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SYSTEMATIC REVIEW AND META-ANALYSIS

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Glutamine Supplementation in Intensive Care Patients

A Meta-Analysis of Randomized Clinical Trials

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Abstract: The role of glutamine (GLN) supplementation in critically ill patients is controversial. Our aim was to analyze its potential effect in patients admitted to intensive care unit (ICU).

We performed a systematic literature review through Medline, Embase, Pubmed, Scopus, Ovid, ISI Web of Science, and the Cochrane-Controlled Trials Register searching for randomized clinical trials (RCTs) published from 1983 to 2014 and comparing GLN supplementation to no supplementation in patients admitted to ICU. A random-effect meta-analysis for each outcome (hospital and ICU mortality and rate of infections) of interest was carried out. The effect size was estimated by the risk ratio (RR).

Thirty RCTs were analyzed with a total of 3696 patients, 1825 (49.4%) receiving GLN and 1859 (50.6%) no GLN (control groups). Hospital mortality rate was 27.6% in the GLN patients and 28.6% in controls with an RR of 0.93 (95% CI = 0.81–1.07; $P = 0.325$, $I^2 = 10.7\%$). ICU mortality was 18.0 % in the patients receiving GLN and 17.6% in controls with an RR of 1.01 (95% CI = 0.86–1.19; $P = 0.932$, $I^2 = 0\%$). The incidence of infections was 39.7% in GLN group versus 41.7% in controls. The effect of GLN was not significant (RR = 0.88; 95% CI = 0.76–1.03; $P = 0.108$, $I^2 = 56.1\%$).

These results do not allow to recommend GLN supplementation in a generic population of critically ills. Further RCTs are needed to explore the effect of GLN in more specific cohort of patients.

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Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, GLN = glutamine, ICU = intensive care unit, ICUS = intensive care unit stay, IHS = in-hospital stay, ITT = intention to treat, IV = intravenous, MD = mean difference, RCT = randomized clinical trial, RR = risk ratio.

INTRODUCTION

There is clear and sufficient evidence from preclinical and phase 2 clinical studies to suggest that glutamine (GLN) plays a central role of in several key metabolic pathways involved in the proper function of many organs.[1] Moreover, GLN has been recognized as an essential substrate and the principal metabolic fuel for rapidly dividing cells, such as enterocytes, lymphocytes, and macrophages. For these reasons, although GLN is classified as a nonessential amino acid, it is commonly described as a conditionally essential amino acid in hypemetabolic states.[2]

During critical illness and the subsequent catabolism and inflammation, GLN plasma levels decrease and this relative deficiency has been associated with increased mortality in intensive care units (ICU).[3,4] Therefore, the rational to supplement ICU patients with GLN has been emphasized repetitively.[5] Indeed, GLN administration in critically ill patients has been associated with reduced mortality in several reports.[6–8] However, large recent randomized clinical trials (RCT)[9] were not able to confirm such an effect or even reported a trend to an harmful outcome.[10]

Since previous meta-analyses[11–13] did not include the latest RCTs,[10–14] the results of GLN supplementation in critically ill patients need to be updated by a more comprehensive meta-analysis to accept or reject the potential benefits of GLN.

METHODS

This research was conducted by following the guidelines and the PRISMA statement for reporting systematic reviews and meta-analyses of studies evaluating healthcare interventions. Ethical approval was not necessary according to local legislation because of the type of study (meta-analysis).

Literature Search

Two authors (MO, SC) independently performed a Medline, Embase, Pubmed, Scopus, Ovid, ISI Web of Science, and Cochrane Central Register of Controlled Trials and Cochrane Library database extended literature search of all studies published as original full-text article published between January 1983 and April 2014. The following medical subject heading terms and words was used for search, in all possible combination: "glutamine," "dipeptide," "L-glutamine," "nutritional support," "artificial nutrition," "enteral nutrition," "parenteral nutrition," "immunonutrition," "pharmaconutrition" AND "critically ill" or "critical care," "intensive care," "critical

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MO, MS, SC, and LN had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: LG, MO, MS. Acquisition of data: MO, SC, MS, LN. Analysis and interpretation of data: LG, MO, MS, LN, SC, DPB. Drafting of the manuscript: LG, MO. Critical revision of the manuscript for important intellectual content and final approval: MO, MS, LN, DPB, SC. Statistical analysis: DPB. Study supervision: LG.
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illness,'' ''intensive care unit,'' ''seriously ill,'' ''critical patients,'' ''surgical intensive care unit'' ''SICU'' ''ICU.''

The ''related article'' function was used to expand the search and the reference lists of articles selected for full-text review were searched for additional articles. In the event of overlap of authors, institutions, or patients, the most recent or highest quality article was chosen.

Study Selection

The term ''glutamine supplementation'' was defined as any treatment containing GLN or GLN dipeptide in combination or not with any form of artificial nutrition as reported in the articles reviewed.

We included trials with the following eligibility criteria:

Studies enrolling patients with age >18 years.
Patients admitted to ICUs.
Randomized trials with parallel group.
GLN supplementation.
Trials reporting at least 1 of the outcomes considered in the meta-analysis.
English language.

We considered all studies irrespectively if GLN was given with parenteral or enteral nutrition, or no artificial nutritional support. We also included studies with control groups who did not received isonitrogenous/isocaloric regimens.

We excluded trials with the following criteria:

GLN combined with other nutrients with potential immunometabolic activity (ie, arginine, nucleotides, and omega-3 fatty acids).
No full-text available articles, opinion pieces, and editorials.
Burn patients, because of their particular clinical features and because of a recent review focusing this specific group of patients.[15]

Data Extraction

An electronic database was created to collect all relevant trial data. The data were extracted independently by 2 investigators (MO and MS) and in case of disagreement 2 superpartes referents (LG and LN) cross-examined doubtful data and the decision was made after consensus meeting. Agreement between authors was calculated in order to investigate the risk of bias (Cohen $\kappa = 0.88$).

Information extracted from the trials involved: first author, country of origin, year of publication, number of patients randomized, type of nutritional support, GLN dosage, route of administration, and period of supplementation, regimen of the control groups, Acute Physiology and Chronic Health Evaluation (APACHE) score, Sequential Organ Failure Assessment (SOFA) score and number of patients in shock at study entry, intention-to-treat (ITT) reporting, double, single or no blindness, and the different outcome measures.

The primary purpose of this meta-analysis was to evaluate if GLN supplementation could affect mortality. As primary relevant outcomes we assessed the rate of in-hospital and ICU mortality. As secondary endpoint of the analysis we considered the rate of infectious morbidity, the length of in-hospital stay (IHS) and ICU stay (ICUS). All studies reporting on infection defined it as positive specimen culture.

Study quality was assessed by 2 independent reviewers (SC and LN) according to the Jadad score.[16]

Statistical Analysis

We performed a random-effects meta-analysis[17] for each outcome of interest. For categorical outcomes (mortality, infectious morbidity) the effects size was estimated by the risk ratio (RR), while for continuous outcome (length of stay) the mean difference (MD) was used. In the calculation of the pooled RR, a correction factor of 0.5 was added to all cell frequencies of studies where no patient had the outcome in either GLN or control groups. We made sure of the absence of any possible bias due to sparse data by applying also the fixed method of Peto (results not shown) which confirmed the results of the present analysis.[18] Mean and standard deviation of length of stay was calculated according to method of Hozo et al[19] for the studies where only median and range (or interquartile range) were reported. The weights assigned to each study were computed according to the inverse of the variance. Heterogeneity was quantified using I^2 and τ^2 indexes and testing the null hypothesis that all studies share a common effect size. We used $I^2 = 30\%$ as a threshold to establish the presence of moderate heterogeneity. Moreover, we investigated the presence of publication bias using funnel plots.[20]

Finally, some stratified analyses were performed according to the following indicators: GLN dosage (>0.3 g/kg/day or ≤0.3 g/kg/day), duration of GLN supplement (>5 days or ≤5 days), route of GLN administration (enteral or parenteral), ITT reporting (yes or not), blinding (single or double), Jadad score (≥3 or <3), and APACHE II score (>15 or ≤15). For all the analyses, we tested the presence of a different effect between subgroups.

P-values <0.05 were considered significant. All the analyses were performed using ''meta'' package within R, version 3.0.2.

RESULTS

Figure 1 depicts the flow diagram of the literature search and article selection. After duplicates removal, we identified 498 potentially relevant references through the electronic

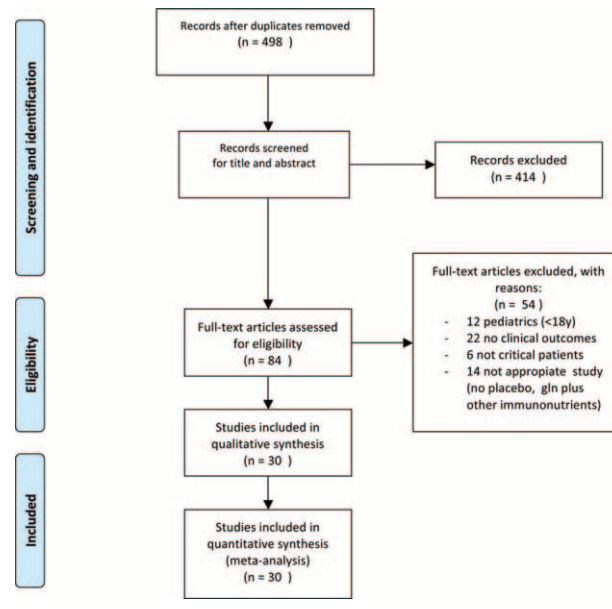


FIGURE 1. Flow diagram of the literature search according to the PRISMA statement.

TABLE 1. Characteristics of the Included Trials

Ref	Author	Year	Country	Population	n GLN	n CTRL	Route	Dosage I.V., g/kg/day	Dosage EN, g/day	Mono/ Mutlicentric	Blindness	Jadad Score	ITT Mortality	ITT Infections	ITT LOS	APACHE GLN	APACHE CTRL
[21]	Powell-Tuck	1999	UK	168	83	85	TPN	20 g/day		Mono	Double	4	Yes	Yes	Yes		
[22]	Jones	1999	UK	50	26	24	EN		20	Mono	Double	3	Yes	Yes	Yes	17.5	16.5
[6]	Goeters	2002	Germany	68	33	35	IV	0.30		Mono	Single	3	No	No	No	14.7	13.9
[23]	Conejero	2002	Spain	84	47	37	EN		30.5	Multi	Single	5	No	No	No	20.0	18.0
[24]	Ockenga	2002	Germany	28	14	14	TPN	0.2		Mono	Double	4	No	No	No	5.7	5.1
[7,8]	Griffiths	1997/2002	UK	84	42	42	TPN	0.25		Mono	Double	5	Yes	Yes	yes	18.0	17.0
[25]	Hall	2003	Australia	363	179	184	EN		19	Mono	Double	3	Yes	Yes	Yes	16.0	16.0
[26]	He	2004	China	41	20	21	IV	0.40		Mono	Single	3	No	No	No		
[27]	Fuentes-Orozco	2004	Mexico	33	17	16	TPN	0.40		Mono	Double	2	Yes	Yes	Yes		
[28]	Ziegler	2005	USA	29	15	14	TPN	0.50		Mono	Double	5	Yes	Yes	Yes	13.0	13.0
[29]	Déchelotte	2006	France	114	58	56	TPN	0.50		Multi	Double	5	Yes	Yes	Yes		
[30]	Spindler-Vesel	2007	Slovenia	87	32	55	EN		10.5	Mono	Double	4	Yes	Yes	Yes	11.0	13.5
[31]	Sahin	2007	Turkey	40	20	20	TPN	0.30		Mono	Single	2	Yes	Yes	Yes		
[33]	Kumar	2007	India	120	63	57	EN		45	Mono	Double	3	Yes	Yes	Yes		
[34]	Estivariz	2008	USA	59	30	29	TPN			Mono	Double	5	No	No	No	13.4	13.1
[35]	Duska	2008	Czech Rep.	20	10	10	TPN	0.30		Mono	Double	4	Yes	Yes	Yes	24.5	24.5
[36]	Fuentes-Orozco	2008	Mexico	44	22	22	TPN	0.40		Mono	Double	4	No	No	No	10.3	10.7
[37]	Perez-Barcena	2008	Spain	30	15	15	TPN	0.35			Single	4	No	No	No	16.6	16.8
[38]	Cai	2008	China	110	55	55	IV	0.29		Mono	Single	3	Yes	Yes	Yes		
[39]	Ozgultekin	2008	Turkey	40	20	20	EN		20	Mono	Single	2	Yes	Yes	Yes	19.0	18.9
[40]	Luo	2008	USA	44	11	9	IV	0.50		Mono	Double	4			Yes		
[40]	Luo	2008	USA	21	12	9	EN		0.5 g/kg/day	Mono	Double	4			Yes		
[41]	Eroglu	2009	Turkey	40	20	20	IV	0.5		Mono	Double	4	Yes	Yes	Yes	26.0	25.0
[42]	Pérez-Bércena	2010	Spain	43	23	20	TPN	0.35		Mono	Single	3	Yes	Yes	Yes	19.2	15.1
[43]	Grau	2011	Spain	127	59	68	TPN	0.50		Mono	Double	4	Yes	Yes	Yes	19.0	18.0
[44]	Wernerman	2011	Scandinavia	413	205	208	IV	0.28		Multi	Double	5	No	No	No	21.0	22.0
[45]	Schneider	2011	Germany	58	29	29	EN		30	Mono	Single	4	No	No	No	22.0	21.1
[9]	Andrews	2011	Scotland	502	250	252	TPN	0.3		Multi	Double	5	Yes	Yes	Yes	21.0	20.0
[46]	Cekmen	2011	Turkey	30	15	15	TPN	0.5		Mono	Double	5	No	No	No	30.6	26.4
[10]	Heyland	2013	Canada,USA, Europe	605	303	302	TPN/EN	0.5	30	Multi	Double	5	Yes	Yes	Yes	26.6	26.0
[47]	Zhao	2013	China	80	40	40	IV			Mono	Double	4	Yes	Yes	Yes	11.3	10.9
[14]	Perez-Barcena	2014	Spain	142	71	71	IV	0.5		Multi	Double	5	Yes	Yes	Yes		

CTRL = control, EN = enteral, GLN = glutamine, ITT = intention to treat, I.V. = intravenous, LOS = length of stay, TPN = total parenteral nutrition.

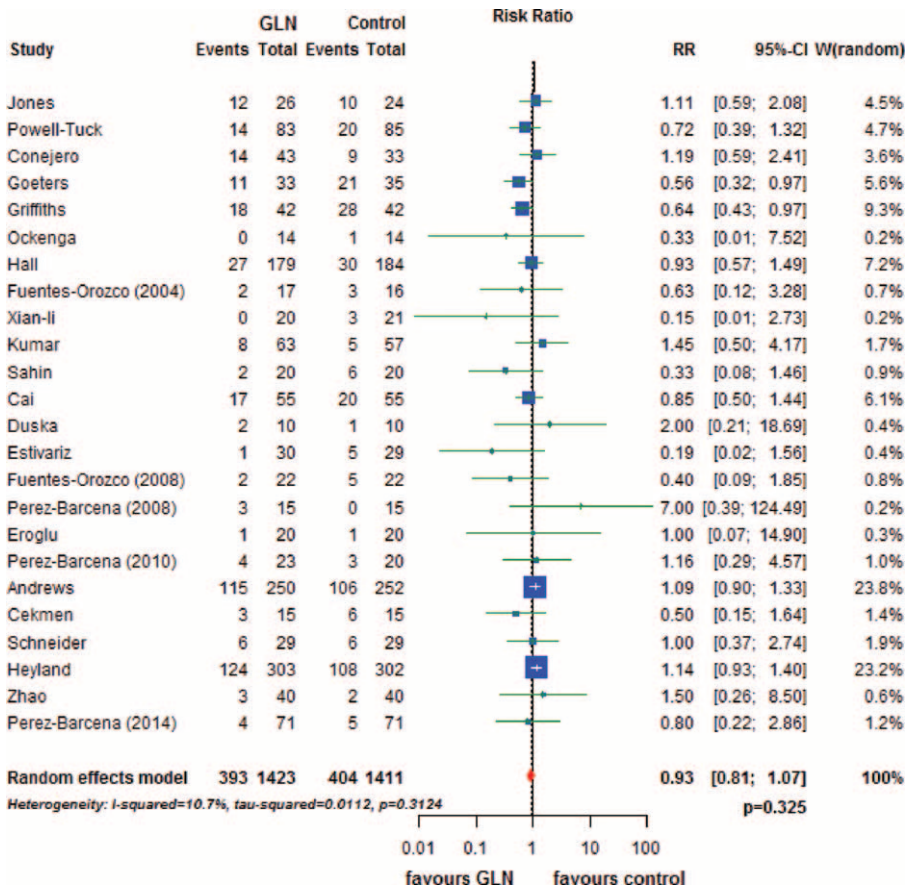


FIGURE 2. Forest plot of the effect of GLN supplementation on in-hospital mortality. Size of squares for RR reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % CI. CI = confidence intervals, GLN = glutamine, RR = relative risk.

searches. A total of 414 studies were excluded screened after title and abstract evaluation, 54 articles were excluded for the following reasons: not critically ill patients (6 studies), pediatric population (12 studies), study design was not appropriate, and GLN administration in addition to other immunonutrients (14 studies). We also excluded 22 trials because they did not provide information on clinical outcomes.

Study Characteristics

Thirty RCTs were finally included in the meta-analysis with a total of 3696 patients, 1825 (49.4%) receiving GLN, and 1859 (50.6%) no GLN (control groups). The mean number of patients/study was 119.7 and 66.6% of the studies had less than 100 patients. Most RCTs were single center (24/30), 20 were double-blind and 10 were single blind, 20 trials (66.6%) reported ITT data, 4 studies (13%) were conducted in patients with acute pancreatitis, 7 studies (23.3%) in victims of trauma, 9 studies (30%) in mixed population, and 33.7% in unspecified critically ill ICU patients. Twenty-one trial used were intravenously GLN, 1 trial used both IV and enteral administration and in 8 trial GLN was supplemented enterally.

The median I.V. GLN dosage was 0.38 g/kg/day, the median enteral dosage was 25 g/day.

Table 1 reports the detailed information on all trials included in the meta-analysis.

Primary Endpoints

Twenty-four trials including 2834 patients (n = 1423 treated and 1411 controls) provided data on hospital mortality. The rate was 27.6% in the patients receiving GLN and 28.6% in controls. The RR was 0.93 (95% CI = 0.81–1.07; $P = 0.325$). Heterogeneity among studies was low ($I^2 = 10.7\%$, $P = 0.312$) (Figure 2). No evidence of publication bias was detectable (Figure 3A).

ICU mortality was reported in 14 studies including a total of 2230 subjects (n = 1112 treated and 1118 control). The rate was 18.0% in the patients receiving GLN and 17.6% in controls. The RR was 1.01 (95% CI = 0.86–1.19; $P = 0.932$). Heterogeneity among studies was absent ($I^2 = 0\%$, $P = 0.989$) (Figure 4). We detected no publication bias after the funnel plot analysis (Figure 3B).

Secondary Endpoints

Fifteen RCTs (2795 patients; 1402 treated and 1393 control) described the rate of infections. The incidence was 39.7% in patients receiving GLN versus 41.7% in controls. The effect of GLN was not significant (RR = 0.88; 95% CI = 0.76–1.03; $P = 0.1082$). The tau-squared test for heterogeneity among studies was 56.1% with a significant P value (0.004) (Figure 5). Funnel plot suggested no evidence of publication bias (Figure 3C).

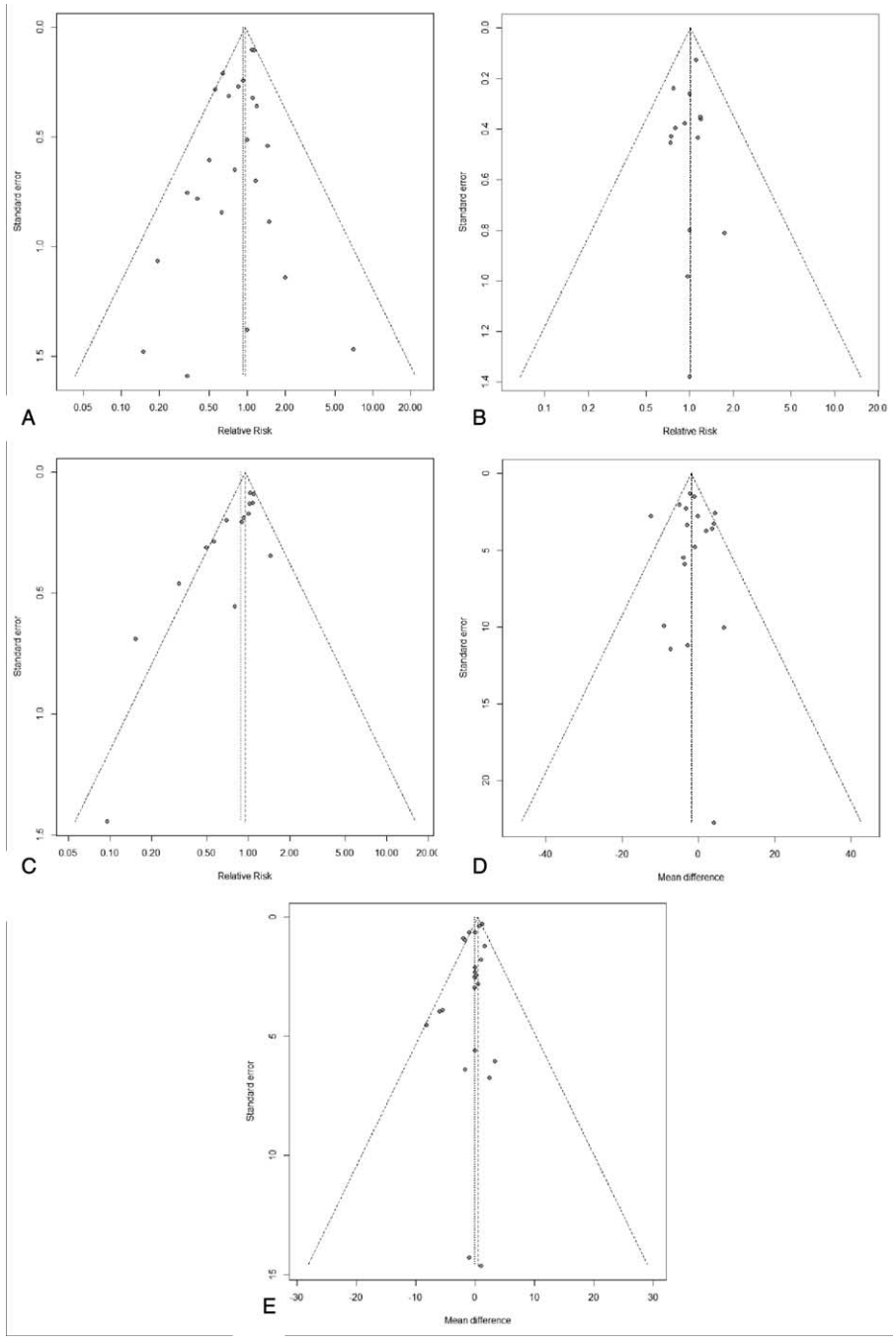


FIGURE 3. Funnel plots for (A) overall mortality, (B) intensive care unit (ICU) mortality, (C) infectious morbidity, (D) length of stay, and (E) ICU length of stay.

The 19 studies reporting on IHS (1314 treated patients and 1321 controls) showed a nonsignificant reduction in the patients receiving GLN (MD = −1.73, 95% CI = −3.76–0.29; $P = 0.094$) with a significant heterogeneity among trials ($I^2 = 44\%$, $P = 0.021$) (Figure 6A). Funnel plot suggested no evidence of publication bias (Figure 3D).

ICUS was described in 24 trials. The overall population analyzed was of 2816 patients (n = 1395 treated and 1421 controls). The mean ICUS was 15.9 days in the GLN supplemented group versus 16.6 days in the control group. The weight MD was a nonsignificant reduction in favor of the treated group (MD = −0.09; 95% CI = −0.76–+0.59) (Figure 6B). No heterogeneity was found (Figure 3E).

Subgroups Analyses

We performed different subgroup analyses to evaluate possible influences of GLN daily dosage (greater than 0.3 g/kg/day versus less or equal than 0.3 g/kg/day), period of supplementation (more than 5 days versus less or equal than 5 days), severity of illness (APACHE II > 15 versus less or equal of 15),

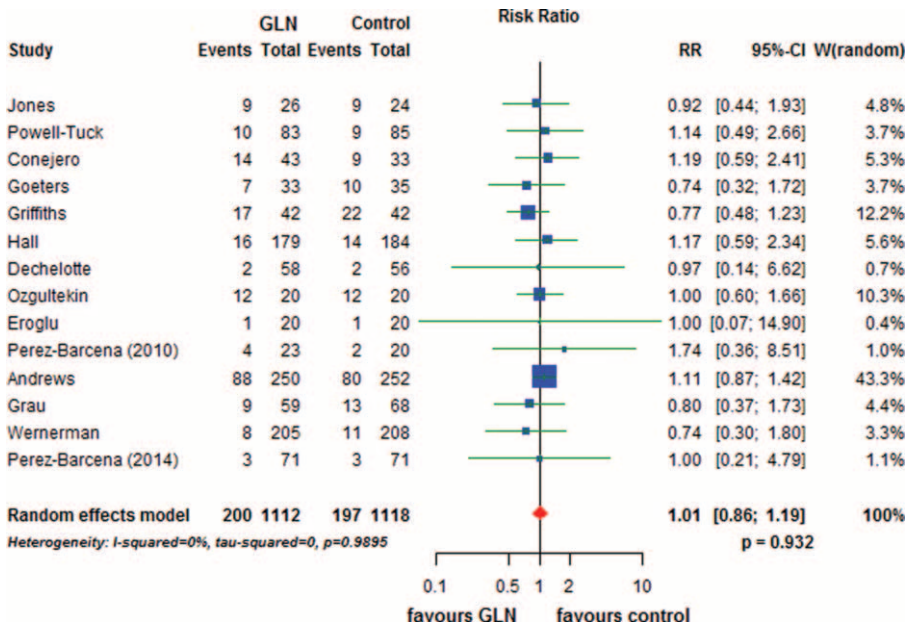


FIGURE 4. Forest plot of the effect of GLN supplementation on ICU mortality. Size of squares for RR reflects the weight of the trial in the pooled analyses. Horizontal bars 95% CI. CI = confidence intervals, GLN = glutamine, ICU = intensive care unit, RR = relative risk.

ITT data reporting, blindness, and quality of trials (Jadad score > 3 points versus ≤3 points). The results are summarized in Table 2.

The daily dose of GLN did not affect any of the endpoints while a duration of supplementation longer than 5 days was associated with a significant reduction of infectious morbidity. A protective effect of GLN on hospital mortality and occurrence of infections was more evident when given parenterally and in less critically ill patients (APACHE II score lower or equal then 15) even though the number of studies and subjects analyzed in this last cohort was extremely limited. In the lower quality studies (Jadad ≤ 3) and lack of blindness we identified a reduction of IHS and ICUS in the treated group.

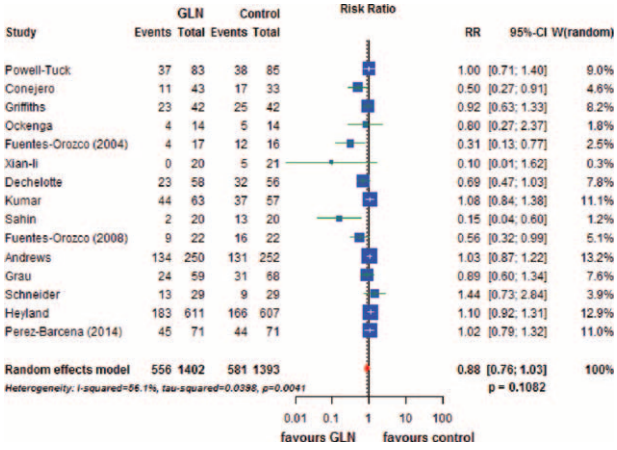


FIGURE 5. Forest plot of the effect of GLN supplementation on infectious morbidity. Size of squares for RR reflects the weight of the trial in the pooled analyses. Horizontal bars 95 % CI. CI = confidence intervals, GLN = glutamine, RR = relative risk.

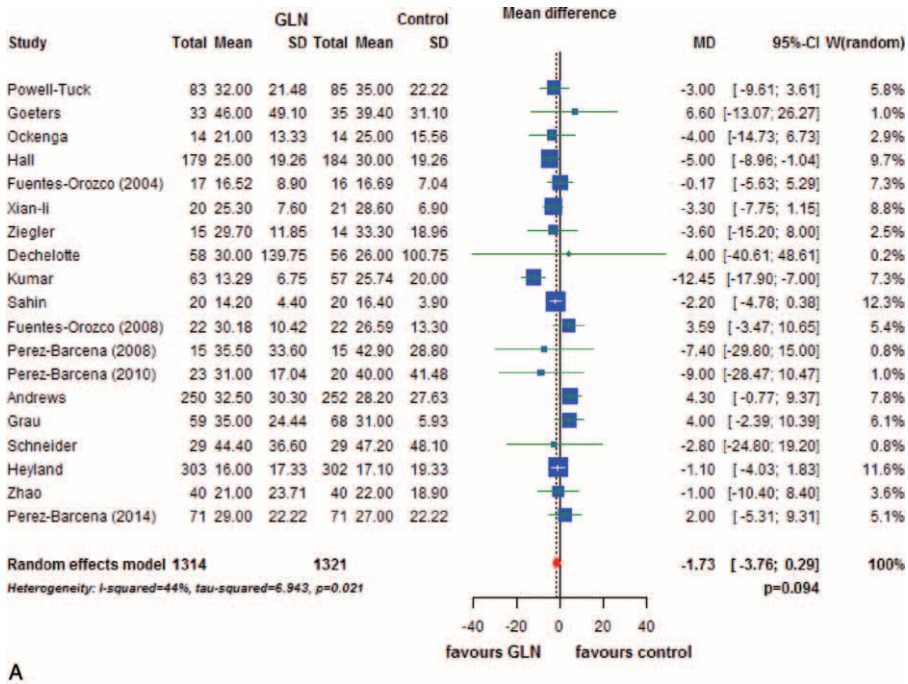
DISCUSSION

The results of the present meta-analysis suggest that GLN supplementation given to a mixed population of critically ill patients does not significantly affect primary outcome measures such as hospital and ICU mortality. The reasons for this lack of benefit are unidentified. The rational reason for giving supernormal doses of GLN in severely ills was the correlation between mortality rate and low levels of this amino acid in the plasma and tissues.[3,4] Nevertheless, it is still unclear if the decline of circulating GLN contributes to death or is a simple marker of disease severity. Moreover, recent findings did not confirm GLN deficiency in ICU patients with shock and multiple organ dysfunction.[10]

Our stratified analysis implies that hospital mortality, but not ICU mortality is decreased only in patients receiving IV GLN and in patients entering in the trials with APACHE II equal or less than 15, keeping in mind that the mortality rate of patients with such score is usually negligible.

This observation is difficult explain. It may be speculated that GLN does not have a protective role on mortality in the most severe patients because in these subjects death is mainly determined by MODS and GLN supplementation is not sufficient to affect the recovery of organ dysfunction. When disease severity is less than GLN supplementation may be effective in modulated function and protect organs.

Overall, we could not even demonstrate a protective effect of GLN on the occurrence infections. This observation is in line with what we recently showed in patients undergoing major abdominal surgery.[48,49] These data suggest that GLN supplementation may be not so effective in preventing the injury-induced immune deficiency as previously reported by others.[50,51] Yet, in subgroup analyses, infectious morbidity was significantly reduced in patients receiving parenteral GLN, for more than 5 days and with less severe disease, although these findings need to be confirmed by a future large RCT designed with these specific inclusion criteria and type of treatment.



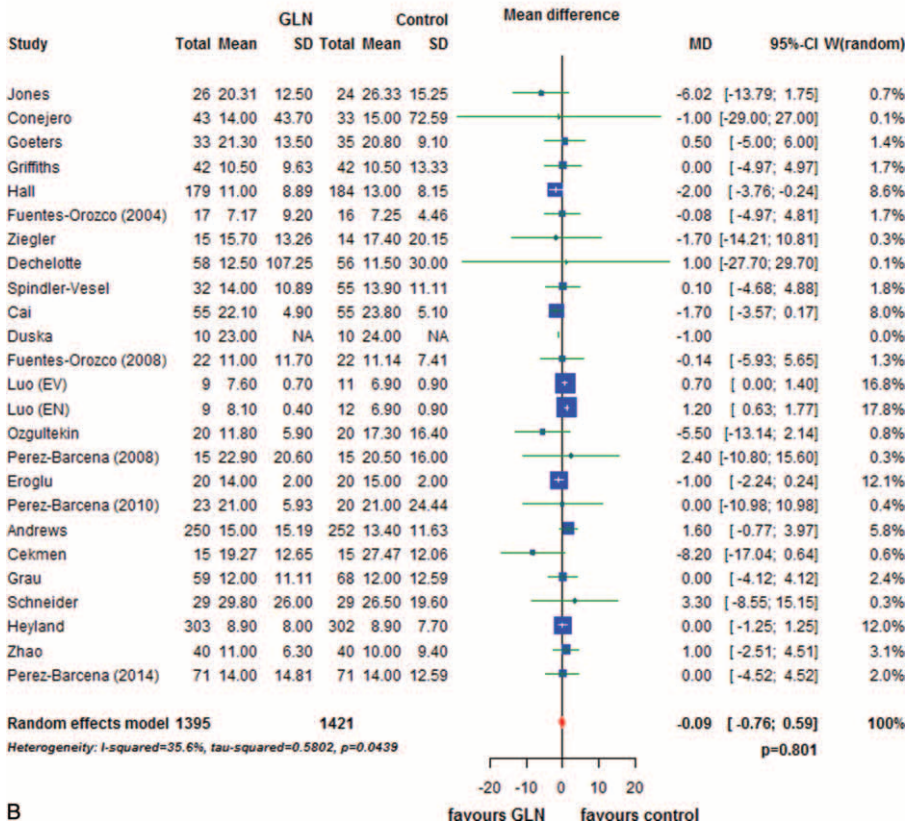


FIGURE 6. Forest plots of the effect of GLN on (A) hospital length of stay and (B) ICU length of stay comparing GLN and control. Size of squares for MD reflects the weight of the trial in the pooled analyses. Horizontal bars 95% CI. CI = confidence intervals, GLN = glutamine, ICU = intensive care unit, MD = mean difference, RR = relative risk

TABLE 2. Subgroup Analyses

Outcome	Category	Study Characteristics	No of Studies	No of Patients		Overall Effect (95% CI)	*P*-Value Subgroup Differences	I^2, %	*P*-Value Heterog
				GLN	Control				
Overall mortality	Dosage of GLN	>0.3 g/kg/day	14	754	735	1.05 (0.88;1.24)	0.164	0	0.500
		≤0.3 g/kg/day	10	669	676	0.86 (0.69;1.07)		27.8	0.188
	Duration of GLN supplement	>5 days	18	1139	1135	0.86 (0.71;1.05)	0.344	30.6	0.107
		≤5 days	3	160	152	1.12 (0.68;1.84)		0	0.781
	Intention to treat	Yes	15	1202	1198	1.02 (0.90;1.14)	0.082	0	0.588
		No	9	221	213	0.69 (0.45;1.05)		14.9	0.309
	Route	TPN or IV	18	780	782	0.78 (0.62;0.97)	0.110	18.0	0.239
		EN	5	340	327	1.06 (0.78;1.43)		0	0.940
	Apache	>15	12	955	946	1.05 (0.93;1.18)	0.009	0	0.501
		≤15	5	139	140	0.54 (0.34;0.88)		0	0.639
	Blinding	Yes	16	1185	1183	1.00 (0.88;1.14)	0.238	2.1	0.429
		No	8	238	228	0.80 (0.56;1.14)		15.2	0.311
	Jadad score	>3	15	987	979	0.97 (0.82;1.15)	0.291	13.8	0.299
		≤3	9	436	432	0.83 (0.64;1.06)		0	0.510
ICU mortality	Dosage of GLN	>0.3 g/kg/day	7	357	353	1.06 (0.71;1.58)	0.780	0	0.984
		≤0.3 g/kg/day	7	755	765	1.00 (0.83;1.19)		0	0.805
	Duration of GLN supplement	>5 days	11	995	1003	1.01 (0.85;1.21)	0.824	0	0.943
		≤5 days	2	97	95	0.94 (0.48;1.83)		0	0.927
	Intention to treat	Yes	11	831	842	1.02 (0.86;1.22)	0.642	0	0.983
		No	3	281	276	0.91 (0.57;1.44)		0	0.601
	Route	TPN or IV	10	844	857	0.99 (0.82;1.20)	0.726	0	0.933
		EN	4	268	261	1.06 (0.77;1.45)		0	0.941
	Apache	>15	10	867	871	1.02 (0.86;1.20)	0.475	0	0.938
		≤15	1	33	35	0.74 (0.32;1.72)		–	–
	Blinding	Yes	10	993	1010	1.00 (0.84;1.20)	0.937	0	0.966
		No	4	119	108	1.02 (0.71;1.46)		0	0.757
	Jadad score	>3	9	831	835	1.01 (0.84;1.22)	0.956	0	0.938
		≤3	5	281	283	1.00 (0.72;1.38)		0	0.876
Infectious morbidity	Dosage of GLN	>0.3 g/kg/day	11	1076	1065	0.87 (0.72;1.05)	0.822	58.1	0.008
		≤0.3 g/kg/day	4	326	328	0.83 (0.55;1.26)		63.1	0.045
	Duration of GLN supplement	>5 days	12	1239	1236	0.79 (0.65;0.97)	0.041	62.4	0.002
		≤5 days	2	134	128	1.05 (0.88;1.25)		0	0.780
	Intention to treat	Yes	10	1274	1274	0.94 (0.81;1.09)	0.264	53.0	0.024
		No	5	128	119	0.69 (0.41;1.17)		51.3	0.084
	Route	TPN or IV	11	656	667	0.81 (0.66;1.00)	0.650	56.8	0.010
		EN	3	135	119	0.93 (0.55;1.58)		70.2	0.035
	Apache	>15	6	1034	1031	0.99 (0.85;1.16)	0.066	35.6	0.170
		≤15	2	36	36	0.61 (0.37;1.00)		0	0.569
	Blinding	Yes	11	1290	1290	0.95 (0.84;1.07)	0.175	36.7	0.106
		No	4	112	103	0.45 (0.16;1.31)		76.9	0.005
	Jadad score	>3	11	1282	1279	0.94 (0.83;1.07)	0.132	34.4	0.123
		≤3	4	120	114	0.34 (0.09;1.27)		86.0	<0.001
Length of stay	Dosage of GLN	>0.3 g/kg/day	13	778	776	−1.95 (−4.80;0.89)	0.795	48.1	0.027
		≤0.3 g/kg/day	6	536	545	−1.38 (−4.58;1.81)		44.7	0.108
	Duration of GLN supplement	>5 days	15	1111	1124	−1.27 (−2.85;0.31)	0.566	13.2	0.306
		≤5 days	2	134	128	−5.44 (−19.6;8.72)		89.6	0.002
	Intention to treat	Yes	13	1181	1185	−1.86 (−4.34;0.63)	0.885	57.7	0.005
		No	6	133	136	−1.55 (−4.96;1.87)		0	0.584
	Route	TPN or IV	15	740	749	−0.74 (−2.33;0.86)	0.026	0	0.520
		EN	3	271	270	−8.02 (−14.2;−1.81)		58.9	0.088
	Apache	>15	7	858	870	−0.53 (−3.99;2.94)	0.767	47.5	0.076
		≤15	5	124	125	0.33 (−4.14;4.79)		0	0.671
	Blinding	Yes	13	1174	1181	−1.35 (−4.16;1.46)	0.529	60.2	0.003
		No	6	140	140	−2.50 (−4.68;−0.32)		0	0.900
	Jadad score	>3	12	959	968	0.31 (−1.60;2.22)	0.017	0	0.692
		≤3	7	355	353	−4.27 (−7.43;−1.02)		58.9	0.024
ICU length of stay	Dosage of GLN	>0.3 g/kg/day	15	708	704	0.48 (-0.06;1.01)	0.086	12.5	0.313
		≤0.3 g/kg/day	9	687	717	−0.78 (−2.10;0.55)		28.7	0.189
	Duration of GLN supplement	>5 days	15	1104	1104	−0.54 (−1.25;0.16)	0.581	0	0.728
		≤5 days	2	97	95	−2.15 (−7.80;3.50)		42.0	0.189
	Intention to treat	Yes	18	1238	1272	−0.09 (−0.81;−0.63)	0.756	46.4	0.016
		No	6	157	149	−0.63 (−3.97;2.71)		0	0.604
	Route	TPN or IV	16	754	762	0.16 (−0.37;0.69)	0.385	0	0.468
		EN	7	338	357	−0.92 (−3.29;1.45)		65.7	0.008
	Apache	>15	13	1034	1034	−0.68 (−1.59;0.24)	0.367	14.7	0.296
		≤15	5	142	166	0.45 (−1.82;2.72)		0	0.992

Outcome	Category	Study Characteristics	No of Studies	No of Patients GLN	No of Patients Control	Overall Effect (95% CI)	*P*-Value Subgroup Differences	I^2, %	*P*-Value Heterog
	Blinding	Yes	17	1177	1214	0.08 (−0.64;0.79)	0.095	42.4	0.034
		No	7	218	207	−1.47 (−3.14;0.20)		0	0.852
	Jadad score	>3	17	1042	1067	0.62 (0.19;1.05)	0.0001	3.9	0.409
		≤3	7	353	354	−1.81 (−2.98;−0.64)		0	0.764

The overall effect is the relative risk (overall mortality, ICU mortality, and infectious morbidity) or the mean difference (length of stay, ICU length of stay). For each category, the sum of the studies does not add up to the total number of studies considered due to missing information. Studies with 0 counts in both groups were excluded from the analysis. CI = confidence interval, EN = enteral, GLN = glutamine, ICU = intensive care unit, IV = intravenous, TPN = total parenteral nutrition.

The dissimilarity of our results with previous meta-analyses[11–13] can be explained mainly by the criteria assumed to select studies and by the recent publication of other large RCTs. The present meta-analysis included 30 RCTs that enrolled patients needing intensive care treatments for several different conditions. We excluded burn injury because of the peculiarity of the patients and care elements which are not comparable with any other types of critical illnesses. In fact, these subjects are treated in specific burn units and not in generic ICUs. Moreover, the GLN effect in this specific cohort was recently reviewed and analyzed by Lin et al.[15]

Bollhalder et al,[11] included 11 RCTs and they concluded with an advantage of GLN on infectious complications and hospital stay. Subgroup analyses suggested that GLN given at a dose greater that 0.2 g/kg/day and for at least 9 days was associated with a decreased mortality rate. The main differences with the present analysis are the exclusion of trials using enteral GLN and the inclusion of burn patients and the additional 9 studies[22,23,25,28,30,32,39,41,43] that we evaluated. Moreover, at the time of their publication, the results of 2 relevant RCTs[10,14] were not yet available.

In 2014, Chen et al[12] published a meta-analysis including the REDOX trial but the authors did not split the 4 different study groups, including therefore also antioxidant supplementation. This did not allowed an independent evaluation on the effect of GLN.[10] However, the results were much more similar to ours showing no benefit of GLN on mortality and LOS, although they reported a significant reduction of infections in the treated group. Conversely, they included burn injury,[52] a quasi randomized trial,[53] and a study where GLN was given in combination with probiotics in adults and children.[54] Once more, we found 16 additional trials to be analyzed.[14,21,24,26,28,30–33,35,38,39,41,43,44]

The systematic review by Wischmeyer et al[13] concluded that GLN was effective in reducing hospital mortality and LOS. There was also a trend toward an improved infectious morbidity rate and ICU stay. The profound divergence with our results may be attributed to the inclusion of 3 trials written in Chinese,[55–57] 2 trials on burns,[52,58] and 1 published in abstract form[59] and the exclusion of 11 studies[10,14,22–25,28,30,32,36,45] that instead we found relevant for a comprehensive review.

The most recent review by Tao et al[60] showed a moderate evidence that GLN supplementation can reduce infections and a low quality evidence that GLN supplementation reduces length of hospital stay for critically ill patients. They reported no effect on the risk of mortality and length of ICU stay in the overall results and in subgroup analyses. Again, the main difference with the present analysis is the different study selection criteria. Tao et al included quasi random studies, RCTs on burn patients,[52,61–67] trials written in Chinese,[68–71] 1 trial written in Hungarian,[72] 1 trial with multiple doses of GLN,[73] and 1 trial without clinical outcomes[74] and did not include 10 studies that we found relevant.[22,27,28,30,33–35,38,39,45]

The present meta-analysis has several limitations. We realize that our results may have been partially skewed by including the data of the REDOX study[10] for its considerable weight on the summary of the analysis. On the contrary, it seems unreasonable to exclude such trial for its strength and scientific robustness including a large and adequate number of patient, blindness, rigorous determination and adjudication of infection, and ITT analysis, all of which augment the validity of the trial. By excluding this RCT, the results of a meta-analysis may artificially appear in favor of the treatment.

To help clinicians in the difficult decision process of accepting or rejecting a treatment, it is necessary to summarize the findings of all published RCTs evaluating the controversial consequences of GLN supplementation. It is also true that the harmful effect of GLN in the REDOX study[10] was mostly driven by a subgroup of patients who died with renal failure as suggested by a post-hoc analysis of the same authors.[75]

Our findings may have also been influenced by pooling trials where GLN was provided only enteral or through both the enteral and parenteral routes. This may appear as a confounding element in the analysis because of the different metabolic pathways and utilization of GLN. In fact, when given enterally GLN should be mainly active on the gut mucosal layer being the preferential substrate for the enterocytes and intestinal immune cells. Subsequently, the intestinal barrier function, which plays a critical role in critically ills, may control permeability and protect against the occurrence of systemic infections by decreasing bacterial translocation. When given intravenously, GLN should protect tissues against oxidative stress, toxic agents, or pathologic insults by increasing gluthation production and enhancing heat shock protein expression. On the other hand, many of the potential protective mechanisms of GLN given enterally or parenterally are overlapping and quite similar.[76] For these reasons, we decided that there was a strong rational in pooling both routes.

An additional shortcoming of the present study is the lack of separate analyses by more specific ICU patient cohorts. Unfortunately in most of the trials, it was difficult or impossible to distinguish further the type of subjects admitted or the attempt to categorization would have compelled an excessive subgrouping with loss of reliability of results. Moreover, the secondary outcome is variable between the present review and the previous ones, but this may be because of subgroup analysis which may throw unexpected results based on differing inclusion criteria and study selection.

In conclusion, at present, our results do not allow to recommend GLN supplementation in a generic population of

critically ill patients. Further RCTs are needed to confirm or deny the potential protective or harmful effect of GLN in more specific cohort of patients treated in ICUs. In particular, as our data suggest that GLN given parenterally, for more than 5 days, in patients with APACHE II < 15 might have a protective role. To confirm this trend a adequately powered RCT with this inclusion criteria is deserved.

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