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PREMIER RESEARCH PAPERS

Carnitine deficiency among hospitalized pediatric patients: A retrospective study of critically ill patients receiving extracorporeal membrane oxygenation therapy

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Abstract

Background: The metabolic demands associated with critical illness place patients at risk for nutrition deficits. Carnitine is a small molecule essential for fatty acid oxidation and gluconeogenesis. Secondary carnitine deficiency can have clinically significant complications and has been observed anecdotally in patients receiving extracorporeal membrane oxygenation (ECMO) therapy at our institution. Guidelines for monitoring and supplementing carnitine are lacking. This retrospective study determined whether critically ill pediatric patients receiving ECMO have an increased risk of carnitine deficiency.

Methods: Acylcarnitine analysis was performed on residual specimens from patients who received ECMO therapy. The control data were a convenience sample gathered by chart review of patients who had been tested for carnitine during a hospitalization.

Results: Acylcarnitines were measured in 217 non-ECMO patients and 81 ECMO patients. Carnitine deficiency, based on age-specific reference ranges, was observed in 41% of ECMO cases compared with 21% of non-ECMO cases. Multivariable analysis of age-matched patients identified that the odds of carnitine deficiency were significantly lower among patients on the floor compared with ECMO patients (odds ratio, 0.21; 95% CI, 0.10–0.44). Age-specific frequency of qualitative carnitine deficiency ranged from 15% (patients >5 years old) to 56% (patients 1 week to 1 month old) in ECMO patients and 15% (patients >5 years old) to 34% (patients 1–5 years old) in non-ECMO patients.

Conclusion: In this study, ECMO patients were carnitine deficient more frequently compared with other inpatients, with the highest rates of deficiency among ECMO patients between 1 week and 1 month old.

KEYWORDS
carnitine deficiency, carnitine supplementation, critical illness, ECMO, extracorporeal membrane oxygenation

CLINICAL RELEVANCY STATEMENT

Critically ill patients are metabolically stressed and can have compromised nutritional intake. Carnitine is a small molecule essential for fatty acid oxidation and is not typically included in parenteral nutrition. Carnitine deficiency can lead to hypoglycemia, cardiomyopathy and skeletal muscle weakness. Supplementation is easy to implement, if clinically indicated, however there are no guidelines for use and monitoring. This retrospective study was performed to address the question of prevalence of carnitine deficiency in hospitalized pediatric patients. The target study population was patients receiving ECMO support as these individuals may be the sickest and most likely to experience extreme clinical conditions that lead to nutritional carnitine deficiency. Our study found that patients on ECMO support are more likely to be carnitine deficient than other pediatric patients admitted to the hospital, however specific drivers (eg, PN use, dialysis, admission duration, etc.) were not identified.

INTRODUCTION

Disease places significant stress and metabolic demands on the body, and critically ill children are at high risk for nutrient deficiencies, which correlate with adverse clinical outcomes.[1–6] The goal of nutrition support in pediatric patients is to meet macronutrient and micronutrient needs while preserving lean body mass. Micronutrient deficiencies in pediatric intensive care unit (PICU) patients may be caused by suboptimal intake prior to admission, redistribution from circulation into tissues, or increased losses from the gastrointestinal tract, kidneys, skin, or drains.[7] Carnitine is a small molecule essential for fat metabolism and production of adenosine triphosphate in mitochondria.[8] Patients with carnitine deficiency can present with hypoglycemia, liver dysfunction, hyperammonemia, cardiomyopathy, and skeletal muscle weakness.[9] Isolated cases of carnitine deficiency have been described in which chronic parenteral nutrition (PN) led to clinically significant symptoms.[10,11] Notably, carnitine is not routinely supplemented in PN. Carnitine deficiency has also been noted in patients receiving dialysis, including both hemodialysis and continuous renal replacement therapy (CRRT) systems, and in the setting of other procedures (eg, fasting preparation for surgery).[10–14] These reports are limited in scope and do not provide broader guidance for nutrition management of carnitine. Although carnitine deficiency does not always cause clinical symptoms, carnitine is easily supplemented both enterally and parenterally to resolve any symptoms.[15,16] Excess supplementation, however, can cause gastrointestinal discomfort, diarrhea, and the production of trimethylamine, a compound with a fishy odor.[17] Given the potential benefits, carnitine supplementation may be an easily implemented practice to improve clinical outcomes; however, there are currently no guidelines for carnitine monitoring or supplementation for hospitalized patients. Most carnitine research has focused on adults, correlating supplementation with improved outcomes.[18–21]

At Seattle Children's Hospital, secondary carnitine deficiency was incidentally observed in children receiving extracorporeal membrane oxygenation (ECMO) therapy (laboratory observation), prompting questions about carnitine deficiency in critically ill pediatric patients. We hypothesized that carnitine deficiency in hospitalized children may be related to renal function, nutrition modalities, and clinical status and those receiving ECMO may represent the sickest patients with the greatest risk of developing carnitine deficiency. To improve patient care and laboratory services, formal studies in critically ill patients are needed to better understand carnitine metabolism and potential avenues of support to improve long-term outcomes. In this study, we evaluated the prevalence of carnitine deficiency among patients receiving ECMO therapy at Seattle Children's Hospital by retrospective analysis of residual blood samples and chart review and tried to identify factors that may be associated with an increased risk for developing carnitine deficiency.

METHODS

Residual plasma or serum samples from patients who received ECMO support at Seattle Children's Hospital between 2017 and 2020 were retained for acylcarnitine analysis. The number of samples per ECMO patient ranged from one to 20, and samples collected approximately 24 h apart were preferentially retained for longitudinal assessment. Residual plasma or serum was stored at −20 °C until acylcarnitine analysis could be performed. The comparison group is a convenience sample of inpatients identified via retrospective data review of plasma samples submitted for acylcarnitine profile or free and total carnitine testing as part of clinical management during 2018. Patients were identified based on order location within the hospital; samples from outpatient visits were excluded. Patients with a known diagnosis of an inborn error of metabolism were also excluded to prevent potential data skewing by patients known to have primary or secondary carnitine deficiency.

Acylcarnitines were quantified using tandem mass spectrometry following standard clinical laboratory procedures.[22,23] Data were collected on either a Waters Xevo TQ-S Micro or Xevo TQ tandem mass spectrometer; both instruments are maintained for clinical testing with routine correlations. Metabolites were quantified using NeoLynx software (Agilent, version 4.0). Free carnitine deficiency is based on age-specific reference ranges established for clinical testing: <1 week old

(10–33 μM), 1 week to 1 month old (16–57 μM), and >1 month old (18–65 μM). Total carnitine is calculated by summing free carnitine with all of the measured acylcarnitine species, ranging from acetylcarnitine (C2) to 3-hydroxy-octadecanoylcarnitine (C18-OH).

Patient demographics (including date of birth, gender, height and weight at time of admission, and dates and times of hospital admission and discharge) and clinical data were collected by retrospective chart review and entered into a REDCap database supported by the Institute for Translational Health Sciences.[24] Chart review included a review of standard chemistry labs for evidence of carnitine deficiency symptoms: low blood glucose or elevated liver function tests (aspartate aminotransferase, alanine aminotransferase, bilirubin-conjugated, unconjugated, or total), triglycerides, blood ammonia, or creatine kinase. Most cases did not measure triglycerides, blood ammonia, or creatine kinase during the 24 h prior to the collection of each blood sample (Table 1). Chart review also recorded the location of service, PELOD (pediatric logistic organ dysfunction) score as an approximation for severity of illness,[25] nutrition modality (oral, enteral, or PN), carnitine supplementation status, use of CRRT dialysis, number of transfusions, and types of blood products transfused (plasma, cryoprecipitate, red blood cells, or platelets) within 24 h prior to the time of sample collection. Medical cause for admission was recorded as part of the chart review; however, these data are highly variable and did not lend itself to categorization. Location at the time of sample draw (neonatal ICU [NICU]/cardiac ICU [CICU]/PICU, or other floor location within the hospital) and PELOD scores were intended as proxies for clinical severity to facilitate patient comparisons.

Descriptive statistics, including mean with SD, median with interquartile range (IQR), and counts with percentages, are summarized. Continuous data were assessed for normality with histograms and Q-Q plots. Samples retrieved from non-ECMO patients were categorized by location (NICU, PICU, and CICU vs other locations) for comparisons to distinguish critically ill patients in this group from those with less serious illness. Within each cohort, clinical exposures prior to sample collection were compared among carnitine-deficient and nondeficient patients using chi-squared or Fisher exact tests, as appropriate for categorical data, and *t*-tests and Mann-Whitney *U* tests for continuous data. Univariable and multivariable logistic regression assessed the association of illness severity (ECMO, other ICU, or floor) and age group (<1 week, 1 week to 1 month, 1 month to 1 year, 1–5 years, or >5 years of age) on the odds of observed carnitine deficiency, adjusting for gender and receipt of carnitine supplementation in the 24 h prior to sample collection. Odds ratios (ORs) with 95% CIs are displayed. An alpha value of 0.05 was used for significance testing. For patients with longitudinal data, the first sample was used for cohort comparisons.

This study was approved by Seattle Children's Hospital institutional review board (IRB) (study ID 1690). This study exclusively used residual clinical specimens. Frequently, there was significant time delay between patient admissions and the acylcarnitine analysis , so research data were not returned to care teams and there was no impact to patient care/clinical management. For all of these reasons and the potential to greatly reduce the pool of patient samples, Seattle Children's IRB approved the waiving of consent.

RESULTS

Hospitalized patients who were not receiving ECMO therapy (n = 217) were identified retrospectively by a review of clinically ordered acylcarnitine or free and total carnitine testing. Patient location at the time of sample collection was distributed throughout the hospital, with the largest number located in the medical/surgical units (Table 2); 43% (n = 93/217) of patients in this cohort were sampled from an ICU. Half of the patients (48 of 93 [52%] of those located in an ICU and 63 of 124 [51%] from non-ICU locations) were male. Acylcarnitines were measured in 81 ECMO patients ranging from 0 to 20 years of age; 40% (n = 32/81) were male. ECMO patients were primarily cared for within the CICU (n = 38/81; 47%), PICU (n = 21/81; 26%), and NICU (n = 22/81; 27%; Table 2). Patients sampled from the floor were older (median [IQR] age of 18.6 [3.6–68.2] months) than patients in the ICU (median age [IQR]; ECMO, 1.0 [0.2–20.9] months; non-ECMO, 2.0 (0.3–16.2) months; $P < .01$).

Carnitine levels and qualitative carnitine deficiency (free carnitine below the lower limit of normal) are described by cohort in Table 3. Given the role of carnitine in transport and the metabolism of acylcarnitines, total carnitine paralleled the free carnitine trends. Qualitative deficiency occurred frequently in each cohort but was most common among patients receiving ECMO (33 of 81 [41%] ECMO, 25 of 93 [27%] other ICU, and 21 of 124 [17%] patients from the floor were carnitine deficient). Age-specific patterns in the frequency of deficiency emerged (Figure 1 and Table 3). The lowest frequency of deficiency was observed among those >5 years of age for both ECMO and non-ECMO ICU patients (ECMO, 15.4% (n =2/13) deficient; median [IQR] free carnitine of 42.84 [29.02–56.37] μM; non-ECMO, 11.8% (n = 2/17) deficient, 31.51 [26.09–42.96] μM). Among ECMO patients, the highest frequency of carnitine deficiency was seen among patients 1 week to 1 month old (55.6% (n = 10/18) deficient, median [IQR] free carnitine of 14.66 [9.30–22.21] μM). Among non-ECMO ICU patients, the highest frequency was seen among patients 1 month to 1 year old (35.7% (n = 10/28) deficient, median (IQR) free carnitine of 26.57 [13.37–33.47] μM). Among patients on the floor, the lowest frequency was observed among patients 1 month to 1 year old (2.4% (n = 1/41) deficient, median [IQR] free carnitine of 29.14 [24.34–34.72] μM) and the highest frequency was seen among those 1–5 years old (34.4% (n = 11/32) deficient, median [IQR] free carnitine of 21.62 [15.28–26.73] μM). Among ECMO patients with longitudinal samples, patterns clustered for individual patients without obvious trends (Figure 3).

Accordingly, adjusted (controlling for age group, gender, and receipt of carnitine supplement) odds of observing free carnitine deficiency were lower among non-ECMO patients compared with ECMO patients; this difference was statistically significant among patients on the floor (OR [95% CI] non-ECMO ICU vs ECMO, 0.55 [0.28–1.09]; non-ECMO floor vs ECMO, 0.21 [0.10–0.44]) (Table 4). By age, the adjusted (controlling for illness severity, gender, and receipt of carnitine supplement) odds of observing free carnitine deficiency were lowest among patients ≥5 years of age; patients 1 week to 1 month and 1–5 years old had significantly increased odds of deficiency. The adjusted ORs and CIs between age groups were calculated (OR [95% CI] <1

TABLE 1 Comparison of clinical characteristics among carnitine-deficient vs nondeficient patients by ECMO status[b]

	ECMO patients			Non-ECMO ICU			Non-ECMO floor		
	Carnitine deficient ($n = 33$)	Normal carnitine ($n = 48$)	*P*-value	Carnitine deficient ($n = 25$)	Normal carnitine ($n = 68$)	*P*-value	Carnitine deficient ($n = 21$)	Normal carnitine ($n = 103$)	*P*-value
PELOD score, mean (SD)[a]	9.64 (4.25)	11.23 (4.60)	.1905	6.4 (5.0)	4.8 (4.2)	.2359	–	–	–
Duration of hospitalization prior to first sample, median days (IQR)	7.0 (2.0–11.4)	3.0 (0.8–13.5)	.1095	1.7 (0.9–3.3)	3.1 (0.9–9.3)	.3791	0.9 (0.1–1.8)	0.5 (0.1–2.2)	.6835
Clinical and nutritional exposures in last 24 h, n (%)									
PN	24 (72.7)	27 (56.3)	.1313	9 (36.0)	17 (25.0)	.2947	0 (0.0)	2 (1.9)	>.99
Supplemental carnitine	8 (24.2)	22 (45.8)	.048	7 (28.0)	33 (48.5)	.0763	1 (4.8)	21 (20.4)	.1192
MCT	2 (6.1)	6 (12.5)	.462	2 (8.0)	13 (19.1)	.3402	0 (0.0)	10 (9.7)	.2095
Transfusion (any type)	30 (90.9)	41 (85.4)	.5163	6 (24.0)	8 (11.8)	.2683	0 (0.0)	0 (0.0)	–
Platelets	17 (51.5)	25 (52.1)	.9599	1 (4.0)	1 (1.5)	.4675	0 (0.0)	0 (0.0)	–
Plasma	19 (57.6)	29 (60.4)	.7982	4 (16.0)	4 (5.9)	.2042	0 (0.0)	0 (0.0)	–
RBC	29 (87.9)	34 (70.8)	.0698	4 (16.0)	6 (8.8)	.4495	0 (0.0)	0 (0.0)	–
Cryoprecipitate	8 (24.2)	8 (16.7)	.4001	1 (4.0)	3 (4.4)	>.99	0 (0.0)	0 (0.0)	–
Dialysis (CRRT)	8 (24.2)	8 (16.7)	.4115	3 (12.0)	5 (7.4)	.7648	0 (0.0)	0 (0.0)	–
Abnormal labs in last 24 h, n (%)									
Blood glucose	3 (9.1)	4 (8.3)	>.99	4 (16.0)	8 (11.8)	.7279	4 (19.1)	13 (12.6)	.4866
LFTs	14 (42.4)	20 (41.7)	.9459	13 (52.0)	28 (41.2)	.3513	6 (28.6)	30 (29.1)	.9593
Triglycerides	0 (0.0)	1 (2.1)	>.99	1 (4.0)	1 (1.5)	.4675	0 (0.0)	2 (1.9)	>.99
Blood ammonia	0 (0.0)	1 (2.1)	>.99	2 (8.0)	2 (2.9)	.292	2 (9.5)	4 (3.9)	.2681
Creatinine kinase	1 (3.0)	0 (0.0)	.4074	1 (4.0)	7 (10.3)	.6776	3 (14.3)	5 (4.9)	.1333

Abbreviations: CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; MCT, medium-chain triglyceride; LFT, liver function test; PELOD, pediatric logistic organ dysfunction; PN, parenteral nutrition; RBC, red blood cell.

[a]Most recently recorded PELOD score within previous 24 h. Data available for 25 carnitine-deficient and 31 nondeficient carnitine patients receiving ECMO and 17 carnitine-deficient and 30 nondeficient patients not receiving ECMO in the ICU.

[b]As represented by free carnitine levels, day 1 sample.

TABLE 2 Descriptive statistics of population by ECMO status

	ECMO ($n = 81$)	Non-ECMO, ICU ($n = 93$)	Non-ECMO, floor ($n = 124$)	*P*-value
Male gender, n (%)	32 (39.5)	48 (51.6)	63 (50.8)	.2
Age, in months, at first sample, median (IQR)	1.0 (0.2–20.9)	2.0 (0.3–16.2)	18.6 (3.6–68.2)	<.0001
Age category at first sample, n (%)				
Under 1 week	23 (28.4)	22 (23.7)	4 (3.2)	
1 week to 1 month	18 (22.2)	17 (18.3)	11 (8.9)	
1 month to 1 year	15 (18.5)	28 (30.1)	41 (33.1)	
1–5 years	12 (14.8)	9 (9.7)	32 (25.8)	
>5 years	13 (16.1)	17 (18.3)	36 (29.0)	
Location, n (%)				
PICU	21 (25.9)	35 (37.6)	0 (0.0)	
CICU	38 (46.9)	20 (21.5)	0 (0.0)	
NICU	22 (27.2)	38 (40.9)	0 (0.0)	
Medical/surgical	0 (0.0)	0 (0.0)	81 (65.3)	
Cancer	0 (0.0)	0 (0.0)	2 (1.6)	
Other	0 (0.0)	0 (0.0)	41 (33.1)	

Abbreviations: CICU, cardiac intensive care unit; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; NICU, neonatal intensive care unit; Other, psychiatry and behavioral medicine or emergency department; PICU, pediatric intensive care unit.

week vs >5 years old, 1.58 [0.60–4.19]; 1 week to 1 month vs >5 years old, 2.70 [1.02–7.19]; 1 month to 1 year vs >5 years old, 1.75 [0.71–4.29]; 1–5 years vs >5 years old, 4.06 [1.61–10.20]; Table 4). To further investigate descriptive patterns by age as described above, multivariable models assessed for interaction between age group and illness severity; this term was not significant.

The frequency of elevated liver function tests and low blood glucose levels was equivalent between the deficient and nondeficient carnitine cases of patients receiving ECMO therapy at 42% ($n = 14/33$ vs $n = 20/48$) and 9%–8% ($n = 3/33$ vs $n = 4/48$), respectively (Table 1). Exposure to supplemental carnitine was significantly more common among nondeficient patients (24% ($n = 8/33$) of deficient patients vs 46% ($n = 22/48$) of nondeficient patients had received supplemental carnitine; $P = .048$). The frequency of exposure to PN, medium-chain triglycerides, transfusions, and dialysis did not differ by deficiency status (Table 1).

DISCUSSION

This study was inspired by incidental findings of profound carnitine deficiency in several patients who received ECMO therapy at Seattle Children's Hospital. These cases spawned general questions about monitoring and supplementing carnitine for hospitalized pediatric patients. The results confirmed the anecdotal observations: ECMO patients were twice as likely to be classified "deficient" as non-ECMO patients (Table 3). Cases were categorized based on age to look for patterns in carnitine deficiency, as we anticipated significant changes in dietary habits in the first year of life compared with school-age children. About 75% of in vivo carnitine comes from dietary protein: meat, eggs, and dairy products. The remaining carnitine can be synthesized endogenously in the liver, so older children and adults are less prone to carnitine deficiency compared with neonates or premature infants.[26,27] Patients were sorted into smaller age brackets for those <1 year of age (<1 week, 1 week to 1 month, and 1 month to 1 year old), as children who consume primarily breastmilk or formula consume relatively less dietary protein compared with most older children. Predicting that dietary habits for many children continue to change throughout their first years of life, we sorted older patients into those 1–5 years or >5 years old. Considering that patients' age may correlate significantly with body mass and dietary trends, free carnitine was also plotted by age (see Figure 2). Inspection of the data for patients <4 months old (120 days), revealed that ECMO patients' free carnitine levels trend lower than the convenience cohort. There were 23 ECMO patients <1 week of age, with a nearly equivalent comparator group of general hospitalized patients ($n = 26$, of whom 22 were from the NICU). Median free carnitine was similar between these groups, 11.3 and 12.5 μM, respectively (Figure 1, Table 3).

The lower limit of normal for free carnitine changes from 10 μM for those <1 week old to 18 μM for those >1 month old. Small variation in plasma free carnitine is expected, so minimally low levels (eg, 16 μM in an individual older than 1 month) may reflect short-term nutrition changes (eg, light protein meals), viral illness, or gastrointestinal symptoms. Carnitine supplementation in such situations is likely unnecessary. Free carnitine <10 μM, particularly for patients >1 month old, may reflect chronic deficiency and justify supplementation.[14,16,28] In our study, 25% of ECMO patients fell into this category. Although there was no evidence of clinical symptoms associated with carnitine deficiency among the ECMO patients in this study, the sample size was small and longitudinal data were restricted to the 24 h prior to each blood sample. It is possible that patients with carnitine deficiency

TABLE 3 Carnitine levels and deficiency status by ECMO status and age group[a]

	ECMO ($n = 81$)	Non-ECMO, ICU ($n = 93$)	Non-ECMO, floor ($n = 124$)
Carnitine deficiency, n (%)			
Free carnitine (overall)	33 (40.7)	25 (26.9)	21 (16.9)
Under 1 week	8/23 (34.8)	6/22 (27.3)	1/4 (25.0)
1 week to 1 month	10/18 (55.6)	4/17 (23.5)	2/11 (18.2)
1 month to 1 year	7/15 (46.7)	10/28 (35.7)	1/41 (2.4)
1–5 years	6/12 (50.0)	3/9 (33.3)	11/32 (34.4)
>5 years	2/13 (15.4)	2/17 (11.8)	6/36 (16.7)
Total carnitine (overall)	30 (37.0)	22 (23.7)	24 (19.4)
Under 1 week	9/23 (39.1)	5/22 (22.7)	1/4 (25.0)
1 week to 1 month	6/18 (33.3)	2/17 (11.8)	1/11 (9.1)
1 month to 1 year	7/15 (46.7)	10/28 (35.7)	2/41 (4.9)
1–5 years	6/12 (50.0)	3/9 (33.3)	13/32 (40.6)
>5 years	2/13 (15.4)	2/17 (11.8)	7/36 (19.4)
Carnitine levels by age group			
Free carnitine, median (IQR)			
Under 1 week	11.29 (7.83–19.83)	13.35 (9.58–19.51)	11.31 (9.51–14.31)
1 week to 1 month	14.66 (9.30–22.21)	31.75 (24.06–39.57)	23.48 (18.91–28.55)
1 month to 1 year	20.37 (9.11–55.35)	26.57 (13.37–33.47)	29.14 (24.34–34.72)
1–5 years	19.90 (10.35–33.71)	20.62 (13.26–32.89)	21.62 (15.28–26.73)
>5 years	42.84 (29.02–56.37)	31.51 (26.09–42.96)	26.89 (19.89–33.36)
Total carnitine, median (IQR)			
Under 1 week	20.35 (14.08–34.14)	23.97 (17.07–38.74)	21.89 (17.40–25.46)
1 week to 1 month	23.13 (15.94–39.70)	44.01 (32.77–55.84)	33.70 (25.61–38.08)
1 month to 1 year	30.88 (15.68–91.44)	36.85 (21.87–46.99)	42.12 (37.15–48.86)
1–5 years	27.49 (20.49–59.64)	45.51 (25.04–55.65)	33.34 (27.06–44.01)
>5 years	51.46 (42.97–100.34)	45.76 (40.06–52.41)	38.08 (32.41–46.20)
Acyl/free carnitine ratio, median (IQR)			
Under 1 week	0.64 (0.45–0.82)	0.62 (0.47–0.80)	0.83 (0.55–1.15)
1 week to 1 month	0.51 (0.41–1.04)	0.38 (0.32–0.47)	0.36 (0.35–0.38)
1 month to 1 year	0.48 (0.29–0.70)	0.46 (0.28–0.76)	0.41 (0.28–0.53)
1–5 years	0.65 (0.47–0.95)	0.69 (0.56–0.89)	0.60 (0.31–1.02)
>5 years	0.46 (0.31–0.50)	0.34 (0.23–0.46)	0.35 (0.25–0.60)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.
[a]For patients with longitudinal data, all carnitine concentrations represent the first sample only.

manifested relevant clinical symptoms outside of the time period reviewed by this study or that supplementation with high dextrose fluids masked the carnitine deficiency symptoms by shifting energy metabolism from the carnitine-dependent beta-oxidation and gluconeogenesis to the catabolism of supplied carbohydrate.

Review of the ECMO patient cohort for trends in the severity of carnitine deficiency did not identify a single driving factor. Our data confirmed that patients receiving carnitine supplementation were less likely to be carnitine deficient (46% (n = 22/48) vs 24% (n = 8/33); P = .048; Table 1). We hypothesized that the longer a patient was hospitalized, the greater the chance of developing carnitine deficiency. However, the PELOD score and the duration of hospitalization prior to sample collection appeared similar between the carnitine-deficient and normal cases. The number of days hospitalized prior to the first tested sample was longer for carnitine-deficient patients (7 days; IQR, 2–11.4 days) but not statistically significant compared with ECMO patients with normal free carnitine concentrations (3 days; IQR, 0.8–13.5 days). This pattern is paralleled by the use of PN among the carnitine-deficient ECMO patients (72.7%; 24 of 33 patients) vs those with normal carnitine levels (56.3%; 27 of 48 patients). A larger patient cohort may have better sensitivity for minor contributions, such as admission duration and nutrition source. Patients for whom

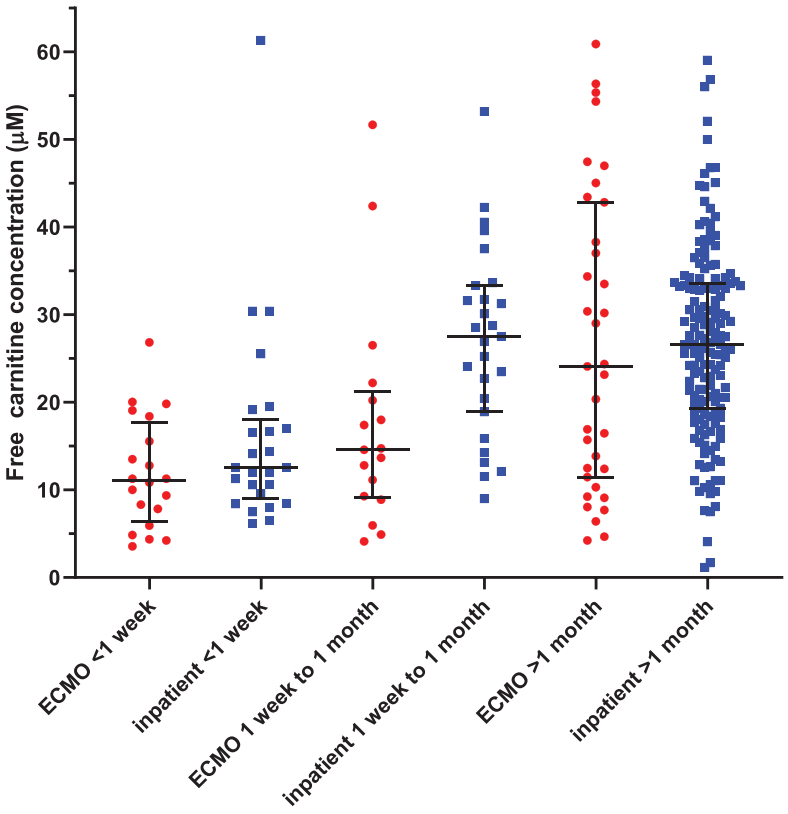

FIGURE 1 Red circles represent free carnitine concentrations of patients receiving ECMO; initial sample measurements only are included. Blue squares represent the comparator cohort, not receiving ECMO therapy. Box and whiskers represent mean and interquartile range. Patients are sorted by age groups established for clinical reference ranges. ECMO, extracorporeal membrane oxygenation

longitudinal samples were available also did not reveal obvious downtrends (Figure 3).

Work is ongoing to investigate correlating factors, such as feeding modalities, massive transfusion events, and dialysis (eg, CRRT). Just as dialysis removes a variety of metabolites, we hypothesize that the transfusion of "normal" blood products may affect a patient's free carnitine. There is no known literature describing patients' carnitine following blood product transfusions. The qualitative status of normal or deficient free carnitine did not reach statistical significance for any specific transfusion product; however, nearly 88% (n = 29/33) of ECMO patients who were carnitine deficient had received a red blood cell transfusion in the 24 h prior to sample collection (see Table 1).

This retrospective study has multiple limitations and was intended to address the initial question of the prevalence of carnitine deficiency in critically ill pediatric patients. This study was a single-center experience, and the number of participants was small, particularly among older patients (>1 year old). ECMO patients were skewed to younger patients compared with the non-ECMO cohort. Pediatric ECMO

TABLE 4 Odds of observed free carnitine deficiency

Among non-ECMO patients on the floor and in ICU compared with ECMO patients				
	Unadjusted OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
ECMO	Ref	–	Ref	–
Non-ECMO, ICU	0.54 (0.28–1.01)	.0544	0.55 (0.28–1.09)	.0884
Non-ECMO, floor	0.30 (0.16–0.57)	.0002	0.21 (0.10–0.44)	<.0001
By age group, compared with patients >5 years of age				
	Unadjusted OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**
Under 1 week	2.47 (1.00–6.12)	.0505	1.58 (0.60–4.19)	.3545
1 week to 1 month	2.99 (1.21–7.39)	.0179	2.70 (1.02–7.19)	.0462
1 month to 1 year	1.53 (0.65–3.58)	.3295	1.75 (0.71–4.29)	.2231
1–5 years	3.39 (1.42–8.12)	.006	4.06 (1.61–10.20)	.0029
>5 years	Ref	–	Ref	–

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OR, odds ratio; Ref, reference.

[a]Adjusted for age category, receipt of carnitine supplement, and gender.

[b]Adjusted for illness severity (ECMO, non-ECMO ICU, or floor), receipt of carnitine supplement, and gender.

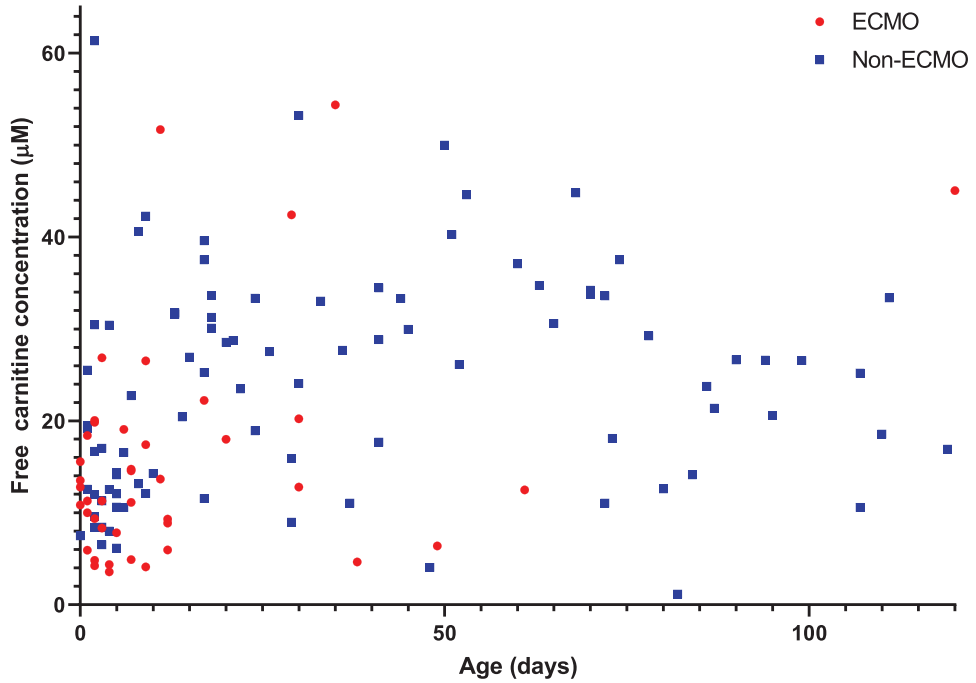

FIGURE 2 Free carnitine in blood by age for ECMO and non-ECMO patients. Note, free carnitine was truncated to the upper limit of normal (65 μM) excluding 6 ECMO and 2 non-ECMO patients with free carnitine above this cut off.

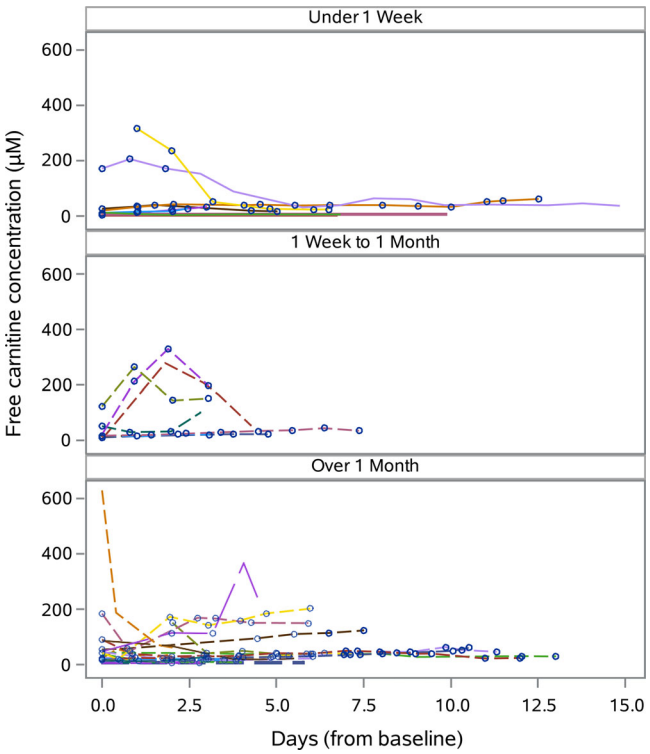

FIGURE 3 Free carnitne concentration trends by age group at baseline, when looking at the first two weeks on ECMO (extracorporeal membrane oxygenation) therapy. Circles represent a sample collected after exposure to carnitine supplementation.

occurs more often in younger children; the average age of children receiving ECMO 1 month.[29] In the ECMO cohort, female patients were overrepresented (60.5%; n = 49/81). This is not expected to significantly impact the observed outcomes, as there are no known gender-specific differences in carnitine metabolism. We attempted to address these concerns by controlling for age, gender, and illness severity in multivariable analyses; however, the sample size may have been insufficient to detect effects from these variables (Table 4). Given the known complications of dialysis and previous studies describing secondary carnitine deficiency from CRRT dialysis, the lack of an association with carnitine deficiency in this study was surprising and may reflect the small sample size (Table 1). Whereas the chart review included nutrition data curation (24 h prior to blood sample), the actual carnitine intake by infants is difficult to assess because they (may have) received a mixture of artificial formulas and breastmilk. Carnitine content of breastmilk will reflect maternal nutrition, but maternal free carnitine could not be tested retrospectively. Although the limited chart review strategy made this pilot study feasible, episodes of symptoms suggestive of carnitine deficiency may have been missed or clinical chemistry may not have been performed. Resources for this project were restricted to 2 years, limiting the study's scope. Despite these limitations, we hope these findings can inform future prospective studies.

Despite the observation of low free carnitine in this study, testing for deficiency should be performed thoughtfully. Our study has not defined demographic or clinical characteristics that increase suspicion for carnitine deficiency, suggesting that broad carnitine

supplementation is not warranted.[27] Pediatric patients have small blood volumes, depending on their weight and clinical status, and laboratory draws can account for nearly 73% of blood loss for critically ill pediatric patients.[30] Although there are potential benefits of identifying carnitine deficiency, blood loss for pediatric patients is a risk if carnitine monitoring is implemented broadly. Metabolic processes take time to shift between anabolism and catabolism and the pharmacokinetics of carnitine are not well characterized to know when a dose of carnitine is fully absorbed. Sporadic evaluation of free carnitine levels may be appropriate for nutrition management, particularly if there are clinical concerns, such as unexpected hypoglycemia, cardiomyopathy, or chronic PN/dialysis use. Prospective studies targeting specific clinical variables, such as renal replacement devices, blood transfusions, or nutrition modalities, are needed to better understand the kinetics of supplementation and clearance in each of these scenarios.

CONCLUSIONS

Carnitine deficiency occurs at a greater frequency among pediatric ECMO patients compared with other patients admitted to the hospital. Older patients may be less prone to carnitine deficiency, because of larger body mass and energy stores, compared with preterm infants and neonates.Total carnitine parallels the observed free carnitine trends between groups, supporting the concern of low free carnitine resulting in reduced metabolic availability of acylcarnitine species for gluconeogenesis.

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CONFLICT OF INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

Jenna Kelley, Erin Sullivan, Marie Norris, Sarah Sullivan, Jennifer Parietti, and Anna I. Scott all equally contributed to the conception and design of the research, data collection, and analysis; Kimberly Kellogg contributed to the acquisition and analysis of the data; and Erin Sullivan, Jenna Kelley, Kimberly Kellogg, and Anna I. Scott drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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