11. Citrulline paper:

This paper will evaluate plasma citrulline levels over time (baseline, mean, peak, AUC, etc) and the relationship of this potential ICU biomarker to clinical outcomes. We will also determine the impact of glutamine administration.

Plasma Citrulline at SICU admission in relation to clinical outcomes

Concept Sheet

Specific Aims:

1. To determine the prevalence of plasma citrulline depletion in SICU patients at the time of enrollment into the GLND study.
2. To determine the relationship between plasma citrulline levels at baseline and clinical outcomes such as in-hospital mortality, 28 day mortality, 6 month mortality, APACHE II score at randomization, SOFA score at randomization and incidence of nosocomial infections in SICU patients enrolled in the GLND study.
3. To determine the relationship between serial plasma citrulline levels and clinical outcomes (listed above) in SICU patients enrolled in the GLND study.
4. To evaluate the relationship between serial plasma citrulline levels and serial plasma glutamine levels in SICU patients enrolled in the GLND study, to determine whether AG-PN administration influences plasma citrulline levels.

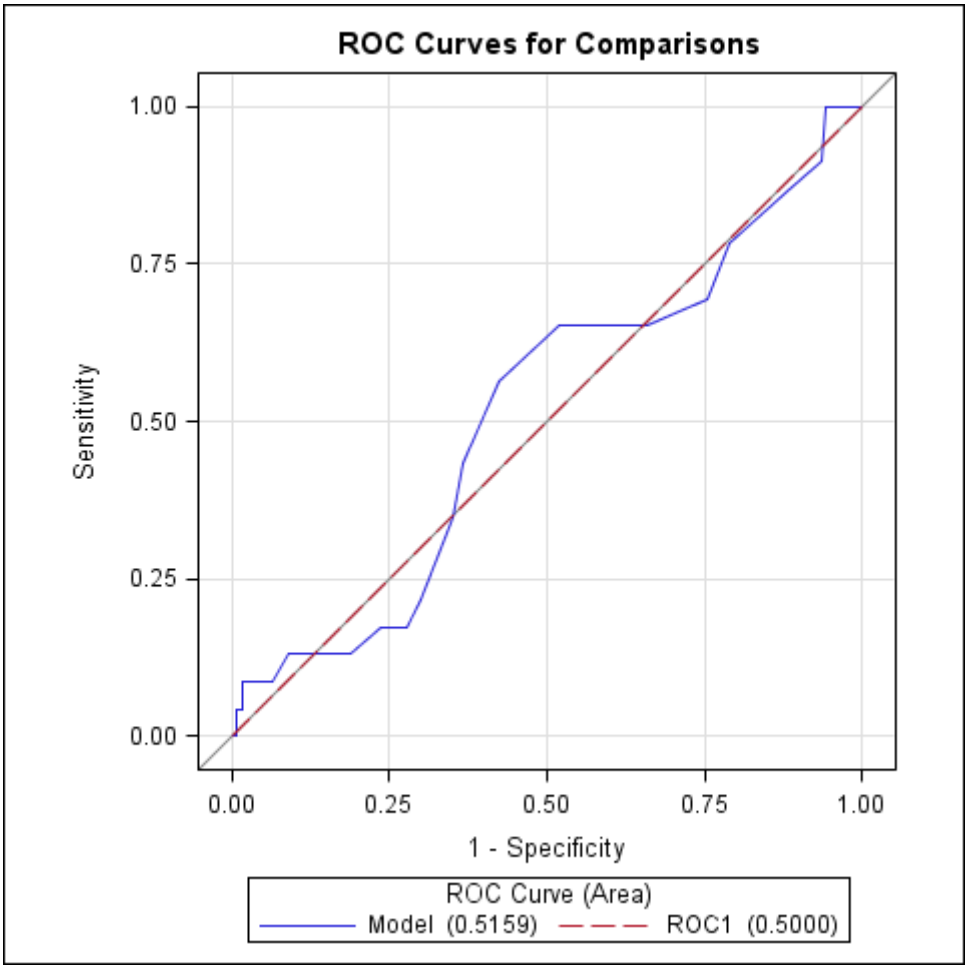
Tables:

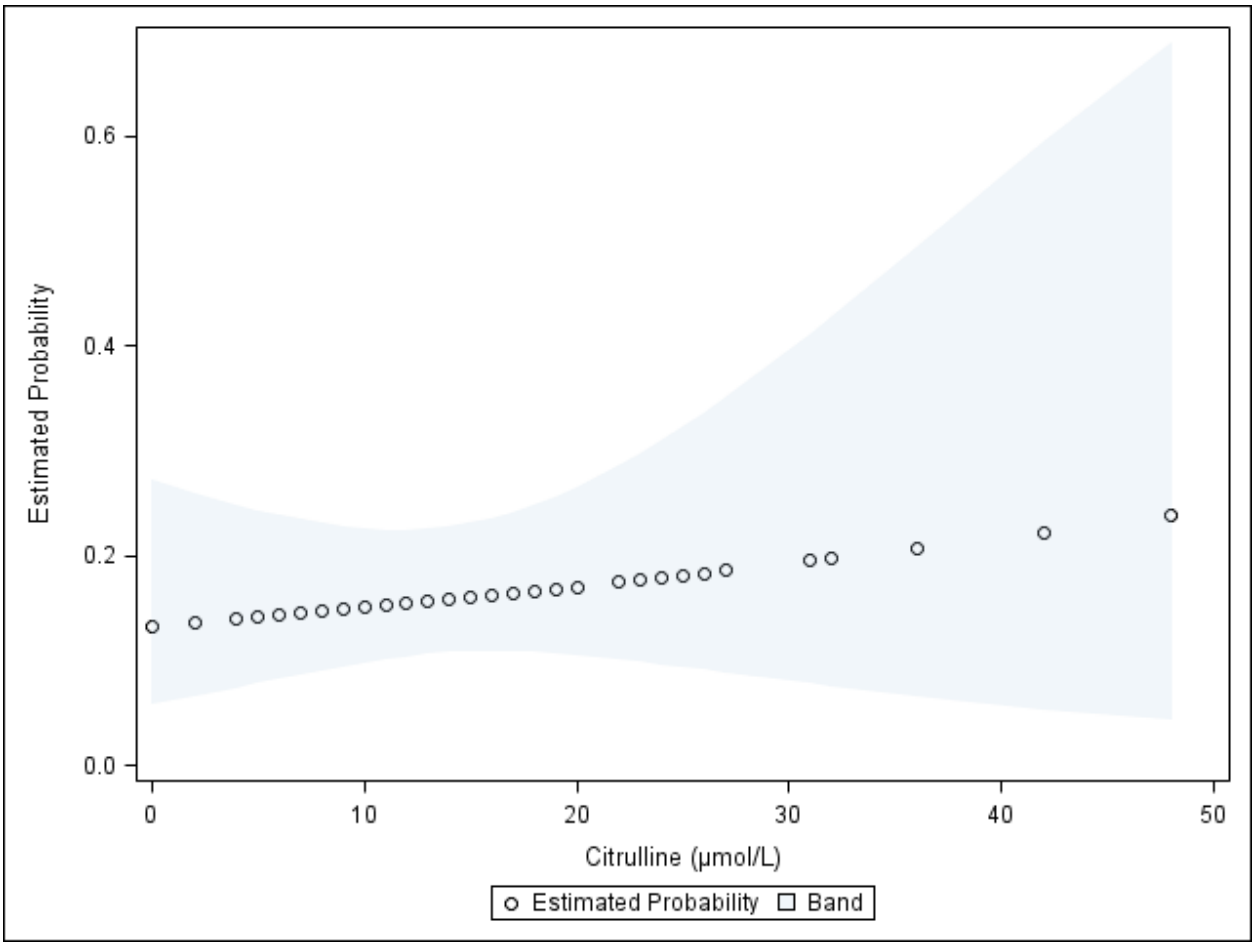
1. Demographics table: age, gender, race, index surgery, APACHE II score at randomization, days in SICU prior to enrollment, days in hospital prior to enrollment, days in SICU post enrollment, days in hospital post enrollment
2. Plasma citrulline levels at baseline in quartiles in relation to age, gender, race, index surgery, APACHE II score, days in hospital, days in SICU, in-hospital mortality, 28 day mortality, 6 month mortality and incidence of nosocomial infections(this data could also be presented in graphs/figures)

Figures:

1. Consort Diagram for the GLND study
2. Graph showing the baseline plasma citrulline on Y axis and 28 day mortality, in-hospital mortality and 6 month mortality on X axis
3. Graph showing the baseline plasma citrulline on Y axis and APACHE II score at randomization on X axis.
4. Graph showing the predicted death rate on the Y axis and the APACHE II score on the X axis for two plasma citrulline groups (one for patients in the normal range and the other for those out of the range).

1. Prevalence of citrulline depletion (<11µM) at GLN enrollment: 58/146 = 39.7 % with 95%CI=[%32.2 - 47.8]




Estimated Probability
0.0
0.2
0.4
0.6
0
10
20
30
40
50
Citrulline (µmol/L)
Estimated Probability
Band

2. Baseline citrulline vs. In-Hospital Mortality(p=0.13)

Baseline Citrulline Quartile Groups	Survivors	Non-Survivors	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	26/123(21.1%)	5/23(21.7%)	1.64[0.40-6.70]	0.92
Citrulline= 8~ 12μm	33/123(26.8%)	3/23(13.0%)	0.77[0.16-3.72]	
Citrulline= 12~ 17μm	30/123(24.4%)	11/23(47.8%)	3.12[0.90-10.83]	
Citrulline>= 17μm	34/123(27.6%)	4/23(17.4%)	1.00	

Interpretation:

- Test of association of baseline citrulline and in-hospital mortality, p=0.13(Fisher exact test): There is no general association between baseline citrulline and in-hospital mortality;
- The estimated odds of in-hospital mortality is 1.64 times higher (95% CI: 0.40 to 6.70) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 0.77[0.16-3.72]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 3.12[0.90-10.83].
- The trend test (p=0.92) indicated the in-hospital mortality has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

3. Baseline citrulline vs. 6-Month Mortality(p=0.14)

Baseline Citrulline Quartile Groups	Survivors	Non-Survivors	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	25/102(24.5%)	6/44(13.6%)	0.46[0.15-1.41]	0.067
Citrulline= 8~ 12μm	28/102(27.4%)	8/44(18.2%)	0.55[0.20-1.54]	
Citrulline= 12~ 17μm	24/102(23.5%)	17/44(38.6%)	1.36[0.55-3.40]	
Citrulline>= 17μm	25/102(24.5%)	13/44(29.6%)	1.00	

Interpretation:

- Test of association of baseline citrulline and 6-month mortality, p=0.14(Fisher exact test): There is no general association between baseline citrulline and 6-month mortality;
- The estimated odds of 6 month mortality is 0.46 times lower (95% CI: 0.15 to 1.41) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 0.55[0.20-1.54]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 1.36[0.55-3.40].
- The trend test (p=0.067) indicated the 6 month mortality has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

4. Baseline citrulline vs. Apache II score at Randomization(p=0.26)

Baseline Citrulline Quartile Groups	APACHE <=15	APACHE >15	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	19/70(27.1%)	12/76(15.8%)	0.41[0.16-1.09]	0.16
Citrulline= 8~ 12μm	15/70(21.4%)	21/76(27.6%)	0.91[0.36-2.31]	
Citrulline= 12~ 17μm	21/70(30.0%)	20/76(26.3%)	0.62[0.25-1.52]	
Citrulline>= 17μm	15/70(21.4%)	23/76(30.3%)	1.00	

Interpretation:

- Test of association of baseline citrulline and Apache II score, p=0.26(Fisher exact test): There is no general association between baseline citrulline and Apache II score;
- The estimated odds of Apache II score>15 is 0.41 times lower (95% CI: 0.16 to 1.09) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 0.91[0.36-2.31]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 0.62[0.25-1.52].
- The trend test (p=0.16) indicated the probability of Apache II score>15 has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

5. Baseline citrulline vs. Apache II score at ICU(p=0.95)

Baseline Citrulline Quartile Groups	APACHE <=15	APACHE >15	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	5/26(19.2%)	26/120(21.7%)	1.39[0.40-4.78]	0.59
Citrulline= 8~ 12μm	6/26(23.1%)	30/120(25.0%)	1.33[0.41-4.31]	
Citrulline= 12~ 17μm	7/26(26.9%)	34/120(28.3%)	1.30[0.42-4.00]	
Citrulline>= 17μm	8/26(30.8%)	30/120(30.3%)	1.00	

Interpretation:

- Test of association of baseline citrulline and Apache II score at ICU, p=0.95(Fisher exact test): There is no general association between baseline citrulline and Apache II score at ICU;
- The estimated odds of Apache II score>15 is 1.39 times higher (95% CI: 0.40 to 4.78) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 1.33[0.41-4.31]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 1.30[0.42-4.00].
- The trend test (p=0.59) indicated the probability of Apache II score>15 at ICU has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

6. Baseline citrulline vs. SOFA score at Randomization(p=0.40)

Baseline Citrulline Quartile Groups	SOFA<=6(Median)	SOFA >6(Median)	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	19/76(25.0%)	12/70(17.1%)	0.51[0.20-1.34]	0.10
Citrulline= 8~ 12μm	21/76(27.6%)	15/70(21.4%)	0.58[0.23-1.45]	
Citrulline= 12~ 17μm	19/76(25.0%)	22/70(31.4%)	0.94[0.39-2.27]	
Citrulline>= 17μm	17/76(22.4%)	21/70(30.0%)	1.00	

Interpretation:

- Test of association of baseline citrulline and SOFA >6(median), p=0.40(Fisher exact test): There is no general association between baseline citrulline and SOFA score;
- The estimated odds of SOFA<6(median) is 0.51 times lower (95% CI: 0.20 to 1.34) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 0.58[0.23-1.45]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 0.94[0.39-2.27].
- The trend test (p=0.10) indicated the probability of SOFA score<6(median) has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

7. Baseline citrulline vs. Incidence of BSI(p=0.97)

Baseline Citrulline Quartile Groups	BSI=No	BSI=Yes	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	25/119(21.0%)	6/27(22.2%)	1.28[0.37-4.45]	0.71
Citrulline= 8~ 12μm	29/119(24.4%)	7/27(25.9%)	1.29[0.39-4.28]	
Citrulline= 12~ 17μm	33/119(27.7%)	8/27(29.6%)	1.29[0.40-4.14]	
Citrulline>= 17μm	32/119(26.9%)	6/27(22.2%)	1.00	

Interpretation:

- Test of association of baseline citrulline and BSI, p=0.97(Fisher exact test): There is no general association between baseline citrulline and BSI;
- The estimated odds of BSI is 1.28 times higher (95% CI: 0.37 to 4.45) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 1.29[0.39-4.28]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 1.29[0.40-4.14].
- The trend test (p=0.71) indicated the BSI rates has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

8. Baseline citrulline vs. Incidence of Pneumonia(p=0.89)

Baseline Citrulline Quartile Groups	Pneumonia =No	Pneumonia =Yes	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	27/125(21.0%)	4/21(22.2%)	0.66[0.17-2.49]	0.57
Citrulline= 8~ 12μm	31/125(24.4%)	5/21(25.9%)	0.71[0.20-2.50]	
Citrulline= 12~ 17μm	36/125(27.7%)	5/21(29.6%)	0.62[0.18-2.13]	
Citrulline>= 17μm	31/125(26.9%)	7/21(22.2%)	1.00	

Interpretation:

- Test of association of baseline citrulline and Incidence of Pneumonia, p=0.89(Fisher exact test): There is no general association between baseline citrulline and Incidence of Pneumonia;
- The estimated odds of Incidence of Pneumonia is 0.66 times lower (95% CI: 0.17 to 2.49) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 0.71[0.20-2.50]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 0.62[0.18-2.13].
- The trend test (p=0.57) indicated the Incidence of Pneumonia has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

9. Baseline citrulline vs. Incidence of Any Infection(p=0.72)

Baseline Citrulline Quartile Groups	Infection=No	Infection=Yes	Odds Ratio	CA Trend Test p-value
Citrulline< 8μm	17/90(19.9%)	14/56(25.0%)	1.78[0.67-4.77]	0.28
Citrulline= 8~ 12μm	22/90(24.4%)	14/56(25.0%)	1.38[0.53-3.59]	
Citrulline= 12~ 17μm	25/90(27.8%)	16/56(28.6%)	1.39[0.55-3.51]	
Citrulline>= 17μm	26/90(28.9%)	12/56(21.4%)	1.00	

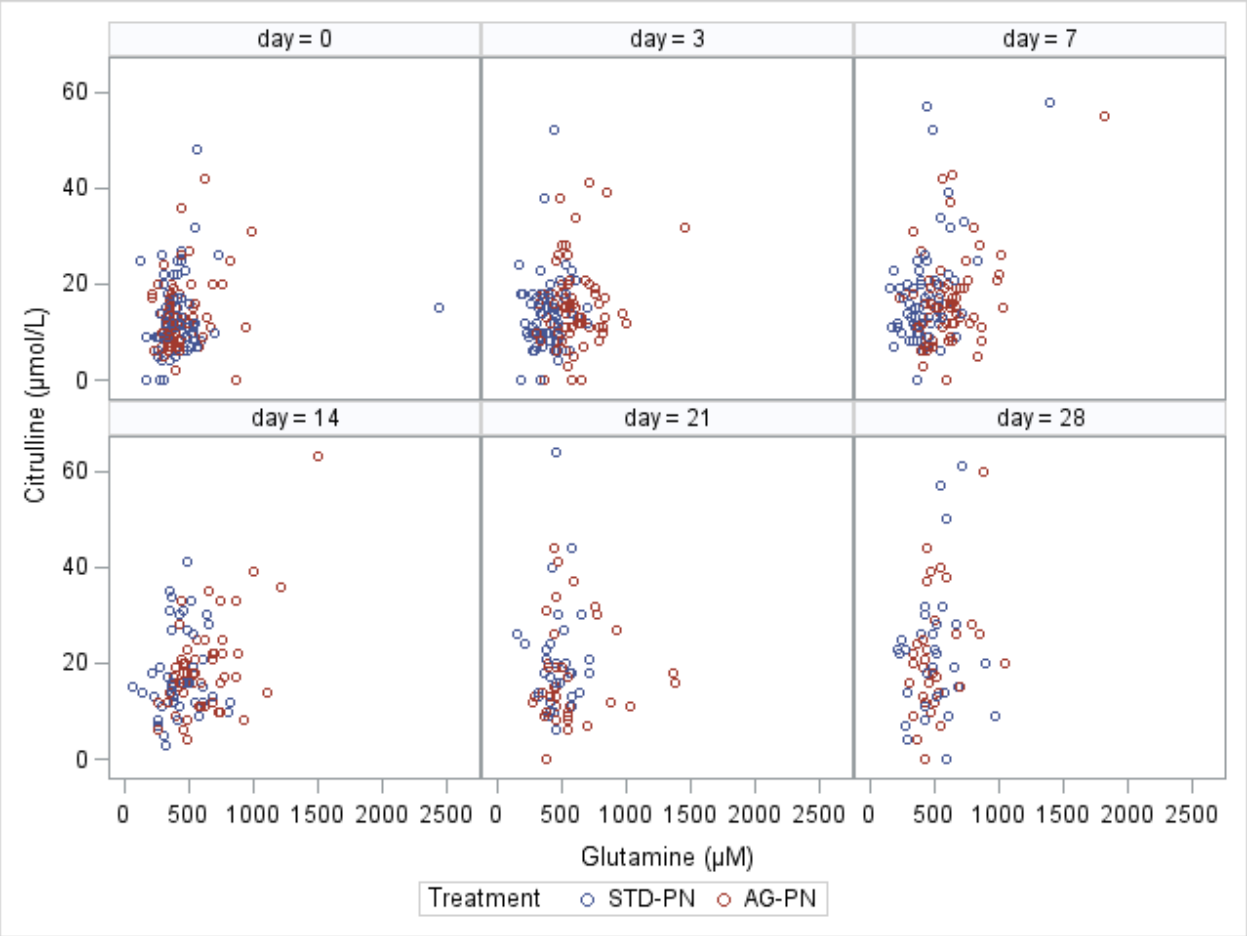
Interpretation:

- Test of association of baseline citrulline and any infection, p=0.72(Fisher exact test): There is no general association between baseline citrulline and any infection;
- The estimated odds of any infection is 1.78 times lower (95% CI: 0.67 to 4.77) for patients with low baseline citrulline (first quartile group) compared to patients with high baseline citrulline (the 4th quartile group); similarly the estimated odds ratio for 2nd quartile group vs 4th quartile group is 1.38[0.53-3.59]; the estimated odds ratio for 3rd quartile group vs 4th quartile group is 1.39[0.55-3.51].
- The trend test (p=0.28) indicated any infection rate has no obvious increasing/decreasing trend with the baseline citrulline level changing from 1st quartile to 4th quartile.

10. Citrulline by Surgery Type: p=0.24(Kruskal-Wallis Test)

Analysis Variable : Citrulline (μmol/L)						
Index Surgery	**N**	**Mean**	**Std Dev**	**Median**	**Q1**	**Q3**
CABG	**5**	22.0	11.6	16.0	15.0	22.0
Cardiac valve	**5**	13.2	5.3	12.0	11.0	13.0
Intestinal resection	**102**	13.0	7.9	11.5	7.0	17.0
Peritonitis	**2**	13.0	5.7	13.0	9.0	17.0
Upper GI resection	**5**	14.6	4.0	15.0	13.0	16.0
Vascular	**31**	12.7	6.2	12.0	9.0	15.0

By GI or not: p=0.31



Day	Citrulline n	Glutamine n	Pearson Correlation	p	Spearman Correlation	p
0	146	146	0.15	0.072	0.16	0.060
3	139	139	0.18	0.038	0.12	0.16
7	131	131	0.39	<0.0001	0.22	0.0097
14	101	99	0.41	<0.0001	0.25	0.013
21	69	69	0.02	0.90	0.11	0.35
28	68	67	0.20	0.10	0.16	0.19

Table: Citrulline at Day 7 by Treatment Group Adjusted for Glutamine Using Multiple Linear Regressions

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
glutamine	1	127	34.29	<.0001
treatment	1	127	0.04	0.8485
glutamine*treatment	1	127	2.03	0.1565

Treatment Group	Sample Size	Adjusted Mean[95%CI]	P value
AG-PN	67	15.2[12.7-17.6]	0.85
STD-PN	64	20.3[17.8-22.9]	

- Mean±SD for Glutamine on Day 7 : 528.4±228.5 (μm)

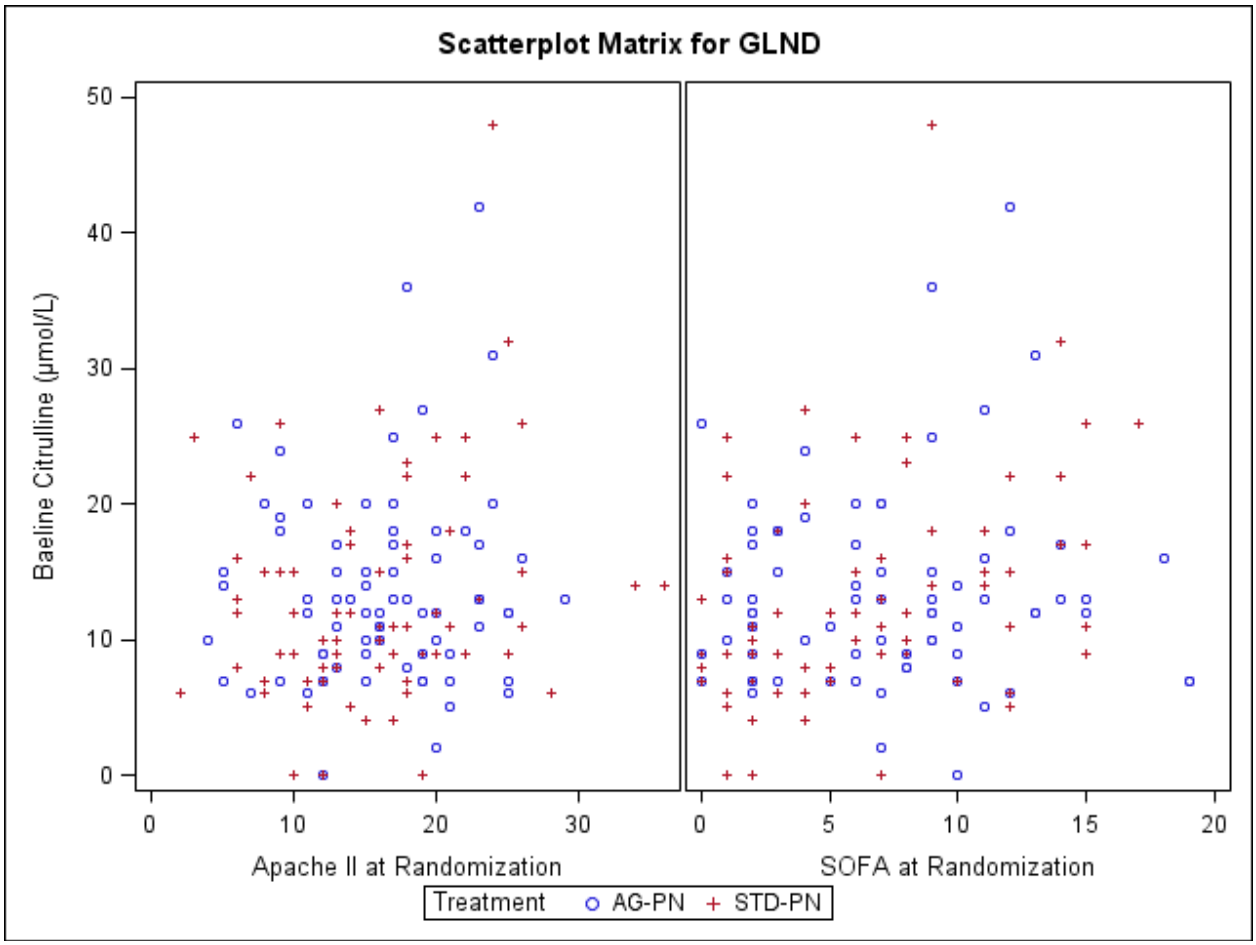

Scatterplot Matrix for GLND
Baeline Citrulline (µmol/L)
0
10
20
30
40
50
0
10
20
30
Apache II at Randomization
0
5
10
15
20
SOFA at Randomization
Treatment
AG-PN
STD-PN

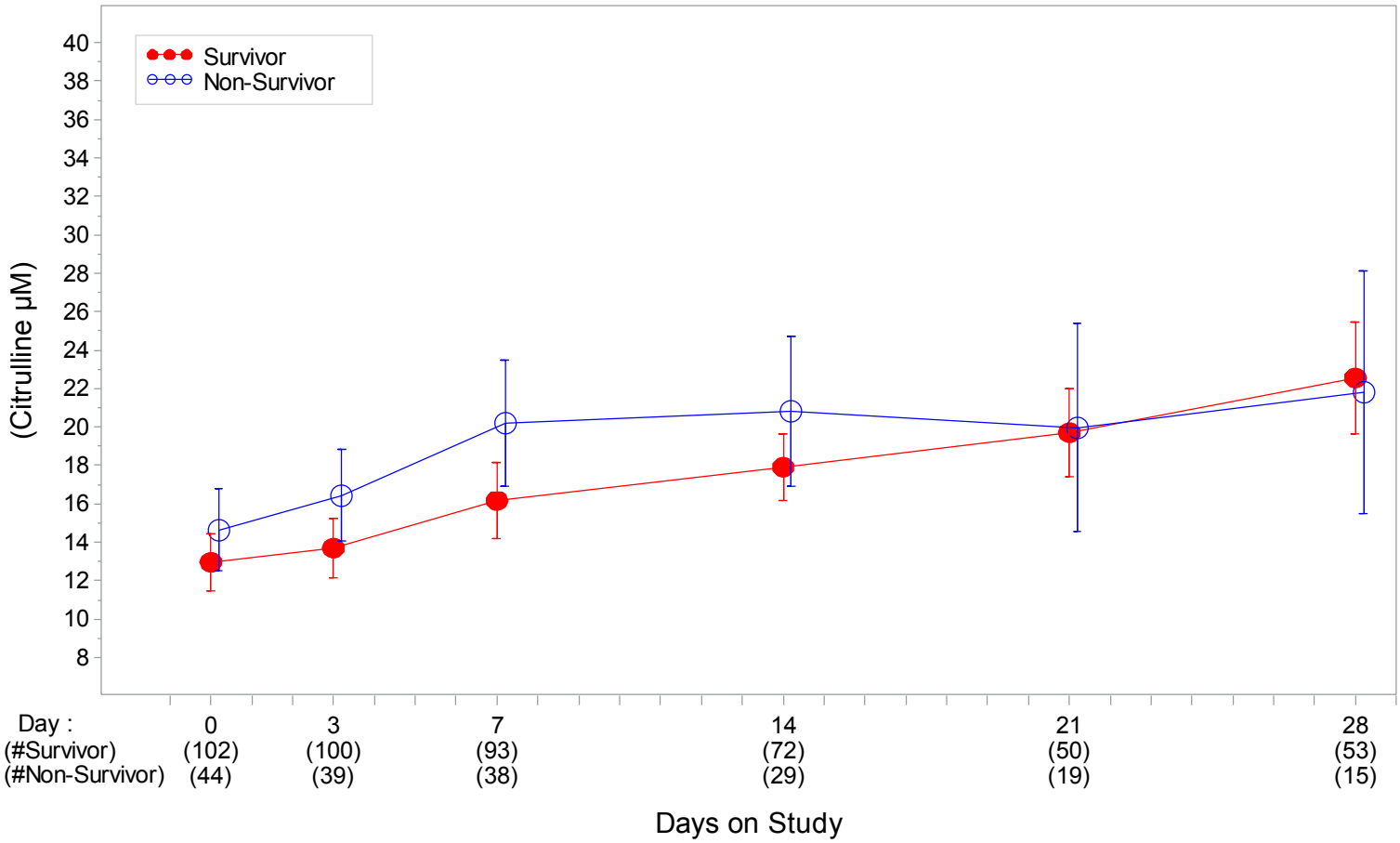
Table1: Citrulline Related Demo

Characteristic	*Overall (n=146)*	*Citrulline< 8μm (n=31)*	*Citrulline= 8~12μm (n=36)*	*Citrulline=12~17μm (n=41)*	*Citrulline>=17μm (n=38)*	*p value*
Age at Consent						
Mean ± SD (N)	60.2 ± 13.2(146)	56.3 ± 14.4(31)	59.3 ± 12.4(36)	62.6 ± 13.7(41)	61.8 ± 11.9(38)	0.20
Median[Q1-Q3]	61.2[53.7 - 68.6]	59.6[49.1 - 66.4]	59.1[53.0 - 68.2]	64.4[56.0 - 73.4]	61.9[54.3 - 69.9]	
[Min-Max]	[22.4 - 86.4]	[22.8 - 86.4]	[33.4 - 81.6]	[22.4 - 82.8]	[33.9 - 83.1]	
Gender						
Female	69/146(47.3%)	15/31(48.4%)	18/36(50.0%)	21/41(51.2%)	15/38(39.5%)	0.74
Male	77/146(52.7%)	16/31(51.6%)	18/36(50.0%)	20/41(48.8%)	23/38(60.5%)	
Race						
White	127/146(87.0%)	26/31(83.9%)	32/36(88.9%)	36/41(87.8%)	33/38(86.8%)	0.94
Black or African American	19/146(13.0%)	5/31(16.1%)	4/36(11.1%)	5/41(12.2%)	5/38(13.2%)	
Surgery Index						
Upper GI resection	5/146(3.4%)	0/31(0.0%)	1/36(2.8%)	3/41(7.3%)	1/38(2.6%)	0.65
Peritonitis	2/146(1.4%)	0/31(0.0%)	1/36(2.8%)	0/41(0.0%)	1/38(2.6%)	
Intestinal resection	98/146(67.1%)	25/31(80.6%)	24/36(66.7%)	23/41(56.1%)	26/38(68.4%)	
Vascular	31/146(21.2%)	6/31(19.4%)	8/36(22.2%)	10/41(24.4%)	7/38(18.4%)	
Cardiac valve	5/146(3.4%)	0/31(0.0%)	2/36(5.6%)	2/41(4.9%)	1/38(2.6%)	
CABG	5/146(3.4%)	0/31(0.0%)	0/36(0.0%)	3/41(7.3%)	2/38(5.3%)	
1.3 APACHE II						
APACHE >15	76/146(52.1%)	12/31(38.7%)	21/36(58.3%)	20/41(48.8%)	23/38(60.5%)	0.26

Characteristic	*Overall (n=146)*	*Citrulline< 8µm (n=31)*	*Citrulline= 8~12µm (n=36)*	*Citrulline=12~17µm (n=41)*	*Citrulline>=17µm (n=38)*	*p value*
APACHE <=15	70/146(47.9%)	19/31(61.3%)	15/36(41.7%)	21/41(51.2%)	15/38(39.5%)	
APACHE at Entry						
Mean ± SD (N)	15.8 ± 6.3(146)	14.5 ± 6.1(31)	15.8 ± 4.8(36)	16.1 ± 7.9(41)	16.4 ± 6.0(38)	0.49
Median[Q1-Q3]	16.0[12.0 - 20.0]	12.0[11.0 - 19.0]	16.0[13.0 - 19.0]	15.0[10.0 - 20.0]	17.0[13.0 - 22.0]	
[Min-Max]	[2.0 - 36.0]	[2.0 - 28.0]	[4.0 - 26.0]	[5.0 - 36.0]	[3.0 - 26.0]	
Days in SICU prior to study entry						
Mean ± SD (N)	4.4 ± 3.5(146)	3.8 ± 2.5(31)	4.4 ± 3.2(36)	5.1 ± 4.9(41)	4.1 ± 2.8(38)	0.51
Median[Q1-Q3]	4.0[2.0 - 6.0]	3.0[2.0 - 5.0]	4.0[2.0 - 6.0]	4.0[3.0 - 6.0]	4.0[2.0 - 6.0]	
[Min-Max]	[1.0 - 31.0]	[1.0 - 13.0]	[1.0 - 14.0]	[1.0 - 31.0]	[1.0 - 14.0]	
Days in ICU post enrollment						
Mean ± SD (N)	11.0 ± 11.7(146)	11.2 ± 15.5(31)	10.8 ± 9.8(36)	10.7 ± 9.5(41)	11.5 ± 12.4(38)	0.94
Median[Q1-Q3]	7.0[3.0 - 16.0]	6.0[3.0 - 16.0]	7.0[2.5 - 17.0]	7.0[3.0 - 19.0]	8.0[5.0 - 15.0]	
[Min-Max]	[0.0 - 81.0]	[1.0 - 81.0]	[1.0 - 34.0]	[0.0 - 30.0]	[0.0 - 56.0]	
Days in Hospital prior to study entry						
Mean ± SD (N)	8.5 ± 9.1(146)	10.7 ± 11.3(31)	7.5 ± 5.3(36)	9.4 ± 11.9(41)	6.6 ± 5.4(38)	0.54
Median[Q1-Q3]	6.0[3.0 - 10.0]	7.0[3.0 - 14.0]	6.0[4.0 - 9.5]	7.0[4.0 - 9.0]	5.5[3.0 - 9.0]	
[Min-Max]	[-1.0 - 71.0]	[1.0 - 52.0]	[2.0 - 24.0]	[1.0 - 71.0]	[-1.0 - 29.0]	
Days in hospital post enrollment						
Mean ± SD (N)	23.1 ± 21.4(146)	24.5 ± 18.9(31)	24.7 ± 15.3(36)	18.4 ± 12.2(41)	25.5 ± 32.9(38)	0.21
Median[Q1-Q3]	19.0[11.0 - 28.0]	20.0[12.0 - 29.0]	20.0[14.5 - 33.5]	18.0[10.0 - 24.0]	16.0[11.0 - 27.0]	
[Min-Max]	[1.0 - 201.0]	[7.0 - 81.0]	[6.0 - 85.0]	[1.0 - 65.0]	[4.0 - 201.0]	

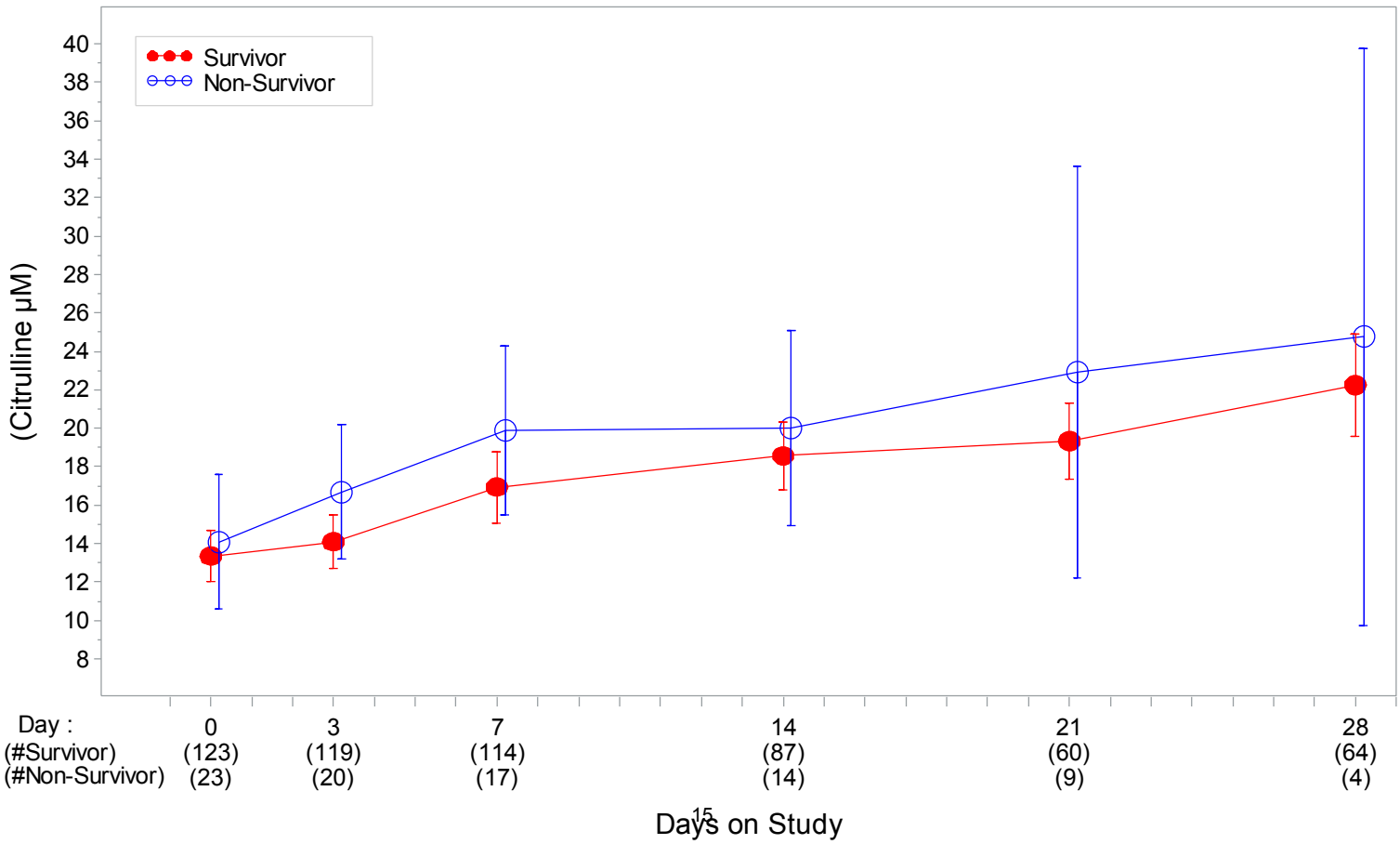
Citrulline by 6-Month Mortality

p(Group)= 0.3134 , p(Days)=<0.0001 , p(Group*Days)= 0.4260



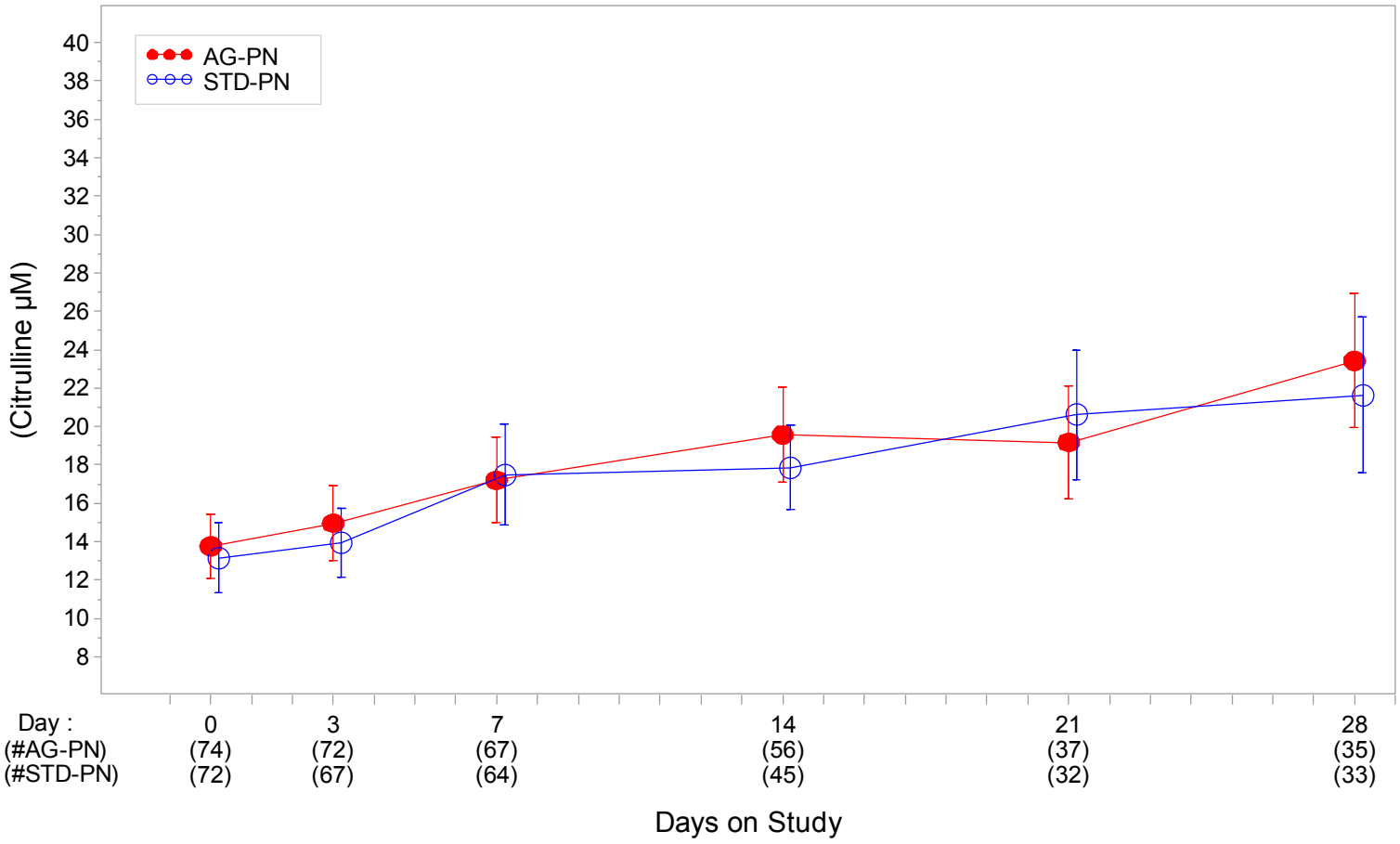
Citrulline by In-Hospital Mortality

p(Group)= 0.4512 , p(Days)=<0.0001 , p(Group*Days)= 0.2473



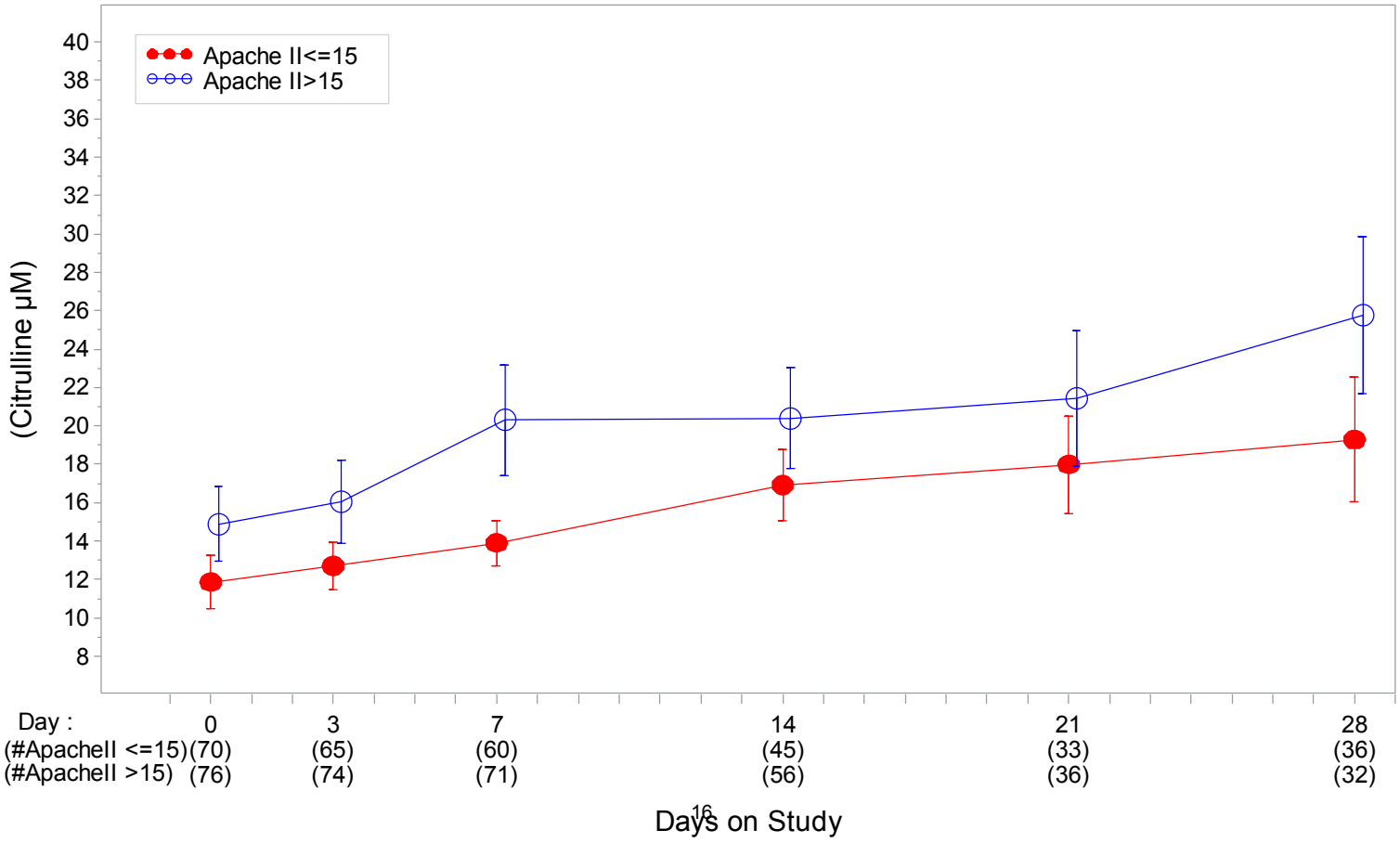
Citrulline by Treatment

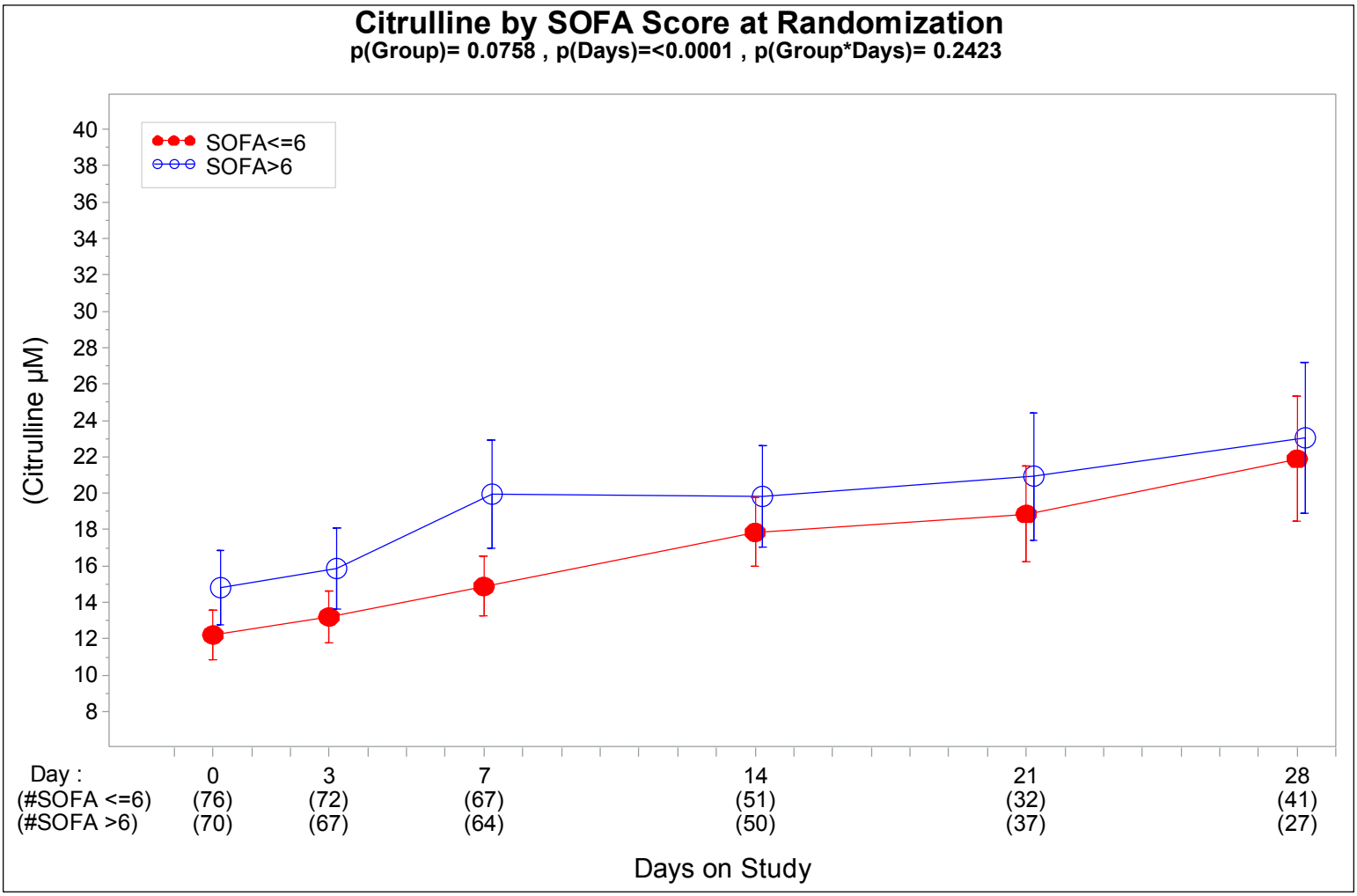
p(Group)= 0.6980 , p(Days)=<0.0001 , p(Group*Days)= 0.3067



Citrulline by Apache II Score at Randomization

p(Group)= 0.0017 , p(Days)=<0.0001 , p(Group*Days)= 0.0707




Citrulline by SOFA Score at Randomization
p(Group)= 0.0758 , p(Days)=<0.0001 , p(Group*Days)= 0.2423
SOFA<=6
SOFA>6
(Citrulline µM)
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
Day :
(#SOFA <=6)
(#SOFA >6)
0 (76) (70)
3 (72) (67)
7 (67) (64)
14 (51) (50)
21 (32) (37)
28 (41) (27)
Days on Study

Model Based Estimate of Citrulline by 6-Month Mortality and Days on Study

Day	*Survivor Mean[95%CI], N*	*Non-Survivor Mean[95%CI], N*
0	13.0(11.5, 14.5), 102	14.6(12.5, 16.8), 44
3	13.7(12.1, 15.2), 100	16.4(14.0, 18.8), 39
7	16.2(14.2, 18.1), 93	20.2(16.9, 23.5), 38
14	17.9(16.2, 19.6), 72	20.8(16.9, 24.7), 29
21	19.7(17.4, 22.0), 50	20.0(14.5, 25.4), 19
28	22.6(19.7, 25.4), 53	21.8(15.5, 28.1), 15

Model Based Estimate of Citrulline by In-Hospital Mortality and Days on Study

Day	*Survivor Mean[95%CI], N*	*Non-Survivor Mean[95%CI], N*
0	13.3(12.0, 14.7), 123	14.1(10.6, 17.6), 23
3	14.1(12.7, 15.5), 119	16.7(13.2, 20.2), 20
7	16.9(15.1, 18.8), 114	19.9(15.5, 24.3), 17
14	18.6(16.8, 20.3), 87	20.0(14.9, 25.1), 14
21	19.3(17.3, 21.3), 60	22.9(12.2, 33.6), 9
28	22.3(19.6, 24.9), 64	24.8(9.8, 39.8), 4

Model Based Estimate of Citrulline by Treatment and Days on Study

Day	*AG-PN Mean[95%CI], N*	*STD-PN Mean[95%CI], N*
0	13.8(12.1, 15.4), 74	13.1(11.3, 15.0), 72
3	15.0(13.0, 16.9), 72	14.0(12.2, 15.8), 67
7	17.2(15.0, 19.4), 67	17.5(14.9, 20.1), 64
14	19.6(17.1, 22.0), 56	17.9(15.7, 20.0), 45
21	19.2(16.3, 22.1), 37	20.6(17.2, 24.0), 32
28	23.4(19.9, 26.9), 35	21.6(17.6, 25.7), 33

Model Based Estimate of Citrulline by Apache>15 and Days on Study

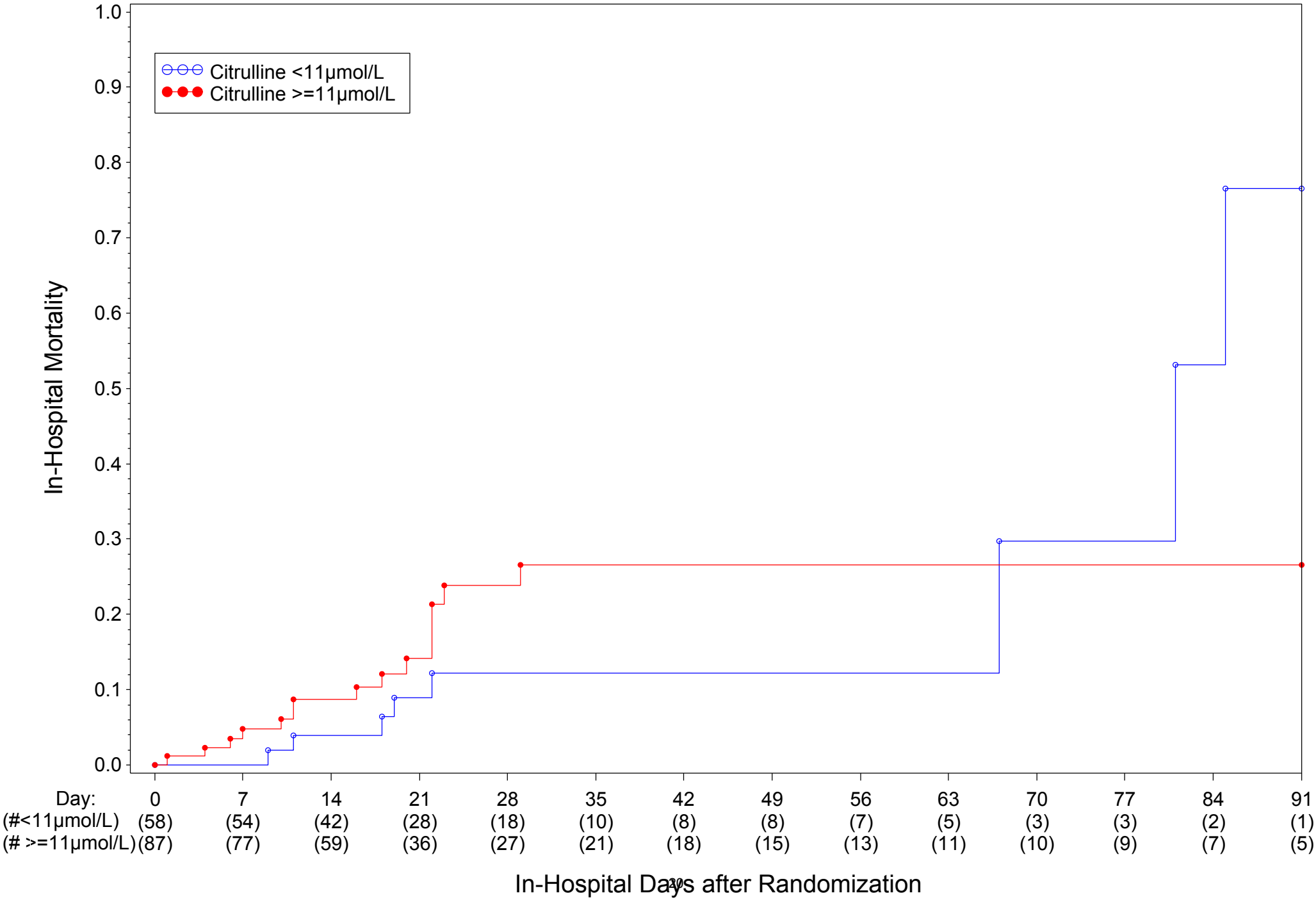
Day	*Apache<=15* *Mean[95%CI], N*	*Apache>15* *Mean[95%CI], N*
0	11.9(10.5, 13.2), 70	14.9(13.0, 16.8), 76
3	12.7(11.4, 14.0), 65	16.1(13.9, 18.2), 74
7	13.9(12.7, 15.1), 60	20.3(17.4, 23.2), 71
14	16.9(15.1, 18.8), 45	20.4(17.8, 23.0), 56
21	18.0(15.4, 20.5), 33	21.4(17.9, 24.9), 36
28	19.3(16.0, 22.5), 36	25.8(21.7, 29.8), 32

Model Based Estimate of Citrulline by SOFA>6(Median) and Days on Study

Day	*SOFA<=6* *Mean[95%CI], N*	*SOFA>6* *Mean[95%CI], N*
0	12.2(10.8, 13.6), 76	14.8(12.7, 16.9), 70
3	13.2(11.8, 14.7), 72	15.9(13.6, 18.1), 67
7	14.9(13.2, 16.5), 67	20.0(17.0, 22.9), 64
14	17.9(16.0, 19.8), 51	19.8(17.0, 22.6), 50
21	18.9(16.2, 21.5), 32	20.9(17.4, 24.4), 37
28	21.9(18.4, 25.3), 41	23.1(18.9, 27.2), 27

In-Hospital Mortality by Baseline Plasma Citrulline Levels (Number of Death=23)

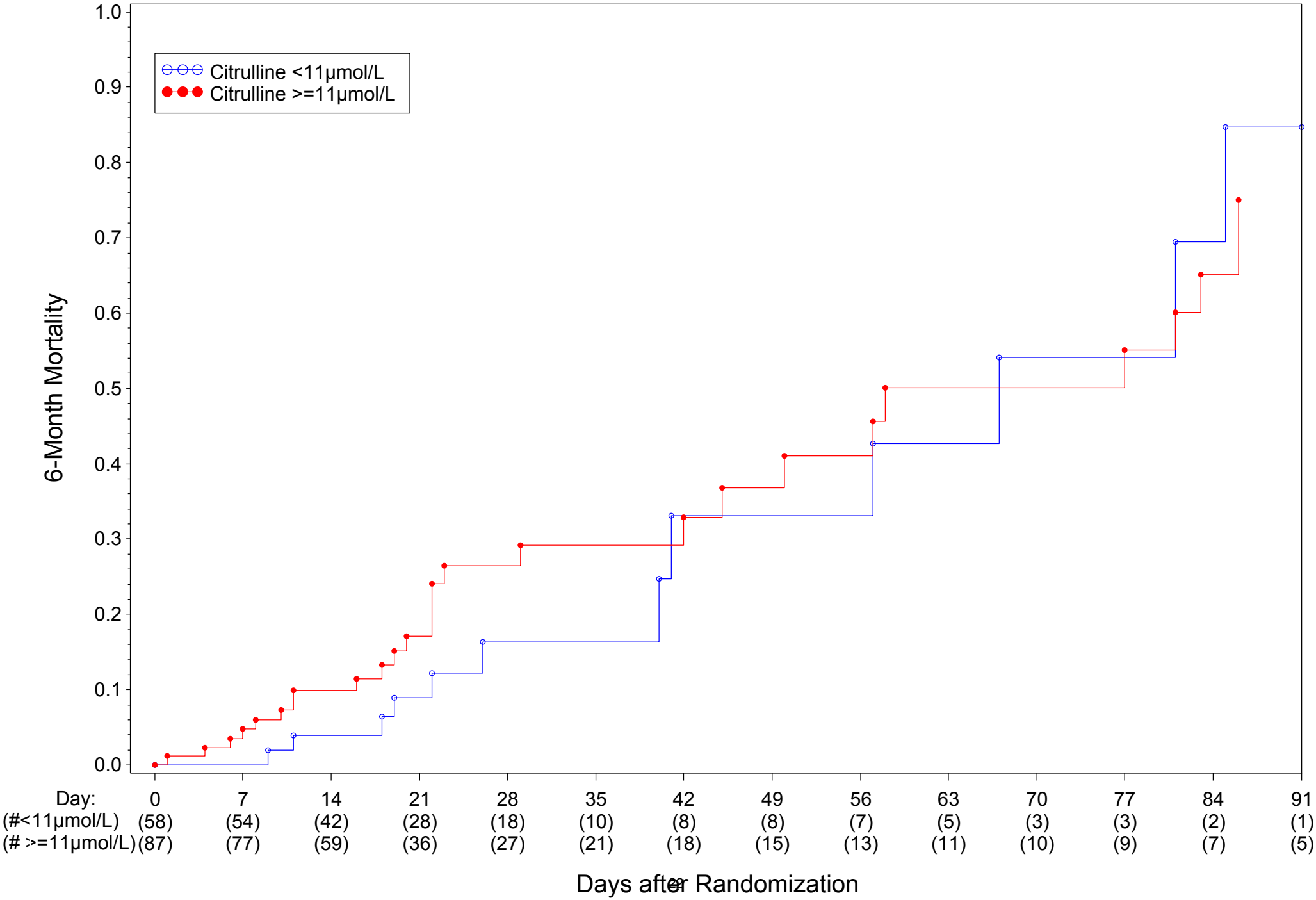
Log-Rank Test: p=0.59



Citrulline	*Days on Study*	*Motality(%)*	*Survival Standard Error*	*Number Left*
<11 µmol/L	30	0.1220	0.0524	16
>=11 µmol/L	30	0.2662	0.0633	25

6-Month Mortality by Baseline Plasma Citrulline Levels (Number of Death=44)

Log-Rank Test: p=0.68



Citrulline	Days on Study	Motality(%)	Survival Standard Error	Number Left
<11 µmol/L	30	0.1639	0.0645	16
>=11 µmol/L	30	0.2915	0.0638	25