

IJMA



INTERNATIONAL JOURNAL OF MEDICAL ARTS

Volume 7, Issue 3 (March 2025)



<http://ijma.journals.ekb.eg/>

P-ISSN: 2636-4174

E-ISSN: 2682-3780



Available online at Journal Website
<https://ijma.journals.ekb.eg/>
 Main Subject [Pediatrics]



Original Article

Evaluation of Serum L-carnitine in Late Onset Neonatal Sepsis

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ABSTRACT

Article information

Received: 08-01-2025

Accepted: 08-02-2025

DOI: [10.21608/ijma.2025.351335.2098](https://doi.org/10.21608/ijma.2025.351335.2098)

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Citation: Elabd DAY, Abdelmaksoud HM, Elshreif AM, Abd Elsamie HS. Evaluation of Serum L-carnitine in Late Onset Neonatal Sepsis. IJMA 2025 Mar; 7 [3]: 5474-5479. DOI: 10.21608/ijma.2025.351335.2098.

Background: Neonatal sepsis is defined as a systemic inflammatory response elicited by blood-stream infection. It is associated with high morbidity and mortality, especially during the first 28 days of life [neonatal period], particularly in resource limited settings.

Aim of work: The aim of the work was to evaluate serum level of carnitine in neonate with sepsis. In addition, to study the relation between L-carnitine concentration with birth data and the presence of neonatal sepsis.

Subjects and methods: This was a case control study, which was conducted at Al-Azhar University Hospital [New Damietta; Egypt]. It included 60 neonates, 30 with neonatal sepsis [the sepsis group], and 30 without sepsis [control group]. All were carefully evaluated by neonatal and maternal history taking, clinical examination and laboratory workup. Serum-L-carnitine was measured and values were compared between groups and correlated with other variables. The predictive power of L-carnitine in diagnosis sepsis and prediction of its associated mortality was calculated.

Results: L-carnitine levels were significantly reduced in sepsis than healthy controls [3.6±0.99 vs. 15.3±2.1 mg/l]. Serum carnitine less than 4.69 had a significant value for sepsis prediction with sensitivity of 90%, specificity of 70% and area under curve of 0.83. In addition, serum carnitine less than 2.97 had a significant value for prediction of mortality [sensitivity of 80%, specificity of 89% and area under curve equal 0.86]. sepsis associated mortality was 16.7%. Finally, there was moderate negative significant correlation between serum carnitine with C-reactive protein [r=-0.68] and total leucocyte count [r=-0.44]; while, there was mild positive significant correlation between serum carnitine and birth weight [r=-0.26] and hemoglobin [r=0.27].

Conclusion: L-carnitine is significantly reduced in neonatal sepsis and it can be used as predictor for neonatal sepsis and sepsis-related mortality.

Keywords: Birth weight; L-carnitine; Neonates; Prediction; Sepsis.



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INTRODUCTION

Neonatal sepsis is defined as a systemic inflammatory response to blood stream infection [bacterial, viral or fungal]. It is marked by hemodynamic changes and other systemic manifestations. Furthermore, the neonatal sepsis is associated with high risk of substantial morbidity and mortality. It is responsible for 15% of neonatal deaths [1-3]. The early onset neonatal sepsis diagnosis is settled when culture proven infection was reported within the first three days of life [4]. However, the late onset neonatal sepsis is defined as postnatal acquisition of infection or positive blood and/or cerebrospinal fluid culture. But in continuously hospitalized very low birth weight neonate, the late onset sepsis is defined as the positive culture at > 72 hours of age [5,6].

L-carnitine is a natural compound that plays a significant role in the metabolism, energy production and oxidation of fatty acids. In addition to its role in the regulation of oxidative stress, inflammation and mitochondrial function [7,8]. However, the role of L-carnitine in sepsis is not fully elucidated. Some researchers suggested that, it may provide beneficial effects. For instance, it may improve cardiac function and decrease the need for vasopressors in septic shock [9-11]. It may also affect the immune response and reduce the cytokine production in response to inflammation in sepsis. L-carnitine deficiency may be the results of sepsis endotoxemia due to impaired lipid metabolism, energy production and oxidation of fatty acids [12].

The aim of this study was to estimate the serum levels of L-carnitine in neonates with sepsis, and examine its possible associations.

PATIENTS AND METHODS

After approval of the local ethics committee of Al-Azhar Faculty of Medicine [New Damietta; Egypt], this case-control study included 60 neonates [30 with neonatal sepsis as the sepsis group and 30 without sepsis as the control group]. They were selected from the neonatal intensive care unit [Al-Azhar University Hospital, New Damietta].

The inclusion criteria were full or pre-term neonates of both sexes. However, the exclusion criteria were neonates with early onset sepsis, those with major congenital anomalies and those who need major surgical intervention.

All eligible neonates were submitted to full clinical assessment in a standard manner and according to the protocol adopted by the institution. Firstly, full history was collected to detect risk factors for sepsis. After that, a detailed clinical examination [from head to toe] was performed with stress on the clinical signs of sepsis [e.g., high temperature, respiratory, circulatory, gastrointestinal [GIT] or neurological dysfunction], hypo- or hyper-glycemia and petechial, bleeding or disseminated intravascular coagulation [DIC].

The assessment then completed by laboratory investigations, which included complete blood count with differential leucocyte count, quantitative assay of C-reactive protein, blood culture and measurement of L-carnitine. The assay of L-carnitine was performed by an enzymatic ultraviolet test through examination of the peripheral venous samples.

Statistical analysis: All data were managed using SPSS 26 for windows [SPSS Inc., Chicago, IL, USA]. The data were tested for normal distribution, and qualitative data were represented as frequencies and relative percentages, while quantitative data were expressed as mean \pm SD [Standard deviation]. Chi square test and fisher exact test was used to calculate difference between categorical variables as indicated. Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. ROC curve analysis was done for prediction of neonatal sepsis and mortality. Pearson correlation was done between serum carnitine and different variables. All statistical comparisons were two tailed with significance Level of P-value \leq 0.05 indicates significance.

RESULTS

Comparing baseline neonatal and maternal data revealed that, both groups were comparable [no significant differences], except significant increase of prematurity, large for gestational age and previous NICU admission in the sepsis than control group [53.3%, 60.0%, 33.3% vs. 10.0%, 16.7% and 10.0%, successively]. However, birth weight was significantly lower in the sepsis than sepsis group [2057 \pm 787 vs 2881 \pm 574.3 g] [Table 1].

Laboratory workup showed that, hemoglobin and L-carnitine values were significantly reduced in the sepsis than the control groups [14.1 \pm 2.6, 3.6 \pm 0.99 vs. 15.3 \pm 2.1 and 4.98 \pm 1.1, respectively]. However, there was significant increase of total leucocyte count [TLC] and CRP in the sepsis than the control group [17.9 \pm 4.2, 115.9 \pm 108.9 vs 8.8 \pm 2.3, and 0 respectively]. All subjects in sepsis group had positive CRP, while all in the control group had negative CRP [Table 2].

Regarding results of the blood culture in the sepsis group showed that, no growth was reported in 11 cases [36.7%]. On the other side, gram negative bacilli, *Staphylococcus aureus*, group D streptococci, Klebsiella, candida and aerobic coagulase negative *Staphylococcus* in 6.7%, 23.3%, 13.3%, 6.7%, 10.0% and 3.3%, successively] [Table 3].

Figure [1] showed that, 16.7% of septic cases died and the remaining 83.3% were improved.

Table 4 and Figures [2 and 3] showed that, serum carnitine less than 4.69 had a significant prediction power for sepsis [AUC 0.83] with sensitivity of 90%, specificity of 70% In addition, serum carnitine less than 2.97 had a significant value for mortality prediction with sensitivity of 80%, specificity of 89% and area under curve equal 0.86.

Table [5] and figures [4 to 7] showed that, there is moderate negative significant correlation between serum carnitine and CRP [$r=-0.68$] and TLC [$r=-0.44$]. On other hand there was mild positive significant correlation between serum carnitine and birth weight [$r=-0.26$] and HB [$r=0.27$].

Table [6] showed that, there was a significant difference in serum carnitine regarding prematurity, Weight for GA, Blood culture and mortality among septic cases [p value <0.05] as the mean serum carnitine was significantly lower among premature, LGA, cases with positive blood culture and died cases than among full term, AGA, cases with negative blood culture and improved cases

Table [1]: Baseline data among sepsis and control groups

		Sepsis [cases] [n=30]	No sepsis [control; n=30]	P value
Gestation age at delivery [weeks]	Mean±SD	36.1±1.0	37.8±0.83	0.07
	Min. – Max.	32- 39	35-39	
Sex [n,%]	Male	16[53.3%]	18[60.0%]	0.60
	Female	14[46.7%]	12[40.0%]	
Prematurity [n,%]		16[53.3%]	3[10.0%]	<0.001*
Birth weight (g)	Mean±SD	2057±787	2881±574.3	<0.001*
	Min. – Max.	1100-3750	1500-3900	
Weight for GA [n,%]	Large for GA	18[60.0%]	5[16.7%]	<0.001*
	Appropriate for GA	12[40.0%]	25[83.3%]	
Postnatal days	Mean±SD	10.1±7.1	6.6±5.5	0.08
	Median [IQR]	7[4-28]	5[3-29]	
Maternal age [year]	Mean±SD	30.9±4.9	30.4±5.4	0.71
	Min. – Max.	20-39	20-39	
Mode of delivery [n,%]	Normal	14[46.7%]	14[46.7%]	1.00
	CS	16[53.3%]	16[53.3%]	
Previous NICU admission [n,%]		10[33.3%]	3[10%]	0.021*
Maternal history	Irrelevant	15[50.0%]	23[76.7%]	0.28
	PROM	4[13.3%]	2[6.7%]	
	Gestational diabetes	5[16.7%]	3 [10.0%]	
	Preeclampsia	2[6.7%]	1 [3.3%]	
	Maternal fever	1[3.3%]	1 [3.3%]	
	UTI	3 [10.0%]	0 [0.0%]	

[*] indicate statistical significance

Table [2]: Laboratory data among sepsis and control groups

		Sepsis [cases] n=30	No sepsis [control; n=30]	P value
Hemoglobin [g/dl]	Mean±SD	14.1±2.6	15.3±2.1	0.05*
	Min. – Max.	8.8-19.2	9.7-19.2	
RBCs [x 10⁶ /ml]	Mean±SD	4.47±0.81	4.5±0.77	0.75
	Min. – Max.	3.1-6.52	3.03-6.39	
TLC [x 10³/ml]	Mean±SD	17.9±4.2	8.8±2.3	<0.001*
	Min. – Max.	12.6-34	5.23-13.7	
Platelets [x 10³/ml]	Mean±SD	272.4±132.3	298±73	0.36
	Min. – Max.	28-535	176-455	
CRP code [n,%]	Negative	0[0%]	30[100%]	<0.001*
	Positive	30[100%]	0[0%]	
CRP values	Mean±SD	115.9±108.9	---	-
	Median [IQR]	64[12-367]	---	
L-carnitine	Mean±SD	3.6±0.99	4.98±1.1	<0.001*
	Min. – Max.	1.65-4.97	2.9-7.98	

[*] indicate statistical significance

Table [3]: Distribution of septic cases regarding the results of blood culture

	Frequency [N=30]	Percentage
No growth	11	36.7%
Gram negative bacilli	2	6.7%
Staphylococcus aureus	7	23.3%
Group D Streptococcus	4	13.3%
Klebsiella	2	6.7%
Candida	3	10%
Aerobic coagulase negative Staphylococcus	1	3.3%

Table [4] Diagnostic performance of serum carnitine for prediction of sepsis and mortality

Serum carnitine	AUC	95% CI	Cut off value	P value	Sensitivity	Specificity	PPV	NPV
Sepsis	0.83	0.73-0.93	<4.69	<0.001*	90%	70%	75%	87.5%
Mortality	0.86	0.68-0.99	<2.97	0.007*	80%	89%	40%	98%

[*] significant at p value <0.05

Table [5]: Correlation between serum carnitine and different variables

	Serum carnitine	
	r	P value
Age [days]	-0.09	0.47
Gestational age	-0.008	0.95
Maternal age	-0.05	0.65
Birth weight	0.26	0.04*
HB	0.27	0.03*
TLC	-0.44	<0.001*
RBC	0.12	0.33
Platelet	0.003	0.98
CRP	-0.68	<0.001*

* significant at p value <0.05

Table [6]: Association between serum carnitine and different variables among cases group

		Serum carnitine		P value
		Mean ±SD	Range	
Prematurity	Preterm	2.9±1.02	1.65-4.34	0.006*
	Full term	3.98±.81	2.64-4.97	
Weight for GA	LGA	3.2±1.01	1.65-4.5	0.03*
	AGA	4.01±0.85	2.38-4.9	
Blood culture	Negative	4.3±0.73	2.6-4.9	0.006*
	Positive	3.3±0.94	1.6-4.9	
Mortality	Improved	3.8±0.85	2.3-4.9	0.01*
	Died	2.7-1.1	1.65-4.5	

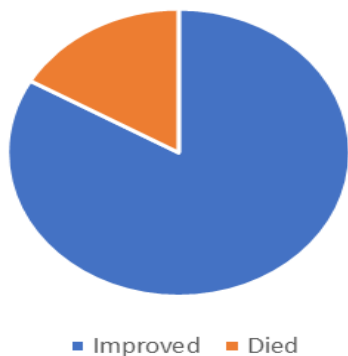


Figure [1]: Outcome among sepsis group

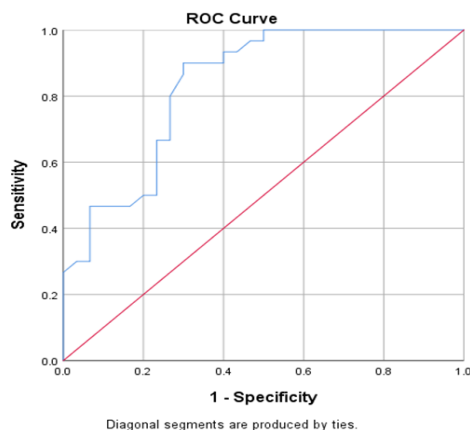


Figure [2]: ROC curve analysis for serum carnitine for prediction of sepsis

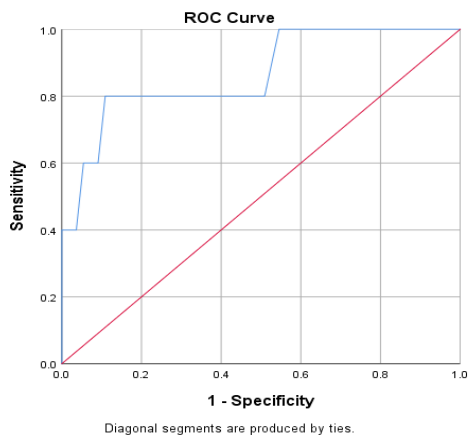


Figure [3]: ROC curve analysis for serum carnitine for prediction of mortality

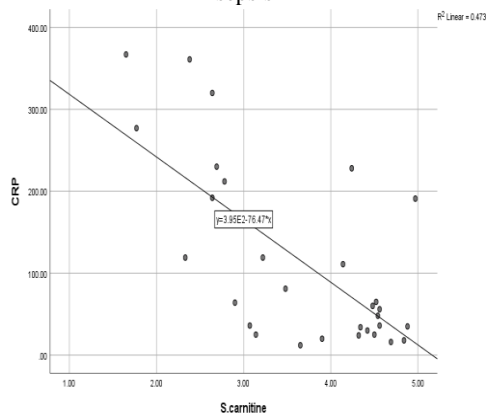


Figure [4]: scatter plot represent correlation between serum carnitine and CRP

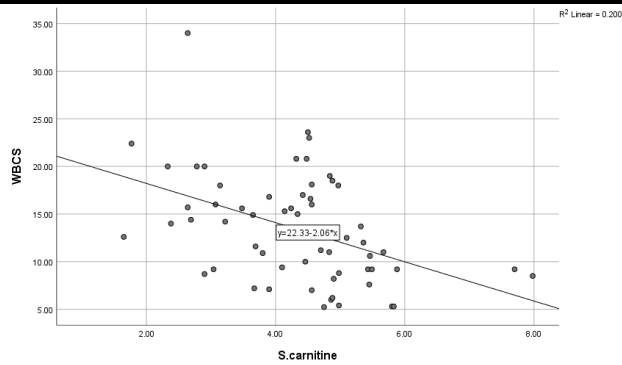


Figure [5]: Scatter plot represent correlation between serum carnitine and TLC

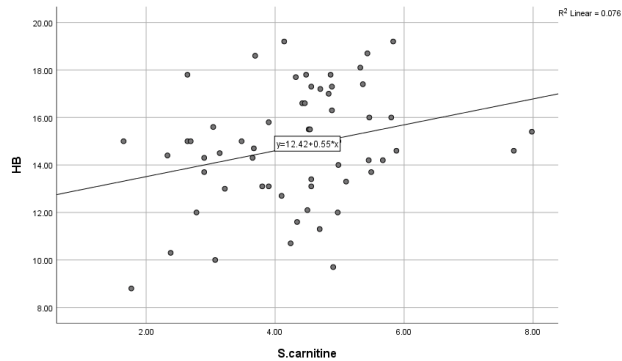


Figure [7]: Scatter plot represent correlation between serum carnitine and Hb.

DISCUSSION

The pattern of bacterial pathogens responsible for neonatal sepsis has changed with time and varies from place to place. There has also been a difference in the causative organism of neonatal sepsis between the developed and developing countries [13].

The present study aimed to evaluate serum level of carnitine in neonate with sepsis, and its relation to gestational age, birth weight, and presence of neonatal sepsis. The main results of the study showed that, L-carnitine was significantly reduced in sepsis than control group. L-carnitine was negative and significantly correlated with total leucocyte count and C-reactive protein, but positively correlated with birth weight and hemoglobin concentrations. Furthermore, L-carnitine was significantly reduced in preterm and LGA neonates. The mortality rate was 16.7% and serum L-carnitine had a good predictive power for neonatal sepsis and its associated mortality. In line with our results, **El-Lahony et al.** [12] reported non-significant differences between neonates with sepsis when compared to healthy control regarding gestational age, neonatal gender, maternal age, mode of delivery, birth weight for gestational age. They also found that healthy group had negative CRP; but, septic group showed positive CRP and significantly lower values of L-carnitine in the sepsis than control groups [2.63 ± 0.35 mg/l vs 5.06 ± 1.03 mg/l]. **Ozkan et al.** [14] reported comparable results, with no significant differences regarding GA and gender.

On the other side, our results do not agree with **El-Lahony et al.** [12] regarding birth weight and weight of gestational age. They did not found any significant differences in the sepsis than control group [$p=0.147$]. This may be explained by different inclusion criteria.

Maternal history in the current work was comparable between the sepsis and control groups. This is consistent with **Puskarich et al.** [15] who

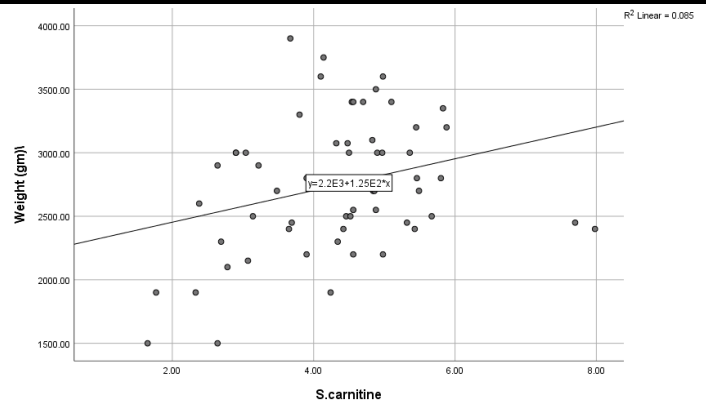


Figure [6]: Scatter plot represent correlation between serum carnitine and birth weight

intended to predict the value of metabolites of L-carnitine treatment in mortality benefit in septic shock. They found non-significance between cases and controls regarding the maternal history. Our results agree with **Omran et al.** [16] who demonstrated that all the case group [sepsis] were positive CRP.

Staphylococcus aureus was the commonest detected organism in sepsis group followed by group β -streptococci [23.3%] then gram negative bacilli [16.7%] and the least was aerobic coagulase negative Staphylococcus aureus [6.7%]. **El-Lahony et al.** [12] who reported that, all patients in their study reported positive blood culture, and the commonest detected organism was gram-negative organisms [71.04%], and gram positive organisms were reported in 28.6% and fungi were reported in 7.7%. **Ozkan et al.** [14] reported that gram negative organisms are the most frequent microorganism. These results are quite different than the current work. This reflected wide and variable distribution of causative organisms of sepsis. This reflected the value of our study and studies like it, aimed to detection of the causative organisms and planning infection control policies

The mortality rate in case group was 16.7% compared to none in the healthy control group. **Puskarich et al.** [17] reported that there was a statistically significant difference between cases and controls regarding mortality [p value < 0.05]. In addition, **Chung et al.** [18] aimed to evaluate the association between serum carnitine and mortality. They demonstrated that serum carnitine can reflect the severity of organ dysfunction, inflammation, and infection in sepsis and can serve as a prognostic biomarker for mortality prediction.

L-carnitine was a good predictor of sepsis and its associated mortality [AUC was 0.83 and 0.86 respectively]. This result agrees with **Yahyapoor et al.** [11] showed that serum carnitine had a significant value for sepsis prediction and it may help to reduce mortality risk in sepsis patients.

L-carnitine supplementation was associated with lower mortality in patients with sepsis. This reflected the role in the development of sepsis, prediction of sepsis and its associated mortality. This was supported by **Evans et al.** [19] who reported a slight significant reduction in one-year mortality rate in response to L-Carnitine supplementation compared to placebo. In addition, **Puskarich et al.** [15] studied the efficacy of L-carnitine infusion for the treatment of vasopressor-dependent septic shock. They reported that serum carnitine predicted for sepsis mortality in neonate and associated with a significant decrease in 28-days mortality among patients who received L-Carnitine supplementation [p=0.048].

Concerning correlation between serum carnitine and different variables, results supporting that of **El-Lahony et al.** [12] who revealed no correlation between l-carnitine and maternal age or gestational age. In addition, **Sánchez-Pintos et al.** [20] who reported that, there was positive significant correlation between serum carnitine and birth weight. L-carnitine deficiency was demonstrated in all very low birth weight babies. However, birth weight restriction has been suggested as a risk factor for impaired carnitine status. Similarity, **Beshir et al.** [21] reported no correlation between L-carnitine and gestational age or maternal age.

In contrast with **El-Lahony et al.** [12] found that there was no correlation between L-carnitine and birth weight. As well, **Beshir et al.** [21] found that there was no correlation between L-carnitine and birth weight. This contrast may be explained by the number of cases and selection criteria.

In conclusion, the current work confirmed the value of L-carnitine in neonatal sepsis as a predictor of the condition and its associated mortality. The reduced levels of L-carnitine in septic group significantly associated with birth weight and prematurity. Thus, L-carnitine supplementation for neonatal sepsis is recommended. However, due to small sample size [a limiting step of the current work], the results of the current work needs further validation in future large scale and multi-centers studies.

Disclosure: None to be disclosed.

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IJMA



INTERNATIONAL JOURNAL OF MEDICAL ARTS

Volume 7, Issue 3 (March 2025)



<http://ijma.journals.ekb.eg/>

P-ISSN: 2636-4174

E-ISSN: 2682-3780