



L-Carnitine Effects on Clinical Status and Mortality Rate in Septic Patients: A Systematic Literature Review

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ABSTRACT

Introduction: Sepsis is one of the major causes of high morbidity and mortality in intensive care units (ICU) and severe sepsis leads to some metabolic disorder. The previous studies indicate that l-carnitine deficiency in septic patients and causing mitochondria dysfunction and worsening metabolic disorder. Reducing mortality in sepsis by nutritional supplements may help mitigate the risk of clinical outcomes in sepsis patients.

Methods: Our systematic search to find relevant studies was performed up to March 2020, using ISI Web of Science, Google Scholar, EMBASE, PubMed/MEDLINE and SCOPUS databases. In this systematic review, the aim was to assess whether l-carnitine or levocarnitine may reduce the risk of mortality in patients with sepsis.

Result: 10 articles were included in our systematic review. The results of the review showed that plasma carnitine levels were significantly associated with the Sequential Organ Failure Assessment score (SOFA) ($p < 0.001$). On the other hand, other studies showed carnitine supplementation had no significant effect on SOFA score change in a short time, while carnitine deficiency was associated with significantly increased SOFA score in critically ill patients. L-carnitine supplementation indicated a significant decline in 28 days' mortality as well.

Conclusion Evidence from limited data suggested that carnitine may help to reduce mortality risk in sepsis patients, but further studies are required with different doses and durations.

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Introduction

Sepsis is a serious situation resulting from the existence of microorganisms in the human bodies and the response to their condition and is a common cause of death in critically ill patients ICU [1]. Despite the considerable progress in the care of sepsis, these patients have a high mortality rate of 30-65% [2, 3]. The current initial care of patients with severe sepsis involves early diagnosis and pharmacological therapies [4]. The standard treatment of severe sepsis is fluid resuscitation, broad-spectrum antibiotics therapy, administration of vasopressors, ventilation, and improving hemodynamic conditions as necessary [2, 5]. Unfortunately, these routine therapies have a low effect on the mortality rate in severe sepsis [6], so public health concern and lack of special therapies for sepsis have remained until now. Sepsis is a metabolic disorder that involves

increased protein catabolism, lipolysis, glycolysis, breakdown of fatty acids, hyperglycemia and hyperlactatemia [7]. Hyperlactatemia due to sepsis is potentially a prognostic factor for death [8]. On the other hand, increased lactate production in sepsis can lead to inhibition of pyruvate dehydrogenase complex [9] and carnitine transferase enzyme thus impairing the Krebs cycle and production of energy, culminating in multiple organ failure [8, 10]. In addition to these effects, evidence suggests that carnitine deficiency has been observed in sepsis with increased urinary excretion and diminished carnitine levels of plasma and muscles [11]. Carnitine (beta-hydroxytrimethyl amino butyrate) is an amino acid quaternary neutral molecular as an essential compound synthesized from lysine and methionine in the kidney and liver or obtained from animal sources [12]. Carnitine plays a main

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function in fatty acid Beta-Oxidation, leading to the transfer of fatty acids to the mitochondrial matrix with carnitine palmitoyltransferase 1(CPT1). When defects occur on beta-oxidation, fatty acyl CoA accumulates, so many of the reactions associated with it will stop; in particular, metabolic disorders in sepsis patients will aggravate in this condition. Recently, there have been studies of novel treatments with dietary supplements, including supplementation of carnitine or L-Carnitine which lead to improving lipid metabolism, antioxidant effects, reducing the incidence of infection and sepsis, lowering blood pressure, improving vital signs and hemodynamic states, as well as SOFA Score [13]. Carnitine may mitigate metabolic disorder of sepsis by increasing fatty acid beta-oxidation in mitochondria and regulating energy metabolism [9]. Animal models of carnitine injection in sepsis demonstrated a positive potential effect on mortality [11]. Preclinical trials of carnitine in sepsis have shown that carnitine might improve the hemodynamic parameters and vital signs [14]. Accordingly, since there is no systematic review assessing the effect of carnitine on sepsis, we aimed to perform a systematic review to summarize the effect of L-Carnitine supplementation on septic patient outcomes hospitalized in intensive care units and relationship between carnitine levels and clinical and biochemical markers in these patients.

Materials and Methods

We searched in electronic databases including ISI web of science, PubMed /Medline, Scopus, Cochrane, Central register of controlled trials and Google Scholar to find published articles assessing the effect of l-carnitine supplementation in sepsis markers from 2000 to March 2020 using the following search terms: "Carnitine" or L Carnitine or L-Carnitine or levo-carnitine or acetyl carnitine or propionyl L Carnitine or Carnitine supplementation "or serum carnitine" in combination with. "Sepsis or Septic shock or Severe sepsis or Critical illness or Multi-organ dysfunction syndrome or Multi-organ failure. Other ways of article identification included searching names of authors of relevant. We restricted the search to articles published in the English language. Only human studies were considered for inclusion. Ten articles were found regarding carnitine levels under septic

conditions. The search was limited by focusing on only interventional studies about carnitine supplementation in sepsis. Besides, a list of references for relevant Randomized controlled trials (RCTs) was searched to find additional articles. We applied the same search strategy to each database. RCTs and observational studies were included. Four authors reviewed all published articles and two independent reviewers assessed the titles and abstracts using the inclusion/exclusion criteria. We using the Jadad scale for quality assessment of included studies and also identified a total of publications that reported at least one of the criteria.

Results

Out of 1729 articles found in the primary search, 10 met the eligibility criteria (Figure 1). The included studies used a variety of study designs. Six studies were designed as clinical trials, two observational studies, one cohort, one pilot, and one case report. The study population in different articles was very heterogeneous, though they were all septic patients. Some of the included studies had enrolled only males [17] or females [24], but most involved both genders [13, 15, 16, 18-23].

All related information from each article is summarized in Tables 1 and 2. Specifically, these articles were reported based on the first author and year of publication, country, study design and population, dosage and administration time, measured variables, clinical outcomes as well as the final result and conclusion of the study. The majority of the studies had measured analytical variables such as acylcarnitine and free carnitine [16-21, 23, 24]. Other outcomes were SOFA, APACHE, and mortality rate.

Chung et al. reported a significant association between plasma carnitine levels and SOFA score ($p < .001$); however, other studies reported that carnitine supplementation had no significant effect on 24h and 48h SOFA score changes [13, 15].

Puskarich et al. reported a significant decrease in 28-days mortality among patients who received L-Carnitine supplementation ($p = .048$) [15]. Evans et al. also reported a slight but not significant reduction in one-year mortality rate in response to L-Carnitine supplementation compared to placebo [17]. In another study in Taiwan, plasma levels of acetylcarnitine were closely related to mortality. Patients with high plasma acetylcarnitine (>6000 ng/ml) had

meaningfully increased 28-days mortality than those with plasma acetylcarnitine less than 6000 ng/ml ($p < 0.001$) [20]. However, some studies have reported no significant association between mortality rate and L-Carnitine supplementation [13]. Some studies have illustrated that carnitine-treated no survivors had also substantially

higher concentrations of carnitine and acylcarnitines following L-Carnitine injection compared with survivors [16, 17]. Nevertheless, Weiss et al. reported a higher acetylcarnitine/carnitine ratio in septic neonates compared to non-septic patients [23].

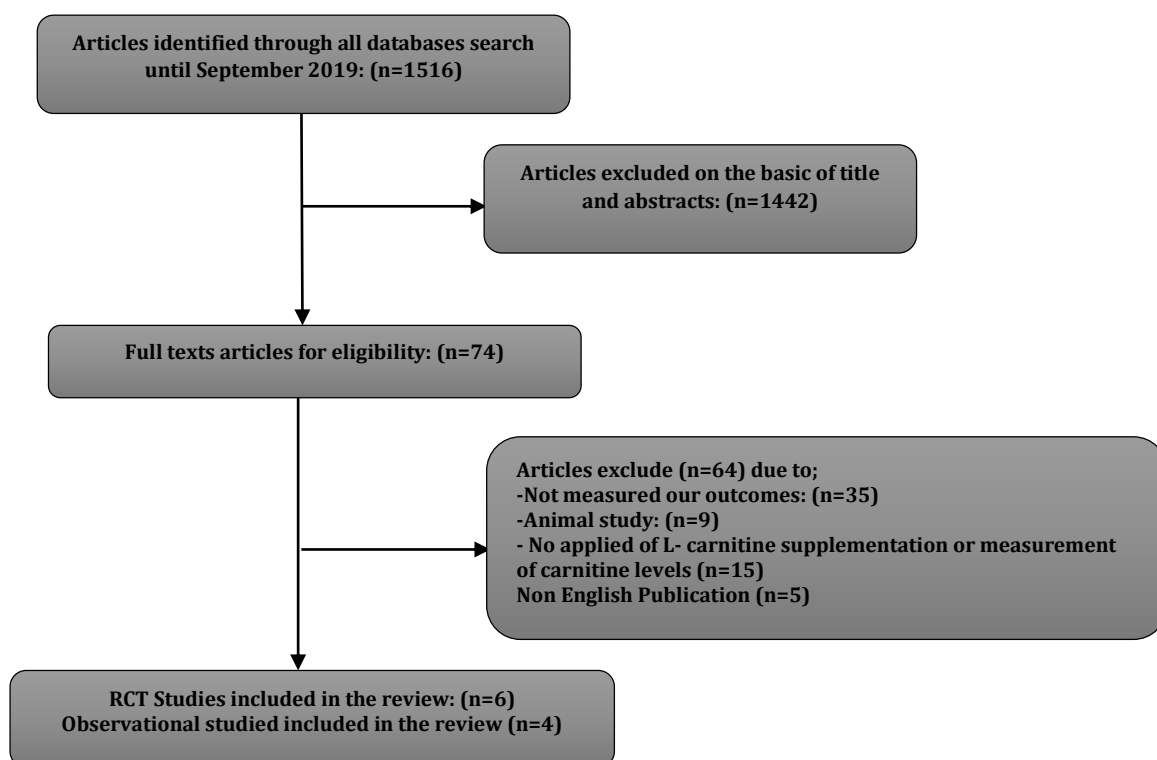


Figure 1. Summary of study selection process

Table 1. Characteristics of included clinical trial studies

Study, year (Author, References)	Quality	Country	Study Design	Participants	Intervention, dose and type	Duration of intervention and follow up	Main Finding
Jones et al. 2018 [13]	Good	USA	Double-blinded, parallel-group randomized clinical trial	250 patients randomized with septic shock, female and male, age >18 y	High dose levocarnitine 18 gr (n=106) Medium dose levocarnitine 12 gr (n=34) Low dose levocarnitine 6 gr (n=35) Placebo group saline (n=75) For each dose of levocarnitine, 33% of the total dose was administered as a 20-mL bolus over 2 to 3 minutes, followed by a fixed-rate continuous	12 hours' intervention 7 days' monitor screen 28 days mortality	None of the examined doses of levocarnitine significantly reduced cumulative organ failure at 48 hours. In the intention-to-treat analysis mean \pm SD changes in the 48 h SOFA score for the low, medium, and high levocarnitine groups were -1.27 ± 0.49 , -1.66 ± 0.38 , and -1.97 ± 0.32 , respectively, vs -1.63 ± 0.35 in the placebo group. The same results were noticed in the per-protocol analysis. Mortality in 28 days was 43.3% (45 of 104) in the high dose group compared with 45.9% (34

Study, year (Author, References)	Quality	Country	Study Design	Participants	Intervention, dose and type	Duration of intervention and follow up	Main Finding
					infusion of 1 L over the next 12 hours.		of 74) in the placebo group. No significant difference was reported in the median ICU length of stay between the groups.
Puskarich et al. 2014 [15]	Good	USA	Double-blind randomized control trials	31 patients with septic shock and SOFA Score >5 Age >18 y	Carnitine group (n=16) 12 gr of carnitine delivered as 4gr bolus injection over 2-3 minutes as infused over 12 hours in the ICU and followed by 8 gr infusion in 1-liter normal saline over the following 12 hours. Placebo groups (n=15) 20 ml bolus normal saline at the same infusion	24- and 48-hours SOFA score and follow up 28 days mortality rate.	There was no difference in SOFA score reduction at 24 hours (p=0.59) or 48 hours (p=0.37), but a significant reduction in 28 days mortality was reported in the L-carnitine group compared with the placebo group (4/16 vs 9/15, P = 0.048). No significant improvement in survival at 1 year was reported (P = 0.06). Data were analyzed using an intention-to-treat analysis.
Puskarich et al. 2018 [16]	Good	USA	Double-blind randomized control trials	31 Patient with septic shock randomized control trials,	Carnitine group (n=16) 12 gr of carnitine delivered as 4gr bolus injection over 2-3 minutes as infused over 12 hours in the ICU and followed by 8 gr infusion in 1-liter normal saline over the following 12 hours. Placebo groups (n=15) 20 ml bolus normal saline at the same infusion	Blood sample collection at admission (T0) 24 hours (T24) 48 Hours (T48) for acylcarnitine measurement by liquid chromatography-mass spectroscopy.	There were no significant differences in the levels of free carnitine and acylcarnitine between the groups at enrollment (p > 0.05). Treatment with L-Carnitine increased levels of all measured carnitine species (C0, C2, C3, C4, C5, C6, and C8), except for C16, in the non-survivors compared to survivors at T0, T24, and T48.
Evans et al. 2019 [17]	Good	USA	Placebo-controlled clinical trial	21 male sepsis patients	Carnitine group 12 gr (n=10) placebo group (n=11) Blood samples were collected, 24h after and 48h after the initiation of a 12h L-carnitine or saline (control) infusion.	24 hours, 48 h metabolic changes and 1-year mortality	One year mortality for carnitine- and placebo-treated males was 45% and 57%, respectively. L -carnitine administration appears to induce few acute metabolic changes aside from increased levels of acylcarnitines (T0h- T24h); (2) L -carnitine treated nonsurvivors in this study, although clinically similar to survivors, were metabolically distinct from them, suggesting that this phenotype has a poor prognosis and may be nonresponsive to intervention with L carnitine supplementation; and (3) that overall, there is broad metabolic heterogeneity in patients with septic shock. We have previously shown that carnitine-treated nonsurvivors also had substantially higher concentrations of carnitine and acylcarnitines following L - carnitine administration compared with survivors.
Gibault et al. 1988 [18]	Fair	USA	RCT	28 septic patients,	13 patient's received carnitine	Basic plasma levels of	In this study, free and total carnitine levels and free/total carnitine ratio were comparable

Study, year (Author, References)	Quality	Country	Study Design	Participants	Intervention, dose and type	Duration of intervention and follow up	Main Finding
				admitted in an intensive care unit,	(2gr/day carnitine) 15 patients' septic without carnitine (control group)	triglycerides, non-esterified fatty acids, free glycerol, phospholipids, ketone bodies remained within physiological limits.	to healthy subjects' reference values. These parameters increased during L-carnitine infusion. This infusion had no effect on exogenous lipid clearance. Carnitine increases the uptake and the hepatic oxidation of circulating fatty acids. Exogenous fatty acids are converted more rapidly into ketone bodies in the presence of carnitine.
Nanni et al. 1985[19]	Fair	USA	RCT	Patients during TPN (8 non septic surgical patients) 11 septic patients received acyl carnitine	Acyl-carnitine infused (100 mg/kg/day) consistent with TPN administration Surgical patients without evidence of infection or malnutrition were considered as control group.	26 patients during total parenteral nutrition D, L-acetyl-carnitine was administered (100 mg/kg/24 hrs., in continuous iv infusion)	The septic state was associated with increased urinary excretion of free carnitine (p-value less than 0.001), as well as with lower plasma levels of short-chain acyl-carnitines (p less than 0.001). Acyl carnitine infusion decreased significantly the respiratory quotient in septic patients suggesting it's important role in the oxidative metabolism in hyper metabolic state. Carnitine supplementation during total parenteral nutrition might be of theoretical benefit in septic patients.

Table Abbreviations: ICU, Intensive Care Units; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; TPN, Total Parenteral Nutrition

Table 2. Characteristics of included observational studies

Study, year (References)	Quality	Country	Study design	Participant	Association	Duration and follow up	Main finding
Chung et.al 2019[20]	Good	Taiwan	Cohort	Patient with sepsis and acute organ dysfunction were enrolled. Recruitment of the derivation (n=90), and validation cohorts(n=120)	Plasma sample was collected immediately after admission, and the levels of carnitine and acyl carnitine were measured by ultra-high performance liquid chromatography-mass spectrometry.	SOFA, APACHE and whole blood sample was obtained immediately and 24h after ICU admission. TNF- α , IL-6, IL-8, IL-10 Plasma concentration were measured.	In this study, the association between carnitine and septic organ dysfunction in sepsis, was significantly associated with SOFA score (p<0.01), hyperlactatemia, systemic inflammation, and mortality. This article confirmed plasma acylcarnitine as a prognostic biomarker for mortality prediction in sepsis patients. Patients with high plasma acetylcarnitine (>6000 ng/ml) had significantly increased 28-day mortality compared with those with plasma Acetylcarnitine less than 6000 ng/ml (p<0.001)
Dalia et.al 2018 [21]	Poor	Egypt	Case-control	40 patient's neonate Healthy groups 20 healthy neonates: 10 preterm 10 full-term 20 neonatal sepsis	No intervention Measurement serum sample carnitine	All neonates subjected to full history taking, clinical examination, and laboratory investigations included measurement of serum l-	There was a significant decrease of serum carnitine level in septic neonates (p<0.001), so they needed assessment and supplementation. There was no correlation between l-carnitine and maternal age (p= 0.867) gestational age (p= 0.322), birth weight (p=0.147) and laboratory

Study, year (References)	Quality	Country	Study design	Participant	Association	Duration and follow up	Main finding
				13 preterm 7 full term		carnitine level, sepsis workup, and other laboratory tests.	investigations in all groups.
Ferrario et al. 2016 [22]	Good	Italy	Pilot study	20 patients with septic shock Sofa score >8	Blood sample obtained on day 1, day 7 Metabolites were measured by mass spectrometry based quantitative metabolomics (acyl carnitine, amino acid, biogenic amines, glycerophospholipids, sphingolipids and sugars.	7 days 28 days' mortality 90 days mortality	In this study, a decrease of these glycerophospholipids was associated to the event at 28-days and 90-days in combination with clinical variables such as cardiovascular SOFA score (28-day mortality model) or renal replacement therapy (90-day mortality model). Early changes in the plasma levels of both lipid species and kynurenine associated with mortality have potential implications for early intervention and discovering new target therapy. Carnitine and butyrylcarnitine increased from D1 to D7 in 28- and 90-day survivors,
Weiss et al. 2012 [23]	fair	US	Prospective Observational study	42 -bed pediatric intensive care unit (PICU) 19 patients <18 y 30 patients with sepsis or septic shock	No intervention	Measurement Plasma asymmetric dimethylarginine and whole blood arginine, cutrullin, ornithine, and acyl carnitine free carnitine ratio were measured daily for septic patients and once for control subjects using tandem mass spectrometry.	There were no differences in the acylcarnitine: free carnitine ratio, between septic group and control patients. (p=0.67) but septic patients had a higher median acylcarnitine; free carnitine ratio on all study days compared to day 1 (p=0.57). free carnitine was not associated with organ dysfunction or outcomes (p=>0.05). There was no difference in age, gender, or ethnicity between groups. Septic patients had higher pediatric index mortality and Pediatric Logistic Organ Dysfunction score and a longer hospital stay (all p<0.001).

Table Abbreviations: ICU, Intensive Care Units; SOFA, Sequential Organ Failure Assessment; PICU, Pediatric Intensive Care Unit; TNF- α , Tumor Necrosis Factor Alpha; IL10, Interleukin 10; IL8, Interleukin 8; IL 6, Interleukin 6

Discussion

In the present review, it was found that the patients who received L-Carnitine supplements had higher elevated plasma levels of carnitine and acetylcarnitine. Besides, the septic condition was correlated with diminished plasma carnitine levels and increased urinary excretions of free carnitine. Further, the mortality rate appeared to be lower but not significant in patients receiving carnitine supplementation.

Carnitine is indispensable for the transfer of long-chain fatty acids into the matrix of mitochondria for beta-oxidation and thus energy production. Accordingly, sepsis is well-known as a metabolic disorder, when the defects occur on beta-oxidation or carnitine deficiency or defect on the shuttle of CPT causing fatty acyl COA accumulation and depletion of COA enzyme. Thus, many of the

reactions associated with it will stop. Meanwhile, metabolic disorders in sepsis patients will deteriorate, so metabolic changes on mitochondrial function during sepsis lead to multiple organ failure, increased length of hospital stay, mechanical ventilation and score of severity disease by SOFA and APACHE scores. Oami et al.'s case study revealed that carnitine deficiency occurred in 23/4 of critically ill patients had a significant correlation with increased SOFA score. Hence, in line with this case study result, carnitine deficiency in critically ill patients has occurred, as sepsis patients have more length of ICU stay and artificial nutrition with enteral or parental. All these results in carnitine deficiency and disorder of beta-oxidation, thus causing failed lipid utilization by vital organs and ketotic hypoglycemia, lipid disorder, lactate production,

Krebs cycle disorder, and defect on energy production. Hence, carnitine supplementation results in the transfer of fatty acids into the mitochondria and improved metabolic and hemodynamic states. Chung et al. observed that increased plasma levels of acylcarnitines in sepsis are associated with organ dysfunctions [20]. Animal studies suggested fatty acid oxidation impairment as a potential explanation for sepsis [25-27]. Carnitine palmitoyltransferase 1 and 2 (CPT1 and CPT2), as well as long-chain acyl-coenzyme A dehydrogenase (LCAD) are all main mitochondrial proteins for β -oxidation. Studies reported that the messenger RNA expressions of CPT1, CPT2, and LCAD were down-regulated in the kidney and liver in animal models of sepsis [25, 26]. Malfunctioning fatty acid oxidation in renal tubular cells leads to adenosine triphosphate exhaustion and cell death, causing hepatic and renal dysfunction in sepsis [28]. As shown in some studies, nonsurvivors had significantly higher plasma levels of acylcarnitine and carnitine compared with survivors, [17, 20]. Acylcarnitine have shown that carnitine metabolism is disordered, since mitochondrial dysfunction may lead to failed lipid utilization by vital organs and consequently diminished fatty acid oxidation in patients who died of sepsis.

One of the largest studies reported that carnitine supplementation in high doses leads to diminished sofa score, but it was not significant for cumulative organ failure reduction at 48 hours [13], perhaps high dose intervention is a short time duration. These data suggest that these methods of supplementation do indeed result in cellular uptake and substrate utilization through the formation of acylcarnitine supporting the biologic plausibility of the treatment.

As L-Carnitine is excreted from the kidney, it can be expected that the difference between plasma carnitine levels in survivors and non-survivors will be due to the renal function, though identical levels of carnitine reported at the enrollment of some studies [16] are contrary to this theory.

Limitation

Two limitations could be stated for the present study. An important limitation of the present study was the number of studies on this subject has been small, and our search has been limited to studies published in English.

Conclusion

In conclusion according to observational studies high plasma carnitine levels help to reduce mortality risk in septic patients but this relationship was observed as a reverse form for acyl carnitine levels and also RCT studies showed that L-Carnitine supplementation had beneficial effects on the mortality rate of septic patients, although these effects on the SOFA scores were controversial. Additional studies with more rigorous study design methods and longer follow-up periods should be adopted.

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Author Contribution

F. Yahyapour and A. Norouzy equally contributed to the conception and design, M. K. Rezaian contributed to the acquisition and analysis of the data; F. Yahyapour and A. norouzy contributed to the interpretation of the data; and F. Y and N. Pahlavani drafted the manuscript. All authors critically revised the final draft of manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. All authors have approved of the final version

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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