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

Jenna Kelley RDN1 | Erin Sullivan MPH2 | Marie Norris RDN1,3 | Sarah Sullivan RDN1 | Jennifer Parietti RDN1 | Kimberly Kellogg RDN1 | Anna I. Scott PhD4,5

1 Department of Nutrition Services, Seattle Children’s Hospital, Seattle, Washington, USA
2 Biostatistics, Epidemiology, and Analytics for Research, Seattle Children’s Hospital, Seattle, Washington, USA
3 Department of Nutrition and Integrative Physiology, University of Utah, Salt Lake City, Utah, USA
4 Department of Laboratories, Seattle Children’s Hospital, Seattle, Washington, USA
5 Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA

Correspondence
Anna I. Scott, PhD, Department of Laboratories, Seattle Children’s Hospital, 4800 Sand Point Way NE, OC.8.740 PO Box 5371, Seattle, WA 98145-5005, USA.
Email: anna.scott@seattlechildrens.org

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.
The goal of nutrition support 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. Carnitine is a small molecule essential for fat metabolism and production of adenosine triphosphate in mitochondria. Patients with carnitine deficiency can present with hypoglycemia, liver dysfunction, hyperammonemia, cardiomyopathy, and skeletal muscle weakness. Isolated cases of carnitine deficiency have been described in which chronic parenteral nutrition (PN) led to clinically significant symptoms. 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). 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. Excess supplementation, however, can cause gastrointestinal discomfort, diarrhea, and the production of trimethylamine, a compound with a fishy odor. 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.

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. 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.

**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. 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. Carnitine is a small molecule essential for fat metabolism and production of adenosine triphosphate in mitochondria. Patients with carnitine deficiency can present with hypoglycemia, liver dysfunction, hyperammonemia, cardiomyopathy, and skeletal muscle weakness. Isolated cases of carnitine deficiency have been described in which chronic parenteral nutrition (PN) led to clinically significant symptoms. 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). 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. Excess supplementation, however, can cause gastrointestinal discomfort, diarrhea, and the production of trimethylamine, a compound with a fishy odor. Given the potential benefits, carnitine supplementation...
(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. 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, 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 ICU (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 ECMO and non-ECMO ICU 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

|                        | ECMO patients | Non-ECMO ICU | Non-ECMO floor |
|------------------------|---------------|--------------|----------------|
|                        | Carnitine     | Normal carnitine | Carnitine      | Normal carnitine | P-value | Carnitine | Normal carnitine | P-value |
|                        | deficient (n = 33) | (n = 48)     | deficient (n = 25) | (n = 68)     |         | deficient (n = 21) | (n = 103) |         |
| PELOD score, mean (SD) | 9.64 (4.25)  | 11.23 (4.60)  | 6.4 (5.0)       | 4.8 (4.2)    | .1905   | 0.9 (0.1–1.8)  | 0.5 (0.1–2.2)  | .6835   |
| Duration of hospitalization prior to first sample, median days (IQR) | 7.0 (2.0–11.4) | 3.0 (0.8–13.5) | 17 (0.9–3.3) | 3.1 (0.9–9.3) | .1095  | -         | -         | -       |

Clinical and nutritional exposures in last 24 h, n (%)

|                        | ECMO patients | Non-ECMO ICU | Non-ECMO floor |
|------------------------|---------------|--------------|----------------|
|                        |               |              |                |
| PN                     | 24 (72.7)     | 27 (56.3)    | 14 (87.9)      |
| Supplemental carnitine | 8 (24.2)      | 22 (45.8)    | 25 (52.1)      |
| MCT                    | 2 (6.1)       | 6 (12.5)     | 25 (52.1)      |
| Transfusion (any type) | 30 (90.9)     | 41 (85.4)    | 23 (43.4)      |
| Platelets              | 17 (51.5)     | 25 (52.1)    | 5 (9.1)        |
| Plasma                 | 19 (57.6)     | 29 (60.4)    | 14 (25.0)      |
| RBC                    | 29 (87.9)     | 34 (70.8)    | 14 (52.0)      |
| Cryoprecipitate        | 8 (24.2)      | 8 (16.7)     | 2 (12.0)       |
| Dialysis (CRRT)        | 8 (24.2)      | 8 (16.7)     | 5 (12.0)       |

Abnormal labs in last 24 h, n (%)

|                        | ECMO patients | Non-ECMO ICU | Non-ECMO floor |
|------------------------|---------------|--------------|----------------|
| Blood glucose          | 3 (9.1)       | 4 (8.3)      | 4 (16.0)       |
| LFTs                   | 14 (42.4)     | 20 (41.7)    | 13 (52.0)      |
| Triglycerides          | 0 (0.0)       | 1 (2.1)      | 1 (4.0)        |
| Blood ammonia          | 0 (0.0)       | 1 (2.1)      | 2 (8.0)        |
| Creatinine kinase      | 1 (3.0)       | 0 (0.0)      | 1 (4.0)        |

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)                |        |
| 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.

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). In our study, 25% of 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 \(\mu M\), respectively (Figure 1, Table 3).

The lower limit of normal for free carnitine changes from 10 \(\mu M\) for those < 1 week old to 18 \(\mu M\) for those > 1 month old. Small variation in plasma free carnitine is expected, so minimally low levels (eg, 16 \(\mu M\) 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 \(\mu M\), 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

|                        | 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 down-trends (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 | | | | |
|----------------|-----------------------------|---|---|---|---|
| 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.

aAdjusted for age category, receipt of carnitine supplement, and gender.

bAdjusted 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 carnitine 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.

ACKNOWLEDGMENTS

Thank you to Elaine Chen, a medical laboratory scientist student, and Sheri Poskanzer, MD, a medical biochemical genetics fellow, for data collection during their laboratory rotations. Also, thanks to Bernhard Kayser, PhD for helpful discussions. Funding for this project was provided by Seattle Children’s Academic Enrichment Fund award. This project was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2 TR002317. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST

None declared.

FUNDING INFORMATION

This study was supported by the Academic Enrichment Fund at the Seattle Children’s Hospital. This project was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2 TR002317. This study was a candidate for the Harry M. Vars Award and was presented at the Premier Paper Session and Vars Award Competition (M20) held March 22, 2021, during the ASPEN 2021 Nutrition Science and Practice Conference (Virtual).

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.

ORCID

Erin Sullivan MPH https://orcid.org/0000-0002-4280-6091
Marie Norris RDN https://orcid.org/0000-0002-2856-775X
Sarah Sullivan RDN https://orcid.org/0000-0002-2694-2958
Kimberly Kellogg RDN https://orcid.org/0000-0003-4798-3537
Anna I. Scott PhD https://orcid.org/0000-0002-6975-8552

REFERENCES

1. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. JPN J Parenter Enteral Nutr. 2017;41(5):706-742.
2. Bechard LJ, Duggan C, Touger-Decker R, et al. Nutritional status based on body mass index is associated with morbidity and mortality in mechanically ventilated critically ill children in the PICU. Crit Care Med. 2016;44(8):1530-1537.
3. Mehta NM, Bechard LJ, Zurakowski D, et al. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. Am J Clin Nutr. 2015;102(1):199-206.
4. Castillo A, Santiago MJ, López-Herce J, et al. Nutritional status and clinical outcome of children on continuous renal replacement therapy: a prospective observational study. BMC Nephrol. 2012;13(125):1-6.
5. Rogers EJ, Gilbertson HR, Heine RG, Henning R. Barriers to adequate nutrition in critically ill children. Nutrition. 2003;19(10):865-868.
6. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in critically ill children: a multicenter, prospective, cohort study. Nutrition. 2004;20(3):123-128.
7. Wong T, Hardy G. Micronutrient requirements in the critically ill child. In: Goday PS, Mehta NM, eds. Pediatric Critical Care Nutrition. McGraw-Hill Companies; 2015:59-60.
8. Crill CM, Helms RA. The use of carnitine in pediatric nutrition. Nutr Clin Pract. 2007;22(2):204-213.
9. Saudubray JM, Baumgartner MR, Walters J, eds. Inborn Metabolic Diseases: Diagnosis and Treatment. 6th ed. Springer; 2016.
10. Bhavsar H, Forster J. G185(P) Carnitine deficiency in long term parenteral nutrition (PN) dependent children. Arch Dis Child. 2017;102(2):A74-A75.
11. Hirose S, Hirata M, Azuma N, Shirai Z, Mitudome A, Oda T. Carnitine depletion during total parenteral nutrition despite oral L-carnitine supplementation. Acta Paediatr Jpn. 1997;39(2):194-200.
12. Sgambat K, Moudgil A. Carnitine deficiency in children receiving continuous renal replacement therapy. Hemodial Int. 2016;20(1):63-67.
13. Evans AM, Faull RJ, Nation RL, et al. Impact of hemodialysis on endogenous plasma and muscle carnitine levels in patients with end-stage renal disease. Kidney Int. 2004;66(4):1527-1534.
14. Borum PR. Carnitine in parenteral nutrition. Gastroenterology. 2009;137(S Suppl):S129-S134.
15. Fu L, Huang M, Chen S. Primary carnitine deficiency and cardiomyopathy. Korean Circ J. 2013;43(12):785-792.
16. Recommended Uniform Screening Panel. Health Resources and Services Administration. Last updated February 2020. Accessed May 21, 2020. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html
17. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012;7:68.
18. Shang R, Sun Z, Li H. Effective dosing of L-carnitine in the secondary prevention of cardiovascular disease: a systematic review and meta-analysis. BMC Cardiovascular Disorders. 2014;14:88.
19. Mingorance C, Rodriguez-Rodriguez R, Justo ML, Alvarez de Sotomayor M, Herrera MD. Critical update for the clinical use of L-carnitine analogs in cardiometabolic disorders. Vasc Health Risk Manag. 2011;7:169-176.
20. Bonafe L, Berger MM, Que YA, et al. Carnitine deficiency in chronic critical illness. Curr Opin Clin Nutr Metab Care. 2014;17(2):200-209.
21. Lee B, Lin JS, Lin YC, et al. Effects of L-carnitine supplementation on oxidative stress and antioxidant enzymes activities in patients with coronary artery disease: a randomized, placebo-controlled trial. Nutr J. 2014;13:79.
22. Chace DH, Hillman SL, Van Hove JL, Naylor EW. Rapid diagnosis of MCAD deficiency: quantitative analysis of octanoylcarnitine and other acylcarnitines in newborn blood spots by tandem mass spectrometry. Clin Chem. 1997;43(11):2106-2113.
23. NeoLynx Research Version 3.5 Application Manager Users Guide. Micromass Ltd; 2003.
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-381.
25. Leteurtre S, Martinet A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet. 2003;362(9379):192-197.
26. Flanagan JL, Simmons PA, Vehige J, Willcox MDP, Garrett Q. Role of carnitine in disease. Nutr Metab (Lond). 2010;7:30.
27. Cairns PA, Stalker DJ. Carnitine supplementation of parenterally fed neonates. Cochrane Database Syst Rev. 2000;2000(4):CD000950.
28. Systemic Primary Carnitine Deficiency. National Organization of Rare Disorders. Updated 2015. Accessed January 19, 2021. https://rarediseases.org/rare-diseases/systemic-primary-carnitine-deficiency/
29. Figueroa Villalba CA, Brogan TV, McMullan DM, et al. Conversion from activated clotting time to anti-xa heparin activity assay for heparin monitoring during extracorporeal membrane oxygenation. Crit Care Med. 2020;48(12):e1179-e1184.
30. Brown SM, Dickerson J. Pediatric Laboratory Medicine. In: Clarke W, Marzinke M, eds. Contemporary Practice in Clinical Chemistry. AACC Press; 2016:763-769.

How to cite this article: Kelley J, Sullivan E, Norris M, et al. Carnitine deficiency among hospitalized pediatric patients: A retrospective study of critically ill patients receiving extracorporeal membrane oxygenation therapy. JPEN J Parenter Enteral Nutr. 2021;45:1663–1672. https://doi.org/10.1002/jpen.2255