



Nutritional interventions in patients with burn injury: an umbrella review of systematic reviews and meta-analyses of randomised clinical trials

Fatemeh Naeini¹, Sheida Zeraattalab-Motlagh², Mehran Rahimlou³, Mahsa Ranjbar¹, Amirhossein Hemmati¹, Sajedeh Habibi¹, Sajjad Moradi⁴ and Hamed Mohammadi^{1*}

¹Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

²Department of Health and Human Performance, University of Houston, Houston, TX, USA

³Department of Nutrition, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

⁴Department of Nutrition and Food Sciences, Research Center for Evidence-Based Health Management, Maragheb University of Medical Sciences, Maragheb, Iran

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Abstract

Multiple reviews have examined the impact of nutritional interventions in patients with burn injuries; however, discrepancies among results cast doubt about their validity. We implemented this review to assess the impact of various nutritional interventions in adult patients with burn injuries. We conducted a thorough search of PubMed, Scopus and Web of Science databases until 1 August 2024, to identify relevant meta-analyses of intervention trials, examining the impact of nutritional interventions on burn patients. We adopted the random-effect models to determine the pooled effect sizes while employing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to examine evidence certainty. Thirty-three original intervention trials from eleven meta-analyses were entered in our review. Early enteral nutrition could substantially reduce overall mortality (relative risk (RR): 0.36, 95% CI: 0.19, 0.68, GRADE = moderate certainty), hospital stay (mean difference (MD): –15.3, 95% CI: –20.4, –10.2, GRADE = moderate certainty) and sepsis risk (RR: 0.23, 95% CI: 0.11, 0.45, GRADE = moderate certainty). Glutamine showed a notable decrease in the length of hospital stay (MD: –6.23, 95% CI: –9.53, –2.94, GRADE = low certainty). However, other nutritional interventions, including combined immunonutrition, branched-chain amino acids, fish oil, ornithine α -ketoglutarate and trace elements, did not significantly affect the assessed clinical outcomes. Early enteral nutrition might impose a beneficial effect on mortality, hospital stay length and incidence of sepsis with moderate evidence. Lower length of hospital stay was also seen in burn patients supplemented with glutamine, although the evidence was weak.

Keywords: Nutritional intervention: Meta-analysis: Review: Trial: Burn: Mortality

Burns are defined by the WHO as ‘an injury to the skin or other organic tissue primarily caused by heat, radiation, radioactivity, electricity, friction or contact with chemicals’⁽¹⁾. Despite significant advancements in techniques to prevent burn incidences, severe burn injuries remain the most catastrophic damage that can be survived, and they pose a global public health concern^(2–4).

Severe burns lead to serious pathophysiological stress reactions and drastically incremented metabolic rate, which might be long lasting⁽⁵⁾. Moreover, severe catabolic state leading to reduced body mass, negative nitrogen balance and whole-body protein breakdown, similar to acute severe

malnourishment, can happen when more than 20% of the total body surface area is involved⁽⁶⁾.

Managing the nutrition of patients who have suffered from severe burns can be a challenging task for healthcare professionals, including physicians and dietitians. Considering the risky hypermetabolic response, intensified losses and requirements, as well as changed glucose metabolism following burn injury^(5,7–11), nutritional interventions depending on the areas of burn, risk of malnutrition or any other concomitant disorders are vital factors for the treatment of patients with severe burns, along with prominent outcome effectors^(5,12). Thus, understanding the beneficial effects of nutritional interventions

Abbreviations: BCAA, branched-chain amino acids; RCT, randomised control trial; SRMA, systematic reviews with meta-analysis.

* **Corresponding author:** Hamed Mohammadi, email hmohamadi@sina.tums.ac.ir, mohamadihd@gmail.com



is vital because this could result in better patient outcomes, including reduced length of hospital stay, as well as mortality. Fortified oral diets, complementary beverages and enteral or parenteral nutrition are some ways in which this support could be provided⁽¹³⁾. Also, arginine, glutamine and *n*-3 fatty acids are among the dietary agents that have been considered for patients with severe burns⁽¹⁴⁾.

Despite numerous systematic reviews and meta-analyses (SRMA) of intervention trials on the impact of various nutritional interventions in patients with burn injury, the findings about the effectiveness of each nutritional intervention remain varied, and the quality of studies has not yet been assessed. For instance, regarding enteral nutrition, one SRMA found no considerable impact on the length of hospital stay and ventilation day⁽¹⁵⁾; however, one SRMA indicated a substantial improvement in mortality⁽¹⁶⁾. Moreover, regarding glutamine supplementation, three SRMA did not reveal any significant effect on outcomes^(17–19); however, two SRMAs showed beneficial effects^(20,21). Considering the value of improving burn-related outcomes in adults and the ambiguity regarding which kind of nutritional interventions are helpful, a thorough umbrella review is required to provide information about effective interventions to improve outcomes in patients with burn injuries. Therefore, this review aimed to assess the impact of various nutritional interventions in patients with burn injuries and rate the certainty of evidence gathered.

Methods

According to the Cochrane Handbook for Systematic Reviews, this umbrella review was conducted⁽²²⁾. The study followed the guidelines of the 'Grading of Recommendations Assessment Development, and Evaluation' handbook⁽²³⁾ and the 'The Preferred Reporting Items for Overviews of Reviews' statement⁽²⁴⁾ (online Supplementary Table S1). The PROSPERO website registered the protocol of this study (CRD42024496620).

Search strategy and eligibility criteria

A search was conducted on PubMed/Medline, Science direct, Scopus, Web of Sciences and Embase databases of systematic reviews from 1990 to August 1, 2024, to locate meta-analyses of intervention trials (online Supplementary Table S2). No language restriction was applied. Removal of duplicates was carried out after importing the identified articles to EndNote.

Eligibility criteria study selection

To be included, the studies met the following criteria: meta-analyses of randomised controlled trials (RCT) investigating associations with seven nutritional interventions (early enteral nutrition, combined immunonutrition, glutamine, branched-chain amino acids (BCAA), fish oil, ornithine α -ketoglutarate and trace elements) among adults with complication-related burn injury, including overall mortality, length of hospital stay, sepsis, pneumonia, overall infection, wound infection and ventilation day. Two reviewers (F.N. and A.H.) conducted independent screening of titles and abstracts to determine relevance and selected studies after reviewing the full text of potentially eligible

articles. Any discrepancies were resolved by discussion with the third reviewer (H.M.). We excluded articles that did not have full text, reviews or meta-analyses of studies with different designs and those that did not include a control group.

Data extraction

The task of data extraction and quality assessment was carried out independently by two reviewers (M.R. and S.H.) and then reviewed by two other reviewers (F.N. and S.Z.M.). Consensus was reached to resolve discrepancies. The meta-analyses of eligible systematic reviews provided information on various aspects including trial and participant numbers, study duration, effect sizes for clinical outcomes, heterogeneity, publication bias risk, population and intervention characteristics and outcome certainty level. We prioritised effect sizes from the meta-analysis with the most RCT if it included an RCT in multiple meta-analyses on the same outcome. The study presents effect sizes along with their corresponding CI and *P* values.

Assessment of methodological quality

We used the A Measurement Tool to Assess Systematic Reviews tool to assess the methodological quality of the systematic reviews⁽²⁵⁾. It contains sixteen questions. The Cochrane risk-of-bias tool was used to evaluate the methodological quality of the RCT included in the meta-analysis (online Supplementary Tables S5)⁽²⁶⁾. The quality assessments were conducted by two independent investigators, S.T. and S.Z.M. A third author was involved in reaching a consensus to resolve any disagreements (H.M.).

Data synthesis and statistical analysis

We included all relevant RCT with data on a clinical outcome for the quantitative synthesis, regardless of their inclusion in any reviews. Then, we obtained effect sizes and 95% CI from the original studies in the largest systematic review. To account for within- and between-study heterogeneity, we applied a conservative random-effects model to recalculate the mean differences or relative risks for each meta-analysis, along with their corresponding 95% CI⁽²⁷⁾. Because of heterogeneity of the included studies in terms of study population and study design, random-effect model was used to homogenised the data for meta-analysis. The I^2 statistic was used to assess and report heterogeneity quantitatively, and a χ^2 test for homogeneity was conducted ($P_{\text{heterogeneity}} > 0.10$). According to the Cochrane Handbook guidance, we interpreted the I^2 values as follows (0–40%, might not be important; moderate heterogeneity may be represented by a range of 30–60% and the range of values, from 50% to 90%, indicates potential heterogeneity; 75–100%, may represent considerable heterogeneity)⁽²⁸⁾. Publication bias was evaluated through visual inspection of funnel plots and using *P* values from the Egger test⁽²⁹⁾.

Grading of the evidence

We used the GRADE criteria to evaluate evidence quality in a meta-analysis, considering five domains: (1) individual study bias, (2) inconsistency, (3) indirectness, (4) imprecision and (5)



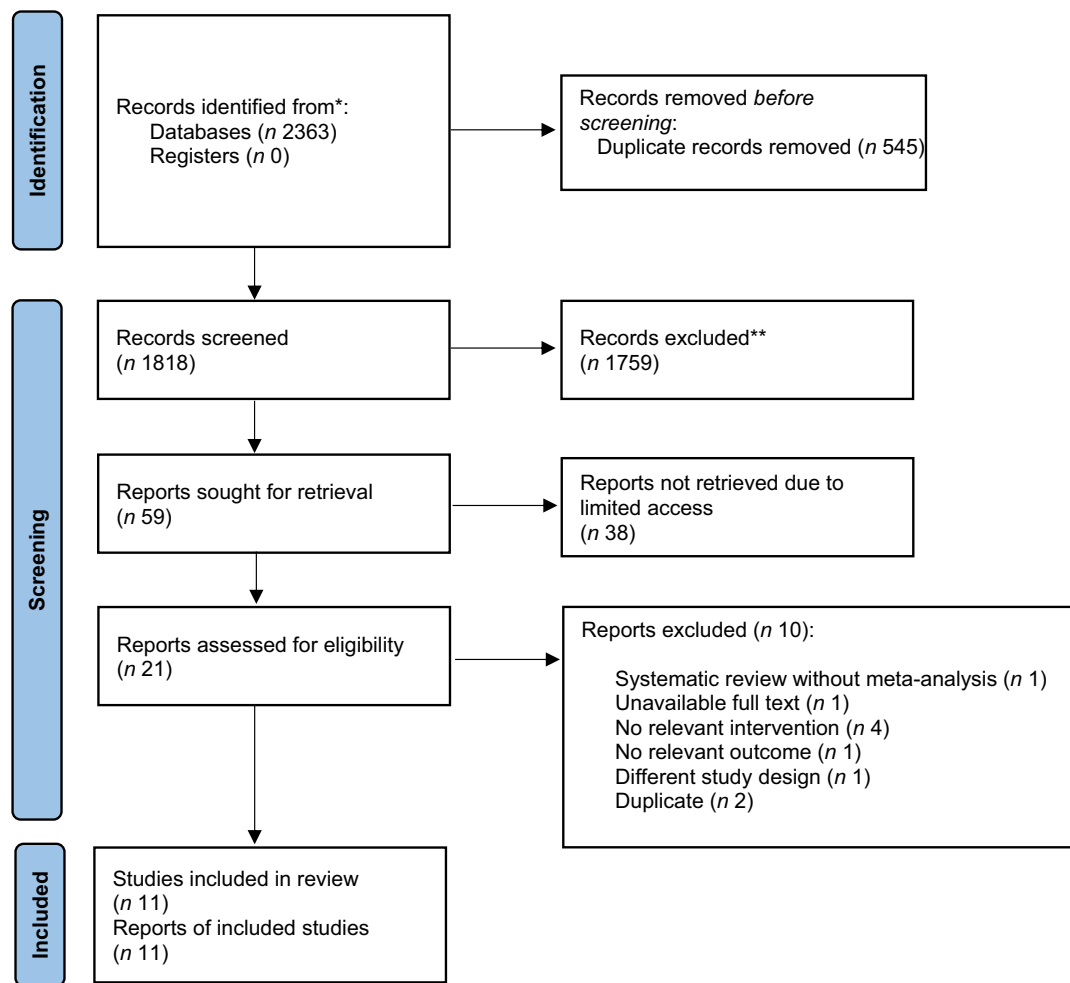


Fig. 1. Literature search and review flow diagram for selection of studies.

publication bias⁽³⁰⁾. We applied the GRADE criteria to evaluate the evidence quality per effect in a meta-analysis, focusing on five domains.

Results

The flow diagram of literature search in electronic databases is indicated in Fig. 1. Following a comprehensive search and after excluding duplicate papers, we recognised 2363 articles, of which 2342 were removed at the titles/abstracts stage screening. Of twenty-one articles that went through full-text reviewing, ten were excluded due to the outlined following reasons: Systematic review without meta-analysis (*n* 1); unavailable full text (*n* 1); no relevant intervention (*n* 4); no relevant outcome (*n* 1); different study design (*n* 1) and duplicate (*n* 2) (online Supplementary Table S3). Finally, eleven meta-analyses were selected for inclusion in our review.

Thirty-three original intervention trials from eleven meta-analyses have been included in our umbrella review. Overall participants and follow-up length were spanned from twenty to 1399 participants (median = 244), as well as 11 d to 24 weeks. The publication year of our selected intervention trials were

between 1990 and 2022. The original intervention trials recorded in the eligible reviews entered seven different types of nutritional interventions (early enteral nutrition, combined immunonutrition, glutamine, BCAA, fish oil, ornithine α -ketoglutarate and trace elements). In addition, the outcomes examined in adult patients with burn injury involved overall mortality, length of hospital stay, sepsis, pneumonia, overall infection, wound infection and ventilation day.

The effect of nutritional interventions on overall mortality

All nutritional interventions examined their impacts on the incidence of overall mortality. In burn patients, early enteral nutrition has been found to significantly reduce the incidence of overall mortality (RR: 0.36, 95% CI: 0.19, 0.68, $I^2 = 0.0\%$; moderate evidence certainty; *n* 4 trials). However, other interventions, including combined immunonutrition (RR: 4.62, 95% CI: 0.25, 86.0), glutamine (RR: 1.02, 95% CI: 0.79, 1.30), BCAA (RR: 2.40, 95% CI: 0.63, 9.96), fish oil (RR: 0.95, 95% CI: 0.59, 1.54), ornithine α -ketoglutarate (RR: 9.92, 95% CI: 0.36, 2.37) and trace elements (RR: 0.47, 95% CI: 0.15, 1.54) did not show a significant impact (Table 1), with moderate to very low

GRADE evidence. All intervention trials showed no significant publication bias (Table 1).

The effect of nutritional interventions on length of hospital stay

All nutritional interventions were examined for their impacts on the length of hospital stay. In burn patients, early enteral nutrition (MD: -15.3 , 95% CI: -20.4 , -10.2 , $I^2 = 0.0\%$; moderate evidence certainty; n 3 trials) and glutamine (MD: -6.23 , 95% CI: -9.53 , -2.94 , $I^2 = 64.5\%$; low evidence certainty; n 10 trials) have been found to significantly reduce the length of hospital stay (Table 1). In contrast, with moderate to very low GRADE evidence, other interventions included combined immunonutrition (MD: 3.36 , 95% CI: -4.38 , 11.1), BCAA (MD: 4.00 , 95% CI: -27.6 , 35.6), fish oil (MD: -1.85 , 95% CI: -8.67 , 4.97), ornithine α -ketoglutarate (MD: -4.21 , 95% CI: -18.8 , 10.4) and trace elements (MD: -8.96 , 95% CI: -24.8 , 6.96) revealed no considerable impact on the length of hospital stay (Table 1). All intervention trials revealed no considerable publication bias (Table 1).

The effect of nutritional interventions on sepsis and pneumonia

Two nutritional interventions, early enteral nutrition and fish oil, were studied for their impact on the incidence of sepsis and pneumonia. While neither intervention significantly reduced the risk of pneumonia, early enteral nutrition significantly reduced the risk of sepsis (RR: 0.23 , 95% CI: 0.11 , 0.45 , $I^2 = 0.0\%$; moderate evidence certainty; n 3 trials).

We also found considerable publication bias for pooled trials that compiled data on the risk of sepsis following fish oil intervention ($P_{\text{egger}} = 0.03$) (Table 1).

The effect of nutritional interventions on infection

Two nutritional interventions, glutamine and fish oil, were studied for their impact on the incidence of overall, as well as wound infection. With low to very low GRADE evidence, glutamine (RR: 0.42 , 95% CI: 0.17 , 1.07) and fish oil (RR: 0.82 , 95% CI: 0.49 , 1.36) interventions had no significant impact on improving the risk of wound infection (Table 1).

We also found considerable publication bias for pooled trials that compiled data on the risk of wound infection following fish oil intervention ($P_{\text{egger}} = 0.008$) (Table 1).

The effect of nutritional interventions on ventilation day

Two nutritional interventions, glutamine and fish oil, were studied for their impact on the ventilation day. With moderate to low GRADE evidence, glutamine (MD: 1.38 , 95% CI: -0.76 , 3.53) and fish oil (MD: -2.11 , 95% CI: -5.03 , 0.82) interventions had no significant impact on reducing the ventilation day (Table 1). Moreover, all intervention trials revealed no considerable publication bias (Table 1).

Methodological quality

Findings of quality assessment of entered reviews are revealed in online Supplementary Table S5. Evidence quality of entered

reviews are 'high', 'low' and 'critically low' at 45.5%, 9% and 45.5%, respectively.

Discussion

The results of the present umbrella review study showed that among the nutritional supplementation effects on patients with burn, with moderate evidence certainty, early enteral nutrition could significantly reduce the overall mortality, length of hospital stay and risk of sepsis. Also, with low certainty of evidence, glutamine supplementation has been shown to improve the length of hospital stay significantly. However, other interventions, including combined immunonutrition, BCAA, fish oil, ornithine α -ketoglutarate and trace elements, had no special effects on clinical outcomes.

The positive changes in clinical results shown in this study align entirely with the physiological reasoning provided to endorse early enteral nutrition in prominent clinical practice guidelines⁽⁸⁾. Early enteral nutrition helps preserve the immune function of the intestinal mucosal barrier, consequently minimising consequences associated with bacterial translocation⁽¹⁶⁾. The digestive system is widely recognised as the most responsive organ to reduced blood flow. For example, in people with good health who engage in light exercise for some time every day, it causes splanchnic hypoperfusion^(31,32). This condition undermines the integrity of epithelial cells, resulting in heightened permeability and the triggering of neutrophils. Shortly following a severe burn injury, individuals are recognised to experience alterations in the gastric and duodenal mucosa, indicative of ischaemic damage⁽³³⁾. These changes may advance to ulcerative erosions, leading to the presence of hidden blood in stools or, in extreme cases, posing a risk of life-threatening bleeding⁽³⁴⁾.

Moreover, these ischaemic alterations in the intestines undermine the immune function, permitting the movement of bacteria from the intestinal tract to other parts of the body⁽³⁵⁾. Apart from raising the likelihood of infectious side effects, the excess presence of gut bacteria stimulates leucocytes and macrophages specific to certain tissues. This activation triggers an inflammatory sequence that sets off subsequent organ failures and contributes to the clinical manifestation of sepsis^(36,37).

It has been reported in some of the cohort and cross-sectional studies among the participants hurt by the burn that those who are administered early enteral nutrition had significantly lower odds of gastrointestinal haemorrhage^(38–40). Animal samples subjected to fluid resuscitation demonstrate that, regardless of cardiac output, the provision of early enteral nutrition leads to a notable rise in blood flow to different parts of the digestive system following a significant burn⁽⁴¹⁾. The maintenance of blood flow through early enteral nutrition sustains the immune function of the gut's physical barrier, leading to a considerable reduction in measurable bacterial translocation^(42,43). The provision of early enteral nutrition also lowers the measurable presence of endotoxin in the bloodstream, dampens the exaggerated cortisol reaction to burn injuries, diminishes tumor necrosis factor α and improves the host's capability to eliminate translocating bacteria^(44,45). Preserving the immune function of



Table 1. The effects of nutritional interventions in burn patients

Nutrition intervention	Number of trials (arms)	Number of Participants	Intervention/Control	Duration of intervention, wk	Dose (range)	Effect size	95 % CI	P-value	I ² (%)	P _{heterogeneity}	Egger's test	GRADE
Early enteral nutrition												
Overall mortality	4	274	146/128	24	Various*	RR, 0.36	0.19, 0.68	0.002	0.0 %	0.47	0.49	Moderate
LOS, day	3	110	63/47	3	Various*	MD, -15.3	-20.4, -10.2	< 0.001	0.0 %	0.60	0.65	Moderate
Sepsis	3	247	132/115	24	Various*	RR, 0.23	0.11, 0.45	< 0.001	0.0 %	0.55	0.61	Moderate
Pneumonia	3	247	132/115	24	Various*	RR, 0.49	0.14, 1.63	0.24	64.2 %	0.06	0.57	Low
Combined immunonutrition												
Overall mortality	1	23	12/11	24	Arginine 10 + n-3 3.5 (Crucial, Nestle Nutrition, Glendale, CA; 1.5 kcal/ml, 94 g protein/l)	RR, 4.62	0.25, 86.0	0.30	-	-	-	Low
LOS, day	2	64	35/29	24/until discharge from the hospital	Arginine 10 + n-3 3.5 (Crucial, Nestle Nutrition, Glendale, CA; 1.5 kcal/ml, 94 g protein/l)	MD, 3.36	-4.38, 11.1	0.39	0.0 %	0.56	-	Very low
Glutamine												
Overall mortality	6	1399	693/706	2-≥ 4/until ICU discharge	0.5 g/kg/d-26 g/d	RR, 1.02	0.79, 1.30	0.90	0.0 %	0.56	0.09	Moderate
LOS, day	10	416	207/209	1-2/until ICU discharge	0.5 g/kg/d-26 g/d	MD, -6.23	-9.53, -2.94	< 0.001	64.5 %	0.003	0.94	Low
Overall infection	6	1384	686/698	12 d-≥ 4 wks/ until the end of the study	0.35 g/kg/d-26 g/d	RR, 0.81	0.64, 1.03	0.08	4.1 %	0.39	0.46	Moderate
Wound infection	2	81	39/42	12 d-until the end of the study	0.35 g/kg/d-26 g/d	RR, 0.42	0.17, 1.07	0.07	0.0 %	0.66	-	Low
Ventilation day, day	3	1282	636/646	≥ 4- until the end of the study	0.5 g/kg/d-26 g/d	MD, 1.38	-0.76, 3.53	0.21	0.0 %	0.64	0.55	Moderate
BCAA												
Overall mortality	1	20	10/10	NR	Modified amino acid solution with 45 % BCAA	RR, 2.40	0.63, 9.96	0.19	-	-	-	Low
LOS, day	1	20	10/10	NR	Modified amino acid solution with 45 % BCAA	MD, 4.00	-27.6, 35.6	0.80	-	-	-	Low
Fish oil												
Overall mortality	7 (8)	316	160/156	11 d-5 wks	1.75 g/l-5 g	RR, 0.95	0.59, 1.54	0.84	0.0 %	0.57	0.48	Moderate
LOS, day	6 (8)	349	150/146	11 d-5 wks	1.75 g/l-5 g	MD, -1.85	-8.67, 4.97	0.59	44 %	0.08	0.75	Low
Sepsis	2 (3)	159	81/78	2-5	5 g	RR, 0.66	0.30, 1.43	0.29	16.9 %	0.30	0.03	Very low
Pneumonia	7 (9)	354	166/161	25 d-5 wks	1.75 g/l-5 g	RR, 0.68	0.44, 1.06	0.09	43 %	0.08	0.30	Moderate
Wound infection	4 (5)	231	118/113	2-5	1.75 g/l-5 g	RR, 0.82	0.49, 1.36	0.44	55 %	0.06	0.008	Very low
Ventilation day, day	4 (5)	244	124/120	11 d-5 wks	5 g-5.6 g/l	MD, -2.11	-5.03, 0.82	0.16	76 %	0.002	0.22	Low
Ornithine α-ketoglutarate												
Overall mortality	2	95	56/39	3	20 g as 2 boluses of 10 g twice daily/supplemented (10, 20 or 30 g/d bolus) or as infusion (10, 20 or 30 g/d)	RR, 9.92	0.36, 2.37	0.87	0.0 %	0.62	-	Very low

Nutritional interventions and burn patients

Table 1. (Continued)

Nutrition intervention	Number of trials (arms)	Number of Participants	Intervention/Control	Duration of intervention, wk	Dose (range)	Effect size	95% CI	P-value	I ² (%)	P _{heterogeneity}	Egger's test	GRADE
LOS, day	1	48	32/16	3	Supplemented (10, 20 or 30 g/d bolus) or as infusion (10, 20 or 30 g/d)	MD, -4.21	-18.8, 10.4	0.57	-	-	-	Very low
Trace elements	5	161	67/94	1-3/until discharge	Various**	RR, 0.47	0.15, 1.54	0.21	0.0%	0.62	0.20	Moderate
Overall mortality	3	42	21/21	1	Various**	MD, -8.96	-24.8, 6.96	0.27	0.0%	0.74	0.06	Moderate

BCAA, branched-chain amino acids; CI, confidence interval; d, day; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LOS, length of hospital stay; MD, mean difference; NR, not reported; RR, relative risk; wk, week.

* As soon as possible after ICU admission: 500 kcal provided in the first 24 h of ICU stay, then increased to reach at least 75% of calculated targets in the next few days (Goals set by the Current formula) or within 24 h of burn injury: EN commenced at 20 ml/h in adults. Rate increased every 6 h as tolerated until goal reached (Goal set using Harris-Benedict) or Within 4 h after admission: 25 ml/h EN via NJT infused by pump during the daytime for 12-16 h over 3-5 d or Within 6 h after injury: 100-125 ml/h via NJT, providing 2000 kcal in the first 24 h. Increased to 4000 kcal over the next 2-3 d or immediately after admission: 50 ml/h 'homemade' EN (1900 kcal/l and 79 g protein/l) via NGT increasing over 3-4 d. Goal set with Curreri formula. Rate did not exceed 150 ml/h.

** 2.4 mg Cu, (15.04 μmol Cu) 82 μg se, (0.434 μmol se) 26.5 mg Zn (194.44 μmol Zn) or Cu (40.4 μmol), se (2.9 μmol), Zn (406 μmol) or 59 μmol Cu, 4.8 μmol se, and 574 μmol Zn or 15 mg elemental Zn or 75 mg/d Zn.

the digestive system through early enteral nutrition emerges as a likely phenomenon behind the significant clinical effects observed in our study. This maintenance of gut integrity results in a decreased damage to the digestive system, reduced infectious side effects, a lowering of subsequent organ failures and a diminished likelihood of sepsis onset^(46,47). The collective advantages of these outcomes contribute to enhanced patient survival and a shorter hospital length of stay.

In the present study, we found that glutamine supplementation significantly reduced the length of hospital stay. However, we could not find any significant improvement in the overall mortality, duration of ventilation and wound infection. In a meta-analysis study by Ortiz-Reyes *et al.*, they showed that glutamine demonstrated a notable decrease in both mortality and instances of infectious complications in one-centre trials, although this effect was not observed in trials conducted across multiple centres⁽¹⁷⁾. In terms of mechanisms, adding glutamine helps reduce inflammation originating from the gut, sustains immune functions, shields against burn-related myocardial injury, preserves muscle metabolism and safeguards cells from injury^(18,48,49). Specific research findings indicated that glutamine exhibited the most significant impact in reducing damage to the intestinal mucosa⁽⁵⁰⁾. Diamine oxidase (DAO) is an enzyme that removes amino groups from histamine and polyamines, reaching its peak activity in the intestinal mucosa across various mammalian species, including humans⁽⁵¹⁾. DAO is primarily located in the small intestine, and its function is strongly linked to the synthesis of nucleic acid and protein in the intestinal tract. The levels of DAO in the bloodstream correspond to the content of DAO and structural alterations in the intestinal mucosa⁽⁵¹⁾. Studies have demonstrated that plasma DAO activity accurately mirrors changes related to mucosal injury in severe trauma cases. Some studies showed a notable rise in DAO activity following burn injuries, and following a 7-d regimen of glutamine treatment, there was a significant reduction in DAO levels⁽⁵¹⁻⁵³⁾.

In this umbrella review study, we could not find any significant effects of other nutritional interventions, including fish oil, combined immunonutrition, BCAA, ornithine α -ketoglutarate and trace elements on other burn-related outcomes. The results of other meta-analysis studies investigating the effect of *n*-3 supplementation in enteral nutrition in critically ill patients have shown that *n*-3 supplementation had no significant effect on outcomes such as mortality or length of hospitalisation⁽⁵⁴⁾.

Based on our knowledge, the present study was the first umbrella review study that examined the effects of different nutritional interventions among patients with burns. However, some limitations in the present study should be considered. First, there were disparities in how metrics and clinical outcomes were reported across studies. Furthermore, most of the meta-analyses incorporated in the study did not assess the severity of burn injuries, including factors like burn depth, baseline organ dysfunction degree or the Nutrition Risk in the Critically Ill Score^(55,56). Consequently, these aspects could not be analysed in our research. Third, the studies did not consider baseline concentrations of some nutrients, such as glutamine. Fourth, not considering lifestyle modification like dietary intakes and level of physical activity in most of the included studies should be considered as one of the important limitations of the present

research. Finally, the certainty of the evidence was weak for some findings in the present study.

Conclusion

In conclusion, our umbrella review comprehensively assessed the impact of various nutritional interventions on clinical outcomes in patients with burn injuries. Early enteral nutrition emerged as a significant contributor, demonstrating a substantial reduction in overall mortality, length of hospital stay and the risk of sepsis. Additionally, glutamine supplementation showed a notable decrease in the length of hospital stay. However, other nutritional interventions, including combined immunonutrition, BCAA, fish oil, ornithine α -ketoglutarate and trace elements, did not exhibit significant effects on the assessed clinical outcomes. Despite some limitations, our study provides valuable information for clinicians and researchers, highlighting the potential benefits of early enteral nutrition and glutamine supplementation in improving outcomes for patients with burn injuries. Further well-designed research addressing the identified limitations such as consideration of lifestyle modification like dietary intakes and level of physical activity of study participants could enhance our understanding of nutritional interventions in this population.

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All authors conceptualised and designed this review. F. N. and A. H. conducted a literature search. M. R. and S. H. collected the data, and S.Z-M. performed analysis. M. R., S. M. and S. Z-M. wrote the first draft. H. M. contributed to critically revising and interpreting the data. All authors read and confirmed the final manuscript.

All authors declare that they have no conflict of interest.

Data described in the manuscript will be made available upon request pending.

Supplementary material

For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114524002344>

References

1. Sepsis ABACCoB, Group I, Greenhalgh DG, Saffle JR, *et al.* (2007) American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res* **28**, 776–790.
2. Wischmeyer PE (2019) Glutamine in burn injury. *Nutr Clin Pract* **34**, 681–687.
3. Erdem D, Sözen İ, Çakırca M, *et al.* (2019) Effect of nutritional support containing arginine, glutamine and β -hydroxy- β -methylbutyrate on the protein balance in patients with major burns. *Turk J Anaesthesiol Reanimation* **47**, 327.
4. Berger MM, Binz PA, Roux C, *et al.* (2022) Exudative glutamine losses contribute to high needs after burn injury. *J Parenteral Enteral Nutr* **46**, 782–788.
5. Clark A, Imran J, Madni T, *et al.* (2017) Nutrition and metabolism in burn patients. *Burns Trauma* **5**, 11.
6. Prelack K, Dylewski M & Sheridan RL (2007) Practical guidelines for nutritional management of burn injury and recovery. *Burns* **33**, 14–24.
7. McClave SA, Taylor BE, Martindale RG, *et al.* (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *JPENJ Parenteral Enteral Nutr* **40**, 159–211.
8. Rousseau A-F, Losser M-R, Ichai C, *et al.* (2013) ESPEN endorsed recommendations: nutritional therapy in major burns. *Clin Nutr* **32**, 497–502.
9. Snell JA, Loh N-HW, Mahambrey T, *et al.* (2013) Clinical review: the critical care management of the burn patient. *Crit Care* **17**, 1–10.
10. Taylor BE, McClave SA, Martindale RG, *et al.* (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *Crit Care Med* **44**, 390–438.
11. Williams FN, Branski LK, Jeschke MG, *et al.* (2011) How, and how much should patients with burns be fed? *Surg Clinics* **91**, 609–629.
12. Natarajan M (2019) Recent concepts in nutritional therapy in critically ill burn patients. *Int J Nutr Pharmacol Neurol Dis* **9**, 4–36.
13. Tan HB, Danilla S, Murray A, *et al.* (2014) Immunonutrition as an adjuvant therapy for burns. *Cochrane Database Syst Rev* 2014, issue 12, CD007174.
14. Heyland DK, Wibbenmeyer L, Pollack JA, *et al.* (2022) A randomized trial of enteral glutamine for treatment of burn injuries. *N Engl J Med* **387**, 1001–1010.
15. Pham CH, Fang M, Vrouwe SQ, *et al.* (2020) Evaluating the safety and efficacy of intraoperative enteral nutrition in critically ill burn patients: a systematic review and meta-analysis. *J Burn Care Res* **41**, 841–848.
16. Pu H, Doig GS, Heighes PT, *et al.* (2018) Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: a meta-analysis of randomized controlled trials. *Crit Care Med* **46**, 2036–2042.
17. Ortiz-Reyes L, Lee Z-Y, Lew CCH, *et al.* (2023) The efficacy of glutamine supplementation in severe adult burn patients: a systematic review with trial sequential meta-analysis. *Crit Care Med* **51**, 1086–1095.
18. van Zanten AR, Dhaliwal R, Garrel D, *et al.* (2015) Enteral glutamine supplementation in critically ill patients: a systematic review and meta-analysis. *Crit Care* **19**, 1–16.
19. Yue H-Y, Wang Y, Zeng J, *et al.* (2023) Enteral glutamine supplements for patients with severe burns: a systematic review and meta-analysis. *Chin J Traumatol* (Epublication ahead of print version 28 June 2023).
20. Lin J-J, Chung X-J, Yang C-Y, *et al.* (2013) A meta-analysis of trials using the intention to treat principle for glutamine supplementation in critically ill patients with burn. *Burns* **39**, 565–570.
21. Mortada H, Alhindi N, Abukhudair A, *et al.* (2023) The effects of glutamine supplementation on reducing mortality and morbidity among burn patients: a systematic review and meta-analysis of randomized controlled trials. *JPRAS Open* **35**, 6–17.
22. Higgins JP & Altman DG (2008) Assessing risk of bias in included studies. In *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*, pp. 187–241 [JP Higgins and S Green, editors]. Chichester: Wiley-Blackwell.
23. Page MJ, Moher D, Bossuyt PM, *et al.* (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* **372**, n160.

24. Gates M, Gates A, Pieper D, *et al.* (2022) Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. *BMJ* **378**, e070849.
25. Shea BJ, Reeves BC, Wells G, *et al.* (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **358**, j4008.
26. Higgins JP, Altman DG, Gøtzsche PC, *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.
27. DerSimonian R & Laird N (1986) Meta-analysis in clinical trials. *Controlled Clin Trials* **7**, 177–188.
28. Cumpston M, Li T, Page MJ, *et al.* (2019) Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Reviews* 2019, issue 10, ED000142.
29. Egger M, Smith GD, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
30. Langendam MW, Akl EA, Dahm P, *et al.* (2013) Assessing and presenting summaries of evidence in Cochrane Reviews. *Syst Rev* **2**, 1–9.
31. Luo G, Tan J, Peng Y, *et al.* (2014) Guideline for diagnosis, prophylaxis and treatment of invasive fungal infection post burn injury in China 2013. *Burns & Trauma* **2**, 2321–3868.130182.
32. Van Wijck K, Lenaerts K, Van Loon IJ, *et al.* (2011) Exercise-induced splanchnic hypoperfusion results in gut dysfunction in healthy men. *PLoS One* **6**, e22366.
33. McClave SA & Heyland DK (2009) The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract* **24**, 305–315.
34. Kumar AS & Sudhakar GV (2014) Upper gastrointestinal lesions and bleed in burn injuries: an endoscopic evaluation. *Indian J Burns* **22**, 72–78.
35. Fayazov A & Akhmedov A (2021) Treatment of acute gastroduodenal bleeding in patients with severe burn injuries. *Supported By* **2021**, 132.
36. Corcione S, Lupia T, De Rosa FG, *et al.* (2020) Microbiome in the setting of burn patients: implications for infections and clinical outcomes. *Burns & Trauma* **8**, tkaa033.
37. Earley ZM, Akhtar S, Green SJ, *et al.* (2015) Burn injury alters the intestinal microbiome and increases gut permeability and bacterial translocation. *PLoS One* **10**, e0129996.
38. Mosier MJ, Pham TN, Klein MB, *et al.* (2011) Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. *J Burn Care Res* **32**, 104–109.
39. Raff T, Germann G & Hartmann B (1997) The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns* **23**, 313–318.
40. Lam NN, Tien NG & Khoa CM (2008) Early enteral feeding for burned patients—an effective method which should be encouraged in developing countries. *Burns* **34**, 192–196.
41. Inoue S, Lukes S, Alexander J, *et al.* (1989) Increased gut blood flow with early enteral feeding in burned guinea pigs. *J Burn Care Rehabilitation* **10**, 300–308.
42. Kurmis R, Nicholls C, Singer Y, *et al.* (2022) An investigation of early enteral nutrition provision in major burn patients in Australia and New Zealand. *Nutr Diet* **79**, 582–589.
43. Shahi N, Skillman HE, Phillips R, *et al.* (2021) Why delay? Early enteral nutrition in pediatric burn patients improves outcomes. *J Burn Care Res* **42**, 171–176.
44. Lu G, Huang J, Yu J, *et al.* (2011) Influence of early post-burn enteral nutrition on clinical outcomes of patients with extensive burns. *J Clin Biochem Nutr* **48**, 222–225.
45. Morvaridzadeh M, Nachvak SM, Agah S, *et al.* (2020) Effect of soy products and isoflavones on oxidative stress parameters: a systematic review and meta-analysis of randomized controlled trials. *Food Res Int* **137**, 109578.
46. Parsi A, Torkashvand M, Hajiani E, *et al.* (2020) The effects of crocus sativus extract on serum lipid profile and liver enzymes in patients with non-alcoholic fatty liver disease: a randomized placebo-controlled study. *Obes Med* **17**, 100165.
47. Wu Y, Liu J, Jin J, *et al.* (2018) Effects of early enteral nutrition in the treatment of patients with severe burns. *Zhonghua Shao Shang za zhi = Zhonghua Shaoshang Zazhi = Chin J Burns* **34**, 40–46.
48. Heyland DK, Wischmeyer P, Jeschke MG, *et al.* (2017) A RandomizEd trial of ENtERal Glutamine to minimIZe thermal injury (The RE-ENERGIZE Trial): a clinical trial protocol. *Scars, Burns Healing* **3**, 2059513117745241.
49. Rahimlu M, Shab-Bidar S & Djafarian K (2017) Body mass index and all-cause mortality in chronic kidney disease: a dose-response meta-analysis of observational studies. *J Renal Nutr* **27**, 225–232.
50. Zhang Y, Yan H, Lv S-G, *et al.* (2013) Effects of glycyl-glutamine dipeptide supplementation on myocardial damage and cardiac function in rats after severe burn injury. *Int J Clin Exp Patb* **6**, 821.
51. Sun Y, Wang L, Zhou Y, *et al.* (2013) Effects of glutamine combined with ulinastatin on inflammatory response of patients with severe burn injury. *Zhonghua Shao Shang za zhi = Zhonghua Shaoshang Zazhi = Chin J Burns* **29**, 349–354.
52. Wang ZE, Zheng JJ, Feng JB, *et al.* (2022) Glutamine relieves the hypermetabolic response and reduces organ damage in severe burn patients: a multicenter, randomized controlled clinical trial. *Burns* **48**, 1606–1617.
53. Hashemi R, Rahimlou M, Baghdadian S, *et al.* (2019) Investigating the effect of DASH diet on blood pressure of patients with type 2 diabetes and prehypertension: randomized clinical trial. *Diabetes Metab Syndrome: Clin Res Rev* **13**, 1–4.
54. Koekkoek WK, Panteleon V & van Zanten AR (2019) Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: a systematic review and meta-analysis. *Nutrition* **59**, 56–68.
55. Ortiz LA, Jiang X, Turgeon AF, *et al.* (2021) Validation of the modified NUTrition Risk Score (mNUTRIC) in mechanically ventilated, severe burn patients: a prospective multinational cohort study. *Burns* **47**, 1739–1747.
56. Ostadrahimi A, Nagili B, Asghari-Jafarabadi M, *et al.* (2016) A proper enteral nutrition support improves sequential organ failure score and decreases length of stay in hospital in burned patients. *Iranian Red Crescent Med J* **18**, e21775.