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Research Article

Plasma Citrulline and Arginine Levels: Early Predictors of Outcome in Critically Ill Children

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Abstract

Background:
Citrulline and arginine are amino acids with essential roles in immune function, nitrogen metabolism, and endothelial regulation. In critical illness, reduced levels of these amino acids may reflect enterocyte dysfunction, systemic inflammation, and impaired recovery. This study evaluated plasma citrulline and arginine levels in critically ill children and their associations with inflammation, illness severity, and clinical outcomes.

Methods:
A prospective observational cohort study was conducted in the Pediatric Intensive Care Unit (PICU) of Lok Nayak Hospital, New Delhi, from May 2018 to January 2019. Children aged 1 month to 12 years were enrolled within 72 hours of developing critical illness. Plasma citrulline and arginine were measured at baseline (12–24 h), Day 3, and Day 7 using tandem mass spectrometry. Inflammatory markers (CRP, PCT) and clinical parameters (PRISM III score, organ dysfunction, outcome) were recorded. Associations between amino acid levels and clinical outcomes were statistically analyzed.

Results:
Seventy-one children (median age 18 months) were included. Favorable outcomes were observed in 49.3%, while 50.7% had unfavorable outcomes, including organ dysfunction or death. Baseline citrulline and arginine levels were lower in children with unfavorable outcomes. Levels in these children remained suppressed on Days 3 and 7, while those with favorable outcomes showed significant rises over time. Amino acid levels were inversely correlated with CRP and PCT, duration of PICU stay, and need for mechanical ventilation. Children who were non-ventilated had higher amino acid levels at all time points.

Conclusion:
Plasma citrulline and arginine levels are significantly reduced in critically ill children, particularly in those with poor outcomes. Their dynamic changes and correlations with inflammatory markers suggest their potential utility as early biomarkers of disease severity, intestinal integrity, and prognosis in pediatric critical care.

Keywords:
Citrulline, Arginine, Critical Illness, Pediatric Intensive Care, Biomarkers

Introduction

Citrulline is a non-essential amino acid primarily synthesized in the enterocytes of the small intestine from glutamine and its derivatives during the urea cycle. It may also be formed from arginine via nitric oxide synthase. Once produced, citrulline is released into circulation and subsequently extracted by the kidneys, where it is converted into L-arginine. Normal plasma citrulline levels range from 20–40 µmol/L and reflect the balance between intestinal synthesis and renal metabolism.[1,2] Arginine, derived from both dietary sources and endogenous citrulline metabolism, is considered a conditionally essential amino acid in stress states. Normal plasma arginine levels in children range from 14–147 µmol/L. [3]

Arginine plays a crucial role as a precursor for protein synthesis and metabolic pathways, including nitric oxide (NO), urea, polyamines, creatine, and proline synthesis. NO, a biologically active molecule produced from arginine in endothelial cells and macrophages, contributes to vasodilation, immune modulation, neurotransmission, and regulation of platelet and leukocyte adhesion. During systemic inflammatory response syndrome (SIRS), NO production increases, reflecting immune activation and contributing to disease pathophysiology.[4]

Critically ill patients often exhibit significantly reduced plasma levels of citrulline and arginine. Impaired enterocyte function, caused by reduced splanchnic perfusion, leads to decreased citrulline synthesis. This intestinal dysfunction, coupled with increased gut permeability and bacterial translocation, contributes to systemic inflammation and sepsis. Consequently, reduced citrulline availability limits renal arginine synthesis, while increased arginase activity and NO production further deplete plasma arginine during critical illness .[3,5]

Several studies have demonstrated that lower levels of citrulline and arginine are associated with poorer clinical outcomes, including multi-organ dysfunction and mortality. These amino acids have shown promise as biomarkers of disease severity and prognostic indicators in critically ill children. Their concentrations are inversely related to markers of inflammation such as C-reactive protein (CRP), and their recovery tends to parallel clinical improvement. Despite emerging evidence, limited pediatric data are available, and the role of supplementation remains under investigation.[6-8]

Given these gaps, this study aimed to evaluate plasma citrulline and arginine levels in critically ill children admitted to a tertiary care PICU and to assess their association with disease severity, inflammation, and clinical outcomes.

Materials and Methods

Study Design and Setting

This was a single-center, observational cohort study conducted in the Pediatric Intensive Care Unit (PICU) of Lok Nayak Hospital, New Delhi, over a nine-month period (May 2018–January 2019).

Participants

Children aged 1 month to 12 years admitted to PICU within 72 hours of onset of critical illness and expected to require ≥3 days of intensive care were eligible. Exclusion criteria included recent gastrointestinal surgery, abdominal radiotherapy, intestinal inflammation or necrosis, underlying chronic systemic illness, major congenital anomalies, or children transferred from other hospitals or presenting in non-salvageable condition.

Study Procedure

After obtaining informed consent from guardians, eligible participants underwent detailed clinical assessment, including history, examination, and laboratory investigations. The Pediatric Risk of Mortality (PRISM III) score was recorded at admission to assess illness severity. [9]

Plasma citrulline and arginine levels were measured at predefined intervals:

1. **Baseline** – within 12–24 hours of PICU admission
2. **Day 3** – 72 hours after admission
3. **Day 7** – for children who remained in PICU for ≥7 days

Acute phase reactants, including CRP and procalcitonin (PCT), were measured concurrently. Clinical progress was monitored for development of new complications (e.g., organ dysfunction, shock) or recovery. Based on outcomes, children were categorized into:

- **Favorable outcome** – recovery and discharge without new complications
- **Unfavorable outcome** – death or new-onset organ dysfunction

Definitions of Organ Dysfunction¹⁴

- **Pulmonary:** $PaO_2/FiO_2 < 300$, $PaCO_2 > 65$ mmHg, or increase of >20 mmHg from baseline
- **Cardiovascular:** Need for vasoactive drugs to maintain perfusion or clinical signs of shock
- **Renal:** Serum creatinine >2× baseline
- **Hematological:** Platelet count <80,000 or 50% fall from baseline, INR >2
- **Hepatic:** ALT >2× baseline or bilirubin >4 mg/dL

- **Neurological:** Glasgow Coma Scale (GCS) <11 or drop in GCS by ≥3 points [10,11]

Sample Collection and Analysis

Three drops of blood were collected on dry filter paper after ≥3 hours of fasting to ensure post-absorptive amino acid levels. Samples were stored at −22°C and later analyzed using tandem mass spectrometry. Serum for CRP and PCT was stored at −80°C and analyzed when reagents were available.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. Group comparisons were made using Chi-square test for categorical data and Mann-Whitney U test or Kruskal-Wallis test for non-parametric continuous data. Changes over time were analyzed using Wilcoxon signed-rank test and Friedman test. Correlation analyses were performed using Spearman's rank correlation coefficient. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the institutional ethics committee. Written informed consent was obtained from the guardians of all participants. Confidentiality and privacy were maintained throughout the study. Participation was voluntary, and families were informed of their right to withdraw at any point without prejudice to care.

Results

A total of 71 children were enrolled, with a median age of 18 months (IQR: 7–84). Of these, 35 (49.3%) had favorable outcomes (Group A), while 36 (50.7%) had unfavorable outcomes (Group B). Group B was further divided into those who developed organ dysfunction (B-I, n=24) and those who died during PICU stay (B-II, n=12). Children with comorbidities, surgical diagnoses, or those who died within 24 hours of admission were excluded.

Respiratory and cardiovascular systems were the most commonly involved. Age and sex distribution were comparable between Groups A and B. However, Group B had significantly higher PRISM III scores (15.36 ± 6.15 vs. 4.23 ± 2.11; $p<0.001$) and greater need for mechanical ventilation (78.8% vs. 20%; $p<0.001$). No significant difference was found in duration of ventilation or PICU stay between the groups. Within Group B, children in B-I were younger than those in B-II (median 13 vs. 72 months; $p=0.042$) and had lower PRISM

III scores (median 12 vs. 20; p=0.007).

Among patients with organ dysfunction, cardiovascular instability was most common (83.3%), followed by hematologic (75%), renal (69.4%), neurologic (66.7%), hepatic (36.1%), and pulmonary dysfunction (30.5%). Hepatic dysfunction and abnormal INR were significantly more frequent in Group B-II. Further comparison among BI and BII is shown in Table1.

CRP and PCT levels declined significantly over time in Group A, while Group B showed persistently elevated PCT levels on Days 3 and 7 (p<0.05). Albumin levels rose in Group A but fell in Group B. Glucose levels were significantly higher in Group B on Days 3 and 7 (p<0.05). Leukocyte counts did not show significant change in Group B-II.

Baseline citrulline levels were lower in Group B than Group A (7.25 ± 3.09 vs. 9.83 ± 4.89 µmol/L; p=0.052), with significant intergroup differences emerging on Days 3 and 7 (p=0.001 and p=0.014, respectively). Arginine levels showed a similar trend, with significantly lower values in Group B on Day 3 (p=0.009). Both citrulline and arginine levels demonstrated rising trends in Group A but remained suppressed in Group B.

Non-ventilated patients had higher citrulline and arginine levels at all time points. This difference was significant for citrulline on Days 1, 3, and 7 (p<0.05) and for arginine on Days 3 and 7 (p=0.01). A rising trend in these biomarkers was associated with shorter PICU stay and reduced duration of ventilation, though not statistically significant. Table 2 is illustrating the citrulline and arginine levels during 1 to 7 days among A, BI and BII. comparison of changes in citrulline and arginine level with ventilation status is depicted in table3.

Negative correlations were observed between PCT and both citrulline and arginine levels, particularly on Days 3 and 7 (p<0.05). CRP also showed a significant negative correlation with citrulline at all time points and with arginine on Days 1 and 3.

Table 1: comparison of group BI and group BII

	B I N = 24	**B II** N = 12	**P value**
Age			.042**
Mean (SD)	35.29 ± 40.52	66.67 ± 49.14	
Median (IQR)	13 (4.5-60.5)	72 (12.25-103)	
Sex			0.289*
Female (%)	14 (58.3)	4 (33.3)	
Male (%)	10(41.7)	8 (66.7)	

Prism III score- Mean (SD) Median (IQR)	13.5 ± 5.83 12(10-17)	19.08 ± 5.14 20 (14-23)	0.007**
Ventilated	70.8%	91.7%	0.321*
Mechanical ventilation (days) Mean (SD) Median (IQR)	7.53 ± 5.20 6 (4-13)	9.82 ± 9.87 5 (3.5-10)	0.887**
PICU stay (days) Mean (SD) Median (IQR)	12.46 ± 8.82 9.5 (6-16.5)	13.75 ± 11.4 7 (4.75-22.75)	0.840**
Complications			
Cardiovascular (required ionotropic support)	20(83.33%)	10 (83.33%)	1.000*
Hepatic dysfunction (i)ALT > 2 times (ii) S.Bilirubin> 4mg/dl	 3 (12.5%) 0	 10 (83.33%) 4 (33.33%)	 0.0001* 0.015*
Pulmonary dysfunction (i)PaO_2/FiO_2 < 300 (ii)$PaCO_2$>65 or rise of 20 mmHg	 3 (12.5%) 6 (25%)	 5 (41.6%) 5 (41.6%)	 0.119* 0.522*
Haematological dysfunction (i)Platelet count <80,000 or reduction from baseline by >50% over 3 days (ii)INR>2	 83% 6 (24%)	 9 (75%) 9 (75%)	 0.466* 0.012*

Neurological dysfunctions (fall in GCS by 3)	15 (62.5%)	9 (75%)	0.708*
AKI	16 (66.67%)	9 (75%)	0.898*
Complications	**B I** N = 24	**B II** N = 12	**P**

Group BI had significantly younger patients. There were more females as compared to males in Group B1 but the difference was not statistically significant. More patients in

Group B II were ventilated and they had higher PRISM III scores. Duration of ventilation and PICU stay was longer in Group B II. Various organ dysfunctions were seen in both group B1 and BII. However hepatic dysfunction and deranged INR were significantly more common in group BII.

Table 2: citrulline and arginine levels in various groups over 7 days

Analyte Mean ± SD Median(IQR)	**Group A**	**Group B**	**P value**	**Group B-I**	**Group B-II**	**P value**
Citrulline						
Day 1	9.83 ± 4.90 8.98(5.79-14.68)	7.25 ± 3.09 7.66(5.13-9.65)	0.052	7.48 ± 3.27 7.93(5.17-9.76)	6.78 ± 2.79 6.45(4.90-8.62)	0.524
Day 3	12.06 ± 8.45 9.54(7.35-13.86)	6.99 ± 3.00 6.34(4.54-8.59)	0.001	7.18 ± 2.88 6.34(5.21-8.61)	6.59 ± 3.33 6.09(4.08-8.04)	0.402
Day 7	14.16 ± 8.75 11.65(8.65-18.79)	8.95 ± 5.43 7.57(6.55-10.00)	O.014	9.52 ± 6.53 7.76(6.46-9.94)	7.93 ± 2.57 7.16(6.78-10.00)	0.821
P value	0.355	0.228		0.444	0.097	

P (D1-D3)	0.149	0.637		0.568	0.875	
P (D1-D7)	0.052	0.054		0.408	0.015	
Arginine						
Day 1	11.81 ± 13.98 7.92(4.45-13.23)	9.19 ±5.36 8.46(4.35-12.67)	0.977	10.43 ± 5.75 9.65(5.87-13.94)	6.71 ± 3.51 4.86(3.88-9.18)	0.107
Day 3	17.77 ± 16.36 12.17 (5.07-24.59)	8.36 ± 5.75 7.3(3.88-10.03)	0.009	9.42 ± 6.00 9.14(4.18-11.36)	6.24 ± 4.73 4.72(3.55-7.54)	0.081
Day 7	17.49 ± 15.29 12.88(5.96-22.61)	11.34 ± 11.33 6.71(4.44-12.07)	0.056	12.84 ± 12.56 8.37(4.79-16.47)	8.66 ± 8.77 5.24(4.44-7.67)	0.396
P value	0.060	0.340		0.444	0.236	
P (D1-D3)	0.036	0.148		0.253	0.433	
P (D1-D7)	0.025	0.677		0.959	0.314	

The difference between the citrulline levels of 2 groups (group A and group B) on D1 just reached level of significance. In group A there was rise in citrulline levels on D3 and D7. However in group B there was fall on D3 and slight rise on D7 which was not significant and was still lower than the baseline value on D1. These differences in citrulline levels were not significant in either of the two groups (group A and B) except for D7 for both groups.There was significant difference in citrulline levels between groups A and B on D3 and D7

Table3: comparison of changes in citrulline and arginine level with ventilation status

Changes in Citrulline level (Mean ± SD)	**Not ventilated**	**Ventilated**	**P value**
Cit1-Cit3	1.38±3.83	0.54±4.02	0.75**

Cit1-Cit7	2.19±8.91	-0.81±6.23	0.11**
Cit3 -Cit7	1.08±10.67	-0.74±4.92	0.07**
Changes in Arg level (Mean ± SD)			
Arg1 -Arg 3	6.03±14.47	-1.10±7.48	0.01**
Arg 1 - Arg 7	4.30±16.16	-0.35±9.43	0.27**
Arg 3 -Arg 7	-2.32±21.01	0.61±8.92	0.74**

******Man Whitney U tests

Citrulline and arginine levels were compared between cases who required ventilation and those who did not require ventilation to see whether there was any change in their level. Their levels were rising in those who did not require ventilation. Their rising trend was found to be significantly more over D3 to D7 in citrulline and D1-D3 in arginine. However it can be associated with the level of sickness in ventilated children (i.e., low citrulline and arginine levels) since, they were more sick than not ventilated children.

Table3: correlation of CRP and PCT level with citrulline and arginine level over 7 days.

		CIT1	**CIT3**	**CIT7**	**ARG1**	**ARG3**	**ARG7**
CRP1	r value##	-.302	-.291	-.334	-.121	-.239	-.145
	p value**	.010	.014	.015	.317	.045	.306
CRP3	r value##	-.343	-.305	-.378	-.156	-.393	-.105
	p value**	.003	.010	.006	.193	.001	.457
CRP7	r value##	-.173	-.257	-.451	-.112	-.283	-.321
	p value**	.208	.059	.001	.416	.036	.020
PCT1	r value##	-.068	-.264	-.470	.069	-.268	-.104
	p value**	.576	.026	.000	.565	.024	.463
PCT3	r value##	-.200	-.295	-.512	.006	-.251	-.268
	p value**	.099	.014	.000	.959	.038	.055
PCT7	r value##	-.290	-.405	-.511	.042	-.326	-.449
	p value**	.031	.002	.000	.762	.015	.001

** Man Whitney U test

spearman's correlation coefficient

Correlation of CRP with CIT- CRP on D1 was significantly negatively correlated with citrulline levels on D1, D3 and D7. Similarly it was also significantly negatively correlated citrulline levels on D3 and D7.

Correlation of PCT with CIT- PCT was negatively correlated with citrulline at all times and it was found to be statistically significant except for D1.

Discussion

This study assessed plasma citrulline and arginine levels in critically ill children and their association with inflammation and clinical outcomes. Our findings show significantly reduced levels of both amino acids in critically ill children, particularly among those with unfavorable outcomes, supporting their potential role as biomarkers of disease severity and gut function.

The median age in our cohort was 18 months (IQR 7–84), higher than the median ages reported by Alonsoa et al. (7.3 months) and Waardenberg et al. (ranging from 1 month to 16 years across subgroups) [3,5]. Differences in age distribution across studies may reflect variable inclusion criteria and illness patterns. Our patients had a median PICU stay of 7 days, with mechanical ventilation used in 49.3%, comparable to the 6-day stay reported by Alonsoa et al., but with lower ventilation rates (90.2% in their study) [3]. Waardenberg et al. reported mechanical ventilation in up to 84.2% of children, depending on the illness category [5].

Our study excluded children with conditions likely to confound citrulline and arginine levels, including abdominal surgery, renal disease, and congenital heart defects. This allowed us to isolate the effect of acute critical illness on amino acid metabolism. Previous studies have shown that reduced plasma citrulline reflects enterocyte dysfunction and impaired gut barrier integrity, common in SIRS and sepsis [12]. Arginine, a semi-essential amino acid, may be depleted due to increased arginase activity and nitric oxide synthesis during systemic inflammation.[13]

The mean citrulline level in our cohort was 8.52±4.26 μmol/L, significantly lower than normal pediatric reference ranges (20–40 μmol/L).[3] Children with favorable outcomes had higher citrulline levels (9.83±4.89 μmol/L) compared to those with unfavorable outcomes (7.25±3.09 μmol/L). Importantly, citrulline levels rose during recovery in the favorable group, consistent with Alonsoa et al., who also found dynamic changes over time [3]. However, levels in both groups remained below normal, indicating sustained enterocyte dysfunction during the illness course.

Arginine levels followed a similar trend. The mean value was 10.48±10.54 μmol/L (normal: 14–147 μmol/L), with higher concentrations in the favorable group (11.81±13.98 μmol/L) than in the unfavorable group (9.19±5.36 μmol/L). While the rise in arginine was significant in children with good outcomes, levels remained low throughout, reflecting ongoing metabolic stress. These results align with reports in both pediatric and

adult critically ill populations [7,14].

Interestingly, amino acid levels in our study were lower than those reported in Western populations. Possible explanations include ethnic variations, poor nutritional status among Indian children, and differences in timing of sample collection. Malnutrition is known to impair intestinal function and amino acid synthesis, which may contribute to these findings. [15,16]

CRP and PCT levels remained higher in the unfavorable outcome group throughout the observation period, inversely correlating with citrulline and arginine. This supports prior findings that inflammatory states suppress amino acid synthesis or increase catabolic use [3,5]. Children with favorable outcomes showed improvement in albumin levels and early enteral feeding, reflecting better gut recovery. In contrast, albumin declined in the unfavorable group, suggesting persistent dysfunction and inadequate nutrition.[17] Group B also showed signs of stress hyperglycemia, commonly associated with critical illness.

Age and gender were not significantly associated with citrulline or arginine levels, consistent with previous literature [3]. However, non-ventilated children showed relatively higher amino acid levels, particularly during recovery, although these differences were not statistically significant. This suggests that less severe illness may be associated with better preservation of gut and metabolic function.

The duration of mechanical ventilation and PICU stay negatively correlated with amino acid levels. Children with longer stays and extended ventilation showed slower recovery in citrulline and arginine levels. This finding highlights the utility of these markers in predicting illness trajectory and supports earlier studies that observed similar correlations [3,5,18].

CRP and PCT showed strong inverse associations with both amino acids across time points, reinforcing their relationship with systemic inflammation. CRP consistently showed negative correlation, while PCT's relationship varied slightly depending on illness stage. These findings underscore the relevance of citrulline and arginine as integrated markers of immune-metabolic balance.[19,20]

Overall, our study supports the utility of citrulline and arginine as early markers of illness severity, intestinal integrity, and prognosis in critically ill children. Persistent low levels were associated with poor outcomes and greater inflammation.

Conclusion

This study highlights the potential of plasma citrulline and arginine as biomarkers of disease severity, intestinal integrity, and prognosis in critically ill children. Persistent low levels, particularly among those with unfavorable outcomes, were inversely correlated with inflammatory markers and clinical severity indicators such as PICU stay and mechanical ventilation. These findings suggest that monitoring citrulline and arginine

alongside inflammatory markers may aid in early risk stratification and guide supportive care. Further studies are needed to validate their prognostic utility and explore their role in optimizing nutritional and clinical management.

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