ^b (median + IQR)	0.15 [0.06-0.35]	0.16 [0.07-0.29]	0.99
PELOD score ^c 1st ICU day (median + IQR)	23 [12-32]	22 [12-32]	0.39
Diagnostic category (n, %)			0.54
Surgical			
Abdominal	0 (0%)	3 (2.5%)	
Cardiac	34 (28.8%)	37 (31.4%)	
Neurosurgery-TBI	12 (10.2%)	9 (7.6%)	
Thoracic	6 (5.1%)	2 (1.7%)	
Orthopedic-trauma	5 (4.2%)	3 (2.5%)	
Other	6 (5.1%)	7 (5.9%)	
Medical			
Cardiac	10 (8.5%)	7 (5.9%)	
Neurologic	8 (6.8%)	13 (11%)	
Respiratory	22 (18.6%)	22 (18.6%)	
Other	15 (12.7%)	15 (12.7%)	
Infection at admission (n, %)	65 (55.1%)	69 (58.5%)	0.59
Liver parameters (mean + SE)			
ALP day 6 - U/L	161 ± 8	157 ± 8	0.45
γGT day 6 - U/L	47 ± 5	50 ± 6	0.73
ALT day 6 - U/L	56 ± 9	133 ± 37	0.10
AST day 6 - U/L	66 ± 9	145 ± 52	0.11

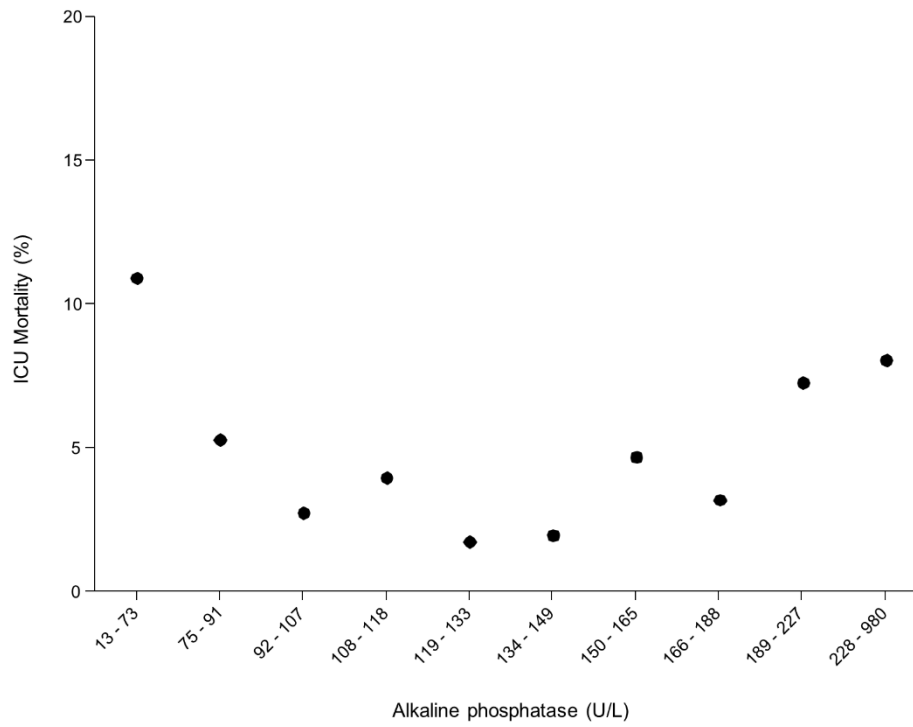
Supplemental Table 1M: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 6 in the PICU.

^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.

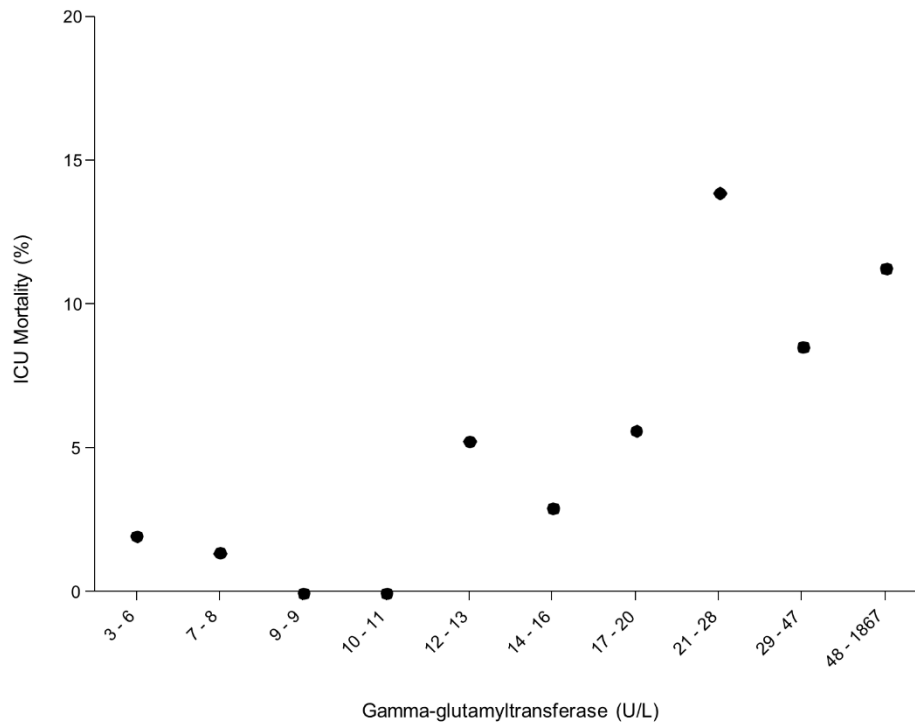
	Early PN group (n=86)	Late PN group (n=86)	P-value
Baseline characteristics			
Gender - male (n, %)	50 (58.1%)	52 (60.5%)	0.75
Age - years (median + IQR)	3.3 [0.4-7.5]	2.6 [0.5-9.6]	0.95
Weight - kg (median + IQR)	15 [6.3-24.4]	12.2 [5.5-28.3]	0.93
STRONGkids risk level ^a (median + IQR)	2 [2-3]	2 [2-3]	0.64
Centre			0.59
Leuven (n, %)	47 (54.7%)	45 (52.3%)	
Rotterdam (n, %)	38 (44.2%)	38 (44.2%)	
Edmonton (n, %)	1 (1.2%)	3 (3.5%)	
Emergency admission (n, %)	64 (74.4%)	64 (74.4%)	0.49
PIM2 probability of death ^b (median + IQR)	0.18 [0.07-0.35]	0.15 [0.07-0.32]	0.62
PELOD score ^c 1st ICU day (median + IQR)	22 [12-32]	22 [12-32]	0.75
Diagnostic category (n, %)			0.30
Surgical			
Abdominal	1 (1.2%)	2 (2.3%)	
Cardiac	24 (27.9%)	26 (30.2%)	
Neurosurgery-TBI	10 (11.6%)	8 (9.3%)	
Thoracic	2 (2.3%)	1 (1.2%)	
Orthopedic-trauma	5 (5.8%)	2 (2.3%)	
Other	3 (3.5%)	11 (12.8%)	
Medical			
Cardiac	6 (7%)	4 (4.7%)	
Neurologic	4 (4.7%)	7 (8.1%)	
Respiratory	14 (16.3%)	16 (18.6%)	
Other	17 (19.8%)	9 (10.5%)	
Infection at admission (n, %)	54 (62.8%)	54 (62.8%)	1.00
Liver parameters (mean + SE)			
ALP day 7 - U/L	163 ± 12	152 ± 9	0.71
γGT day 7 - U/L	62 ± 8	56 ± 9	0.32
ALT day 7 - U/L	53 ± 15	123 ± 36	0.07
AST day 7 - U/L	79 ± 24	93 ± 21	0.16

Supplemental Table 1N: Baseline characteristics and plasma ALT, AST, γGT and ALP concentrations of the propensity matched subset from patients with available liver enzyme tests on day 7 in the PICU.

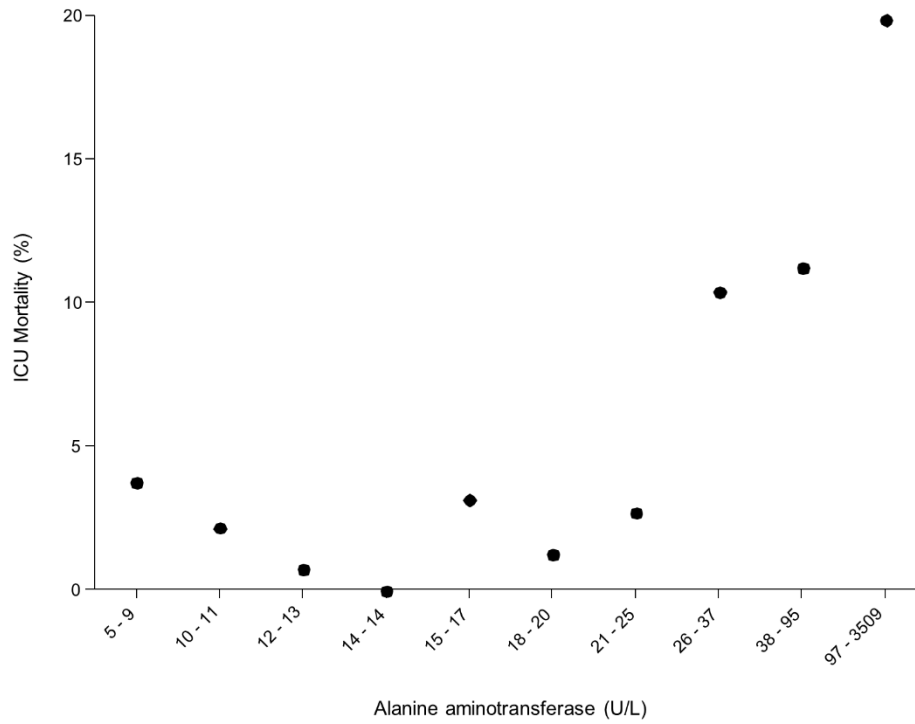
^a: Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5 with a score of 0 indicating low risk, 1 to 3 indicating medium risk and 4 to 5 indicating high risk on malnutrition. ^b: Probability of death assessed by the Pediatric Index of Mortality-2 (PIM2) score, estimating mortality risk at admission. ^c: Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h, ranging from 0 to 71, with the highest scores indicating more severe illness.



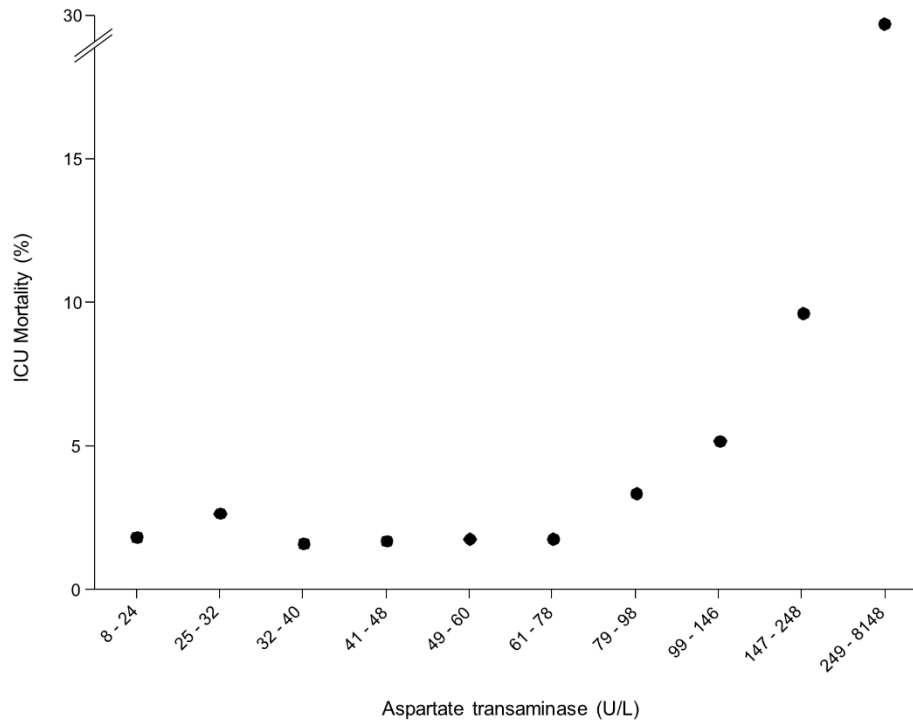
Supplement Figure 3: U-shaped relationship between plasma alkaline phosphatase (ALP) concentrations on day 1 and PICU mortality. Each interval represents 10% of all patients with an available liver enzyme tests on day 1 (n=982)



Supplement Figure 4: Relationship between plasma gamma-glutamyltransferase (γ GT) concentrations on day 1 and PICU mortality. Each interval represents 10% of all patients with an available liver enzyme tests on day 1 (n=982)



Supplement Figure 5: Relationship between plasma alanine aminotransferase (ALT) concentrations on day 1 and PICU mortality. Each interval represents 10% of all patients with an available liver enzyme tests on day 1 (n=982)



Supplement Figure 6: Relationship between plasma aspartate transaminase (AST) concentrations on day 1 and PICU mortality. Each interval represents 10% of all patients with an available liver enzyme tests on day 1 (n=982)