Original Article

Glutamine supported early enteral therapy for severe acute pancreatitis: A systematic review and meta-analysis

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Background and Objectives: Several studies have shown that glutamine (Gln) may play an important role in energy metabolism, inflammatory reactions, and immune processes in patients with severe acute pancreatitis (SAP). Nevertheless, the results of individual randomized controlled trials (RCTs) on Gln nutrition support for SAP are contradictory. This systematic review and meta-analysis evaluated the clinical benefit of Gln-supported early enteral nutrition (G+EEN) in patients with SAP. **Methods and Study Design:** Cochrane Library, PubMed, Embase, CNKI, Wan Fang, and Chinese Biomedical Literature Database were searched for relevant studies published before December 2018. RCTs of G+EEN versus standard early enteral nutrition (EEN) for SAP were selected, with both started within 48 h of admission. **Results:** Seven clinical RCTs including a total of 433 patients (EEN group: 218 patients; G+EEN group: 215 patients) were included. Compared with EEN, G+EEN increased serum albumin (standard mean difference [SMD]=0.74; 95% confidence interval [CI], 0.33–1.15; $p<0.01$), reduced serum hypersensitive C-reactive protein (SMD=−1.62; 95% CI, −1.98 to −1.26; $p<0.01$) and risks of mortality risk (risk ratio=0.38; 95% CI, 0.16–0.90; $p=0.03$) and multiple organ dysfunction syndrome (MODS)(risk ratio=0.37; 95% CI, 0.15–0.94; $p<0.01$), and shortened length of hospital stay (SMD=−1.19; 95% CI, −1.88 to 0.49; $p<0.01$); moreover, it did not significantly increase the incidence of infection-related complications, operative interventions, or APACHE II scores. **Conclusions:** G+EEN is beneficial in SAP management.

Key Words: glutamine, early enteral nutrition, meta-analysis, severe acute pancreatitis

INTRODUCTION

Severe acute pancreatitis (SAP) can be fatal (mortality rate, 15%–40%); patients with SAP are likely to require adequate nutritional support.[1,2] SAP is associated with the systemic inflammatory response syndrome (SIRS),[2] with distinctive patterns of metabolism, such as increased basal metabolic rate, altered protein metabolism, and negative nitrogen balance.[3] In patients with acute pancreatitis (AP), acute malnutrition is associated with immune disorders, sepsis-related complications, and delayed surgical wound healing. This acute malnutrition may lead to the multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF), further increasing morbidity and mortality.[4] In SAP, the stressed state impairs immune function, which facilitates the entry of intestinal bacteria and endotoxins into the circulation; this contributes to MODS development, so worsening patient status with attendant complications.[5]

Nutritional support is considered key in the management of the hypercatabolism secondary to pancreatic inflammation and other complications. Supplementary energy provision in SAP may improve patient survival. Parenteral nutrition (PN), preferred in the past, is associated with a higher incidence of complications.[6] Enteral nutrition (EN) can significantly reduce the incidence of infectious complications, mortality, MODS, and surgical intervention rates in SAP when compared with PN.[6-8] In addition, blood glucose can be better controlled with EN.[9] SAP prognosis can be further improved through early EN (EEN).[10] Current consensus and guidelines[11] for nutrition therapy in pancreatitis recommend EEN support as the preferred treatment method for patients with SAP.[12] Our previous work has demonstrated that patients with SAP receiving EEN within 48 h of admission have a decreased incidence of MOF, surgical interventions, systemic infections, and local sepsis complications.[13] It remains to determine whether advanced EEN is more beneficial than

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Manuscript received 09 October 2019. Initial review completed 16 February 2020. Revision accepted 10 March 2020.
doi: 10.6133/apjcn.202007_29(2).0007

standard EEN.

Of the candidate substances that provide enteral nutrients, glutamine (Gln) is involved in various metabolic and immune functions. It is a conditionally essential amino acid richly available in the human body. Furthermore, it is widely found in rapidly proliferating cells, such as the mucosal epithelial cells of the small intestine and lymphocytes, which is the preferred energy source for cell proliferation and differentiation.[14,15] Gln can effectively stimulate the proliferation of the ileum and colon mucosal cells, promote mucin biosynthesis and nitrogen balance, maintain intestinal mucosal integrity, and prevent bacterial ectopic or intestinal toxins from entering the bloodstream.[16] Catabolic stress states, such as severe trauma, burns, and major surgery,[17,18] considerably increase the need for Gln. AP is associated with Gln deficiency,[19] immune disorders, intestinal barrier failure, intestinal permeability, and bacterial displacement - all of which may exacerbate SIRS and MODS development.[20,21]

Gln can not only provide nutritional support for the patients but also improve the function of the immune system. However, whether the combination of Gln and EEN can complement each other and improve the effectiveness of the treatment remains unknown. Although EN is the recommended pillar for nutritional management in patients with AP, the absence of any significant differences in the effects of between Gln-supported EEN (G+EEN) and standard EEN in previously conducted meta-analyses[22,23] may be due to the inclusion of a limited number of samples. The purpose of this study was to systematically review, evaluate, and statistically summarize the clinically meaningful results of all relevant Randomized controlled trials (RCTs) on the treatment with G+EEN.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24]

Search strategy

The search terms “severe acute pancreatitis,” “SAP” AND “glutamine,” “Gln” AND “enteral nutrition,” “early enteral nutrition,” “enteral feeding” OR “EN” were used. Two authors independently searched the Cochrane Library, PubMed, Embase, CNKI, Wan Fang, and Chinese Biomedical Literature Database for relevant studies published before December 2018. No language restriction was applied, and the search was limited to human studies.

Study selection criteria

Inclusion criteria were as follows:

1. Study type was RCT.
2. Target patients were diagnosed as having SAP and were aged ≥18 years.
3. G+EEN was controlled using standard EEN (both starting within 48 h after admission), and the G+EEN group received supplementation with Gln and/or in combination with other nutrients (oral or intravenous route).

Exclusion criteria were as follows:

1. Study type was not RCT.
2. Patient age was <18 years.
3. The timing of EEN was not defined or EEN was not initiated within 48 h of admission.
4. Detailed information was not provided, when required.

Types of outcome measures

The clinical outcomes of this study were as follows: serum albumin (Alb); serum high-sensitivity C-reactive protein (hs-CRP); infection complications; mortality; length of stay in days; operative intervention; MODS; and APACHE II scores.

Data acquisition and quality assessment

Data acquisition

Two independent reviewers used a standard form for data abstraction. The extracted data were crosschecked by the reviewers. The basic information included the first author; publication year; country of origin; SAP diagnostic criteria; patient age, gender, and demographics; number of patients in the G+EEN and EEN groups; Gln administration route; composition of Gln preparation; duration of intervention; and amount of Gln supplied.

Quality assessment

The methodological quality of the included studies was assessed according to the methodological criteria of Cochrane Collaboration. The risk of bias was assessed in seven domains: generation of allocation sequences, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, management of incomplete outcome data, selective outcome reporting, and other potential sources of bias.[25]

Statistical analysis

Meta-analysis was performed using Cochrane Collaboration RevMan 5.2. Infection complications, MODS, mortality, and operative intervention were statistically analyzed by measuring the risk ratio (RR) and 95% confidence interval (CI). Alb, hs-CRP, length of stay (in days), and APACHE II scores were statistically analyzed using standardized mean difference (SMD) or mean difference with the 95% CI. A p of <0.05 was considered statistically significant. The I^2 test was used to analyze the heterogeneity among the included studies; $I^2 \leq 50\%$ indicated significant heterogeneity, and the fixed-effect model was used to make estimates, whereas $I^2 > 50\%$ indicated a clear heterogeneity between the selected studies, and a random-effect model as applied to the statistical analysis, and the heterogeneity source should be analyzed. A funnel plot was used to uncover potential publication bias.

RESULTS

Search results

The study selection process is summarized in Figure 1. A total of 460 articles were screened. Finally, 7 RCTs[26-32] comprising 324 patients (EEN group, 159 patients; G+EEN group, 165 patients) were included in this meta-analysis. The basic data of the articles are presented in Tables 1 and 2.

Study characteristics

Of the seven RCTs included in this study, four provided complete data on the generation of allocation sequences

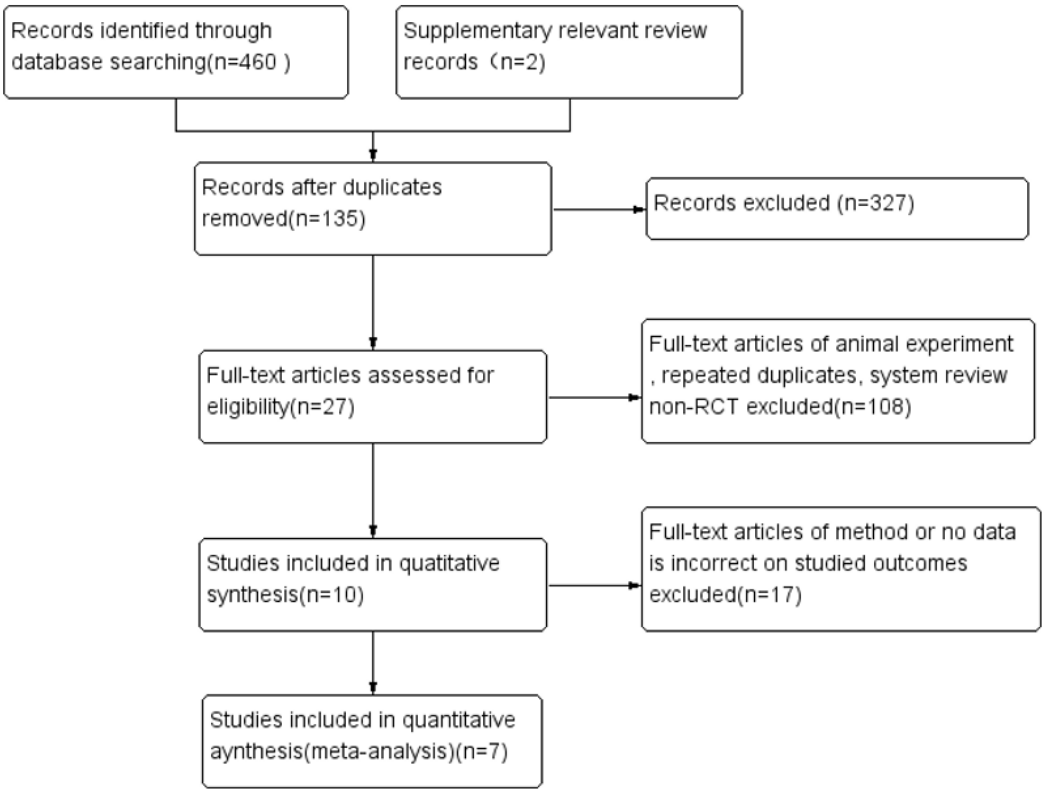

Figure 1. PRISMA flow diagram showing the selection process for the inclusion of studies

and one provided sufficient information regarding the use of the blinding method. Allocation concealment was adequate in all studies. Figure 2 and 3 summarize the risks of bias assessment, most of which are of moderate quality. Six studies[26-31] used Gln as the sole nutrient, whereas only one study used Gln with another nutrient (i.e., arginine). Gln doses ranged from 0.1 to 0.5 g/kg/day (Table 1). According to this study plan, the duration of Gln supplementation ranged from 1 to 2 weeks.

Impact on serum Alb

Alb data were collected in 5 studies[26-30] comprising 260 patients (130 patients each in the G+EEN and EEN groups). A fixed-effects model was used because the results were homogenous (I^2=57%). The meta-analysis results demonstrated serum Alb were significantly higher in the G+EEN group than in the EEN group (SMD=0.74; 95% CI, 0.33 to 1.15; p<0.01; Figure 4A).

Impact on serum hs-CRP

The impact of serum on hs-CRP was reported in 2 studies[29,30] comprising 162 patients. The I^2 for heterogeneity was 0%. The meta-analysis results demonstrated that serum hs-CRP were significantly lower in the G+EEN group than in the EEN group, (SMD=−1.62; 95% CI, −1.98 to −1.26; p<0.01; Figure 4B).

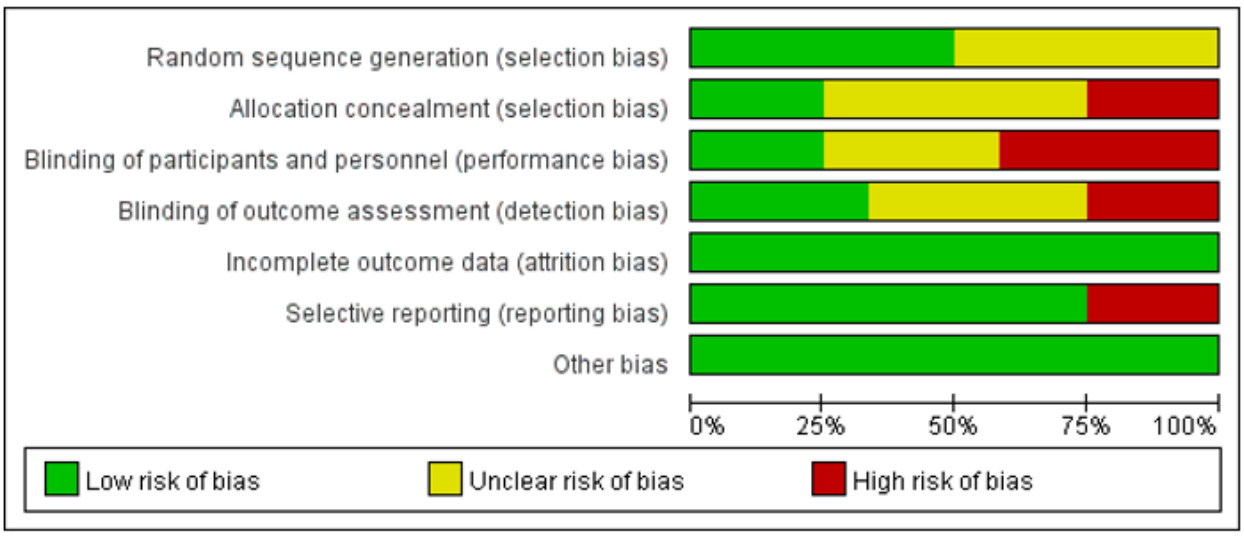

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item for all the included studies

Table 1. The characteristics of participating restaurants (n=324)

Study	Country	Year	Total of patients	Patients (G+EEN/EEN)	Mean age (G+EEN/EEN)	Male/ female	Severity criteria used
Hallay et al[32]	Hungary	2001	19	11/8	NR	NR	Ranson
Wu et al[26]	China	2011	30	15/15	NR	NR	1
Hadju et al [31]	Hungary	2012	45	24/21	59.5/51.8	42/3	Glasgow
Zhou et al[27]	China	2013	40	20/20	NR	39/21	1
Yang et al[28]	China	2013	28	14/14	42.82/42.35	14/14	1
Cui et al[29]	China	2018	94	47/47	52.7/53.5	66/28	1
Hu et al[30]	China	2018	68	34/34	51.6/51.8	27/41	CT; APACHE II

Study	Route of nutrition	Intervention	Feeding start	Duration of intervention	Glutamine dosage
Hallay et al[32]	Nasojejunal	Glutamine; arginine	<24 h of admission	5d	NR
Wu et al[26]	Nasojejunal	Glutamine	<72h of admission	14d	0.1-0.3 g/kg/day
Hadju et al [31]	Nasojejunal	Glutamine	<24 h of admission	7 d	0.5 g/kg/day
Zhou et al[27]	Nasojejunal	Glutamine	<24-48h of admission	10d	0.27 g/kg/day
Yang et al[28]	Nasojejunal	Glutamine	<72h of admission	14d	0.2 g/kg/day
Cui et al[29]	Nasojejunal	Glutamine	<24h of admission	7d	0.4 g/kg/day
Hu et al[30]	Nasojejunal	Glutamine	<24-48h of admission	14d	1.2-1.8 g/day

1: Guidelines for the diagnosis and treatment of acute pancreatitis in China.

Table 2. Summary of clinical outcomes of included studies

Study	Number of patients	ALB	CRP	Infectious complications	Mortality	The surgical rate	MODS	Length of stay days
Hallay et al	11/8	Not stated	Not stated	2/3	3/2	Not stated	Not stated	Not stated
Wu et al	15/15	40.0±2.71/38.5±2.51	Not stated	2/2	Not stated	Not stated	1/2	33.5±5.6/35.0±4.8
Hadju et al	24/21	Not stated	Not stated	10/9	0/3	0/3	0/3	10.6±3.5/15.9±3.6
Zhou et al	20/20	37.2±3.6/35.4±3.5	Not stated	8/9	1/1	1/2	1/3	13.1±1.9/17.4±2.1
Yang et al	14/14	35.7±1.98/35.4±2.03	Not stated	1/2	1/2	Not stated	2/4	55.79±5.72/58.29±8.97
Cui et al	47/47	29.4±3.47/25.4±2.81	0.64±0.52/2.13±1.22	Not stated	Not stated	Not stated	Not stated	Not stated

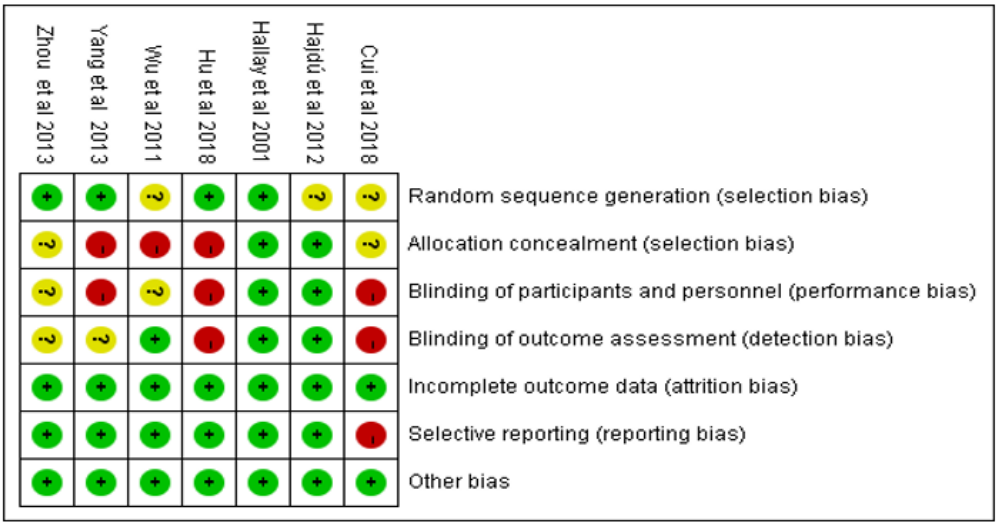

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Impact on length of hospital stay

The impact on the length of hospital stay was evaluated in 5 studies[26-28,30,31] comprising 211 patients. The results were homogenous (I^2=80%); thus, a random-effects model was used. After aggregating the data, G+EEN displayed advantages over EEN in reducing the days of hospitalization (SMD=−1.19; 95% CI, −1.88 to 0.49; p<0.01; Figure 4C).

Impact on APACHE II scores

The impact on APACHE II scores was assessed in 3 studies.[26,28,30] Significant heterogeneity was detected (I^2=84%; p<0.05); therefore, a random-effects model was used. When the APACHE II score data were aggregated, no statistically significant change after the use of the Gln support was noted (SMD=−0.56; 95% CI, −1.50 to 0.38; p=0.24; Figure 4D).

Impact on infectious complications

Six studies[26-28,30-32] reported the impact on infectious complications in a total of 230 patients. No significant heterogeneity was observed between the trials (I^2=0%). Furthermore, a lower tendency for decreased infectious complications was observed in the G+EEN group compared with the EEN group, but the difference was nonsignificant (RR=0.67; 95% CI, 0.43–1.02; p=0.06; Figure 5A).

Impact on mortality

Mortality was reported in 5 studies[27,28,30-32] comprising 193 patients (I^2=0). A significant reduction in mortality was observed in the G+EEN group compared to the EEN group (RR=0.38; 95% CI, 0.16–0.90; p=0.03; Figure 5B).

Impact on operative intervention

Information on the impact on operative intervention was collected in 2 studies[27,32] comprising 85 patients. The I^2 for heterogeneity was 0%. No significant difference in operative intervention benefit was evident after Gln use (RR=0.26; 95% CI, 0.04–1.46; p=0.13; Figure 5C).

Impact on MODS

Five studies[26-28,30,32] comprising 211 patients (107 in the G+EEN group and 104 in the EEN group) reported the impact on MODS. No significant heterogeneity was observed between the studies (I^2=0%). In this outcome, G+EEN displayed an advantage over EEN in reducing MODS risk (RR=0.37; 95% CI, 0.15–1.13; p=0.04; Figure 5D).

DISCUSSION

It is demonstrated that, compared with EEN, G+EEN could effectively increase serum Alb, reduce serum hs-CRP and mortality and MODS risks, and shorten the length of hospital stay in patients with SAP.

The motility and the mucosal barrier of the intestines are involved in SAP. Intestinal motility dysfunction may be caused by intestinal motility disorder and ischemia, whereas intestinal mucosal barrier dysfunction is caused by an imbalance in the intestinal flora, excessive cytokine secretion, and excessive apoptosis of the intestinal mucosal epithelial cells.[33] Bacterial translocation and pathogen overgrowth can be detected during the early stages of AP.[34] Early bacterial invasion may exacerbate SIRS, making patients more susceptible to MODS. In the early stages of SAP, patients undergo catabolic stress due to the occurrence of SIRS followed by MODS, thereby resulting in a significant increase in the demand for nutrition.[35,36]

Long-term PN can cause many side effects, such as damage to the intestinal mucosa leading to cell atrophy, increase in mucosal permeability, decrease in intestinal function, and disorder of the intestinal flora, resulting in bacterial and/or endotoxin translocation and SIRS aggravation; this leads to MODS occurrence. EN prevents atrophic changes in the intestinal mucosa because the absorption of nutrients in the intestinal epithelial cells comes directly from the intestinal lumen. Moreover, because of high nutrient permeability, EN promotes intestinal peristalsis and restores intestinal function.[37] These pathophysiological mechanisms can prevent abnormal overgrowth of the intestinal flora and increase intestinal mucosal permeability, thereby reducing or preventing bacterial translocation and maintaining the function of the

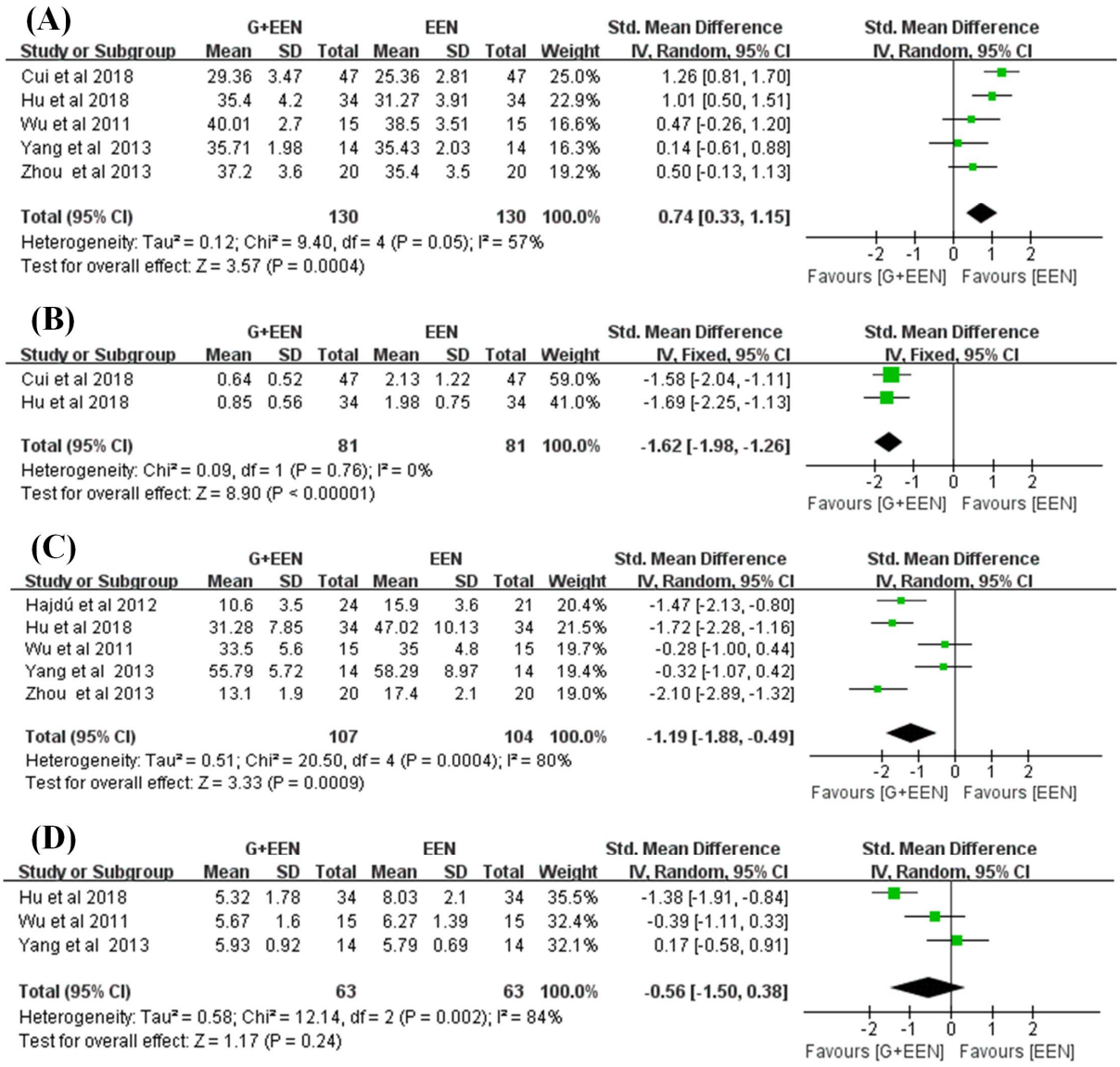

Figure 4. Effect of Gln supplementation on (A) serum Alb, (B) serum hs-CRP, (C) length of hospital stay, and (D) APACHE II scores.

intestinal mucosal barrier. Therefore, it is reasonable to start EN as early as possible. EN can significantly reduce the complications of infection[7,38,39] and has been identified as a key component in SAP management.[40] The meta-analysis by Petrov et al[41] comprising 11 RCTs on AP, demonstrated a significant reduction in the risks of MOF, complications of pancreatic infection, and mortality in patients with EN (started within 48 h of admission).

Gln is the most abundant amino acid in plasma, muscle, and cells, and it plays an important and unique role in organs and tissues.[42] In SAP, the persistent decrease in plasma Gln is due to the significant increase in its utilization by intestinal mucosal epithelial cells and immune cells. In addition, the production of endogenous Gln is relatively insufficient, resulting in a sharp decrease in its concentration in the blood. Gln may be considered as a critical "essential" amino acid for patients with SAP, who remain in a state of stress.[43]

In a previous meta-analysis, EN supplementation with Gln, arginine, and omega-3 fatty acids failed to show any clinically beneficial effects compared to standard EN in patients with AP, probably due to the limited number of studies included in the analysis (three RCTs).[22] Another meta-analysis showed a significant reduction in mortality and infectious complication rates in AP patients receiving Gln supplementation, but no significant effect on hospital stay was reported; however, the total sample size in that analysis was also relatively small (n=185).[23] Here we discuss the alternatives and clinical decision-making in the circumstances, with the aid of a logistic diagram (Figure 6), weighing up the benefits, risks and costs. In the current study, Glu was mostly administered orally, but rarely intravenously, in both groups. Previous reviews indicate that EN supplemented by intravenous Gln reduces the rate of complications and shortens the length of hospital stay.[37] Thus, intravenous Gln support and early enteral feeding may prove more beneficial for the patients. Our study demonstrated that the EN in all the included RCTs included Gln alone; only one RCT combined Gln with arginine. Enteral nutrients supplemented by nutrition formulas include Gln, arginine, nucleotides, omega-3 fatty acids, probiotics, which may be a better choice. The cost of hospitalization should be considered to determine a more reasonable nutritional formula to improve SAP.

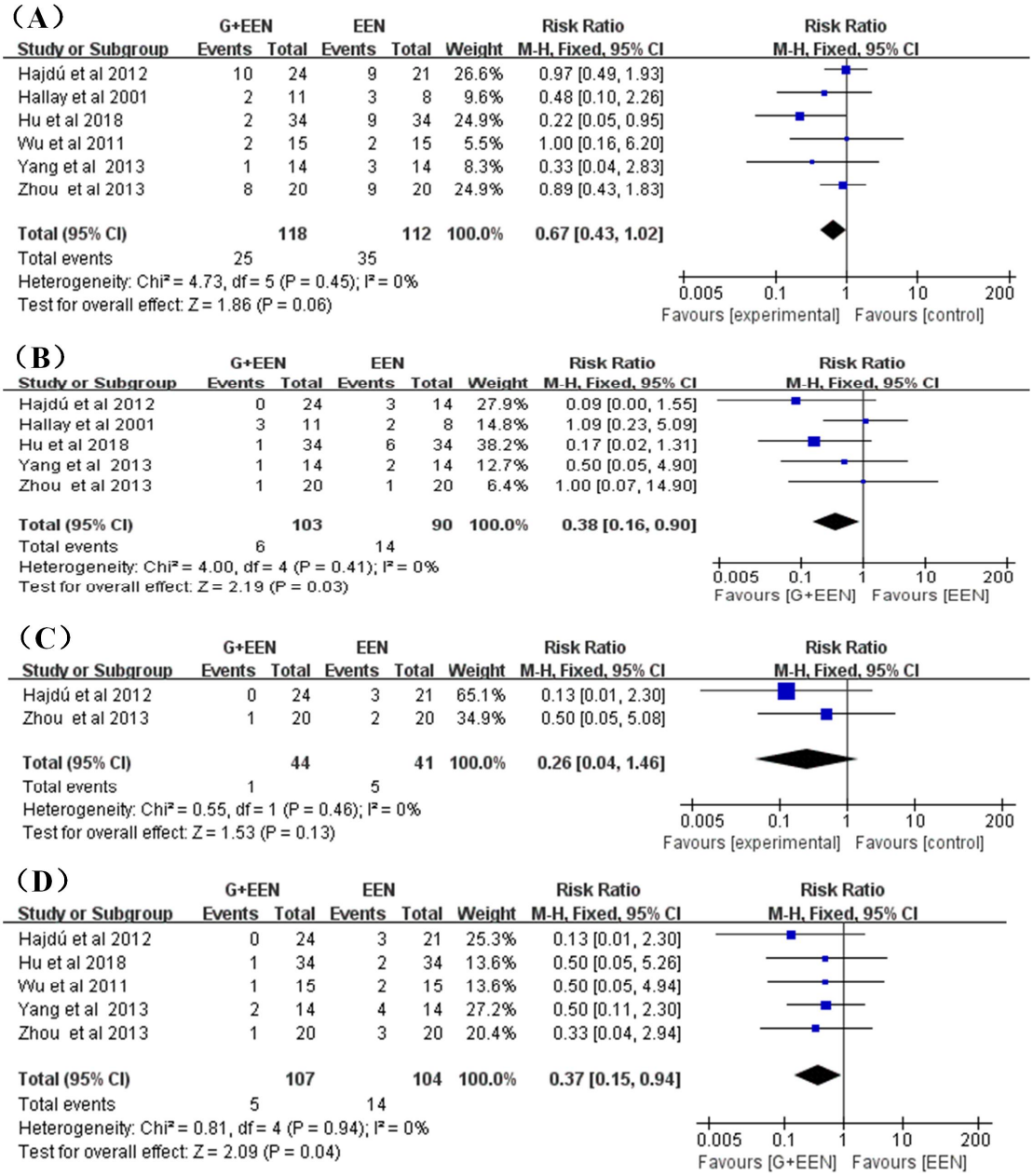

Figure 5. Effect of Gln supplementation on (A) infectious complications, (B) mortality, (C) operative intervention, and (D) MODS.

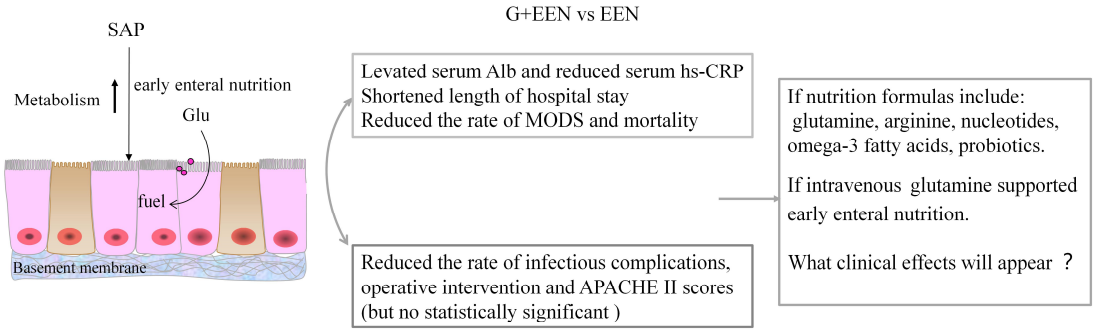

Figure 6. Study summary

This meta-analysis has some limitations. First, only seven clinical RCTs were selected, some of which were single-centered studies with a small sample size. However, the sample size and number of studies included in this analysis were greater than those included in previous meta-analyses. Second, the methodological quality of the RCTs was moderate. Randomized methods were unclear, and the allocation schemes were not perfect in all the included studies. Finally, the SAP diagnostic criteria, the severity of the patient condition, and the outcome index

were not the identical among the studies. The dose, timing, and duration of Gln support and feed composition of standard EN were not consistent in all the RCTs. This could have confounding effects on the outcomes, but the effect is likely to be nondifferential.

Conclusions

Although the evidence was not completely convincing, this meta-analysis demonstrated that G+EEN was superior to standard EEN in terms of the serum Alb, serum hs-CRP, mortality, MODS, and length of hospital stay in patients with SAP. Additional high-quality, large-scale RCTs involving multicentered collaborative research and a contemporary design are warranted.

AUTHOR DISCLOSURES

The authors declare that they have no conflict of interest. This study was funded in full by grants from the National Natural Science Foundation of China (grant number: 81673801, 81473512).

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