Effect of Glutamine Enriched Nutrition Support on Surgical Patients with Gastrointestinal Tumor: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Associations between glutamine (Gln) enriched nutrition support and surgical patients with gastrointestinal (GI) tumor remain controversy. The purpose of this meta-analysis was to assess the effect of Gln enriched nutrition support on surgical patients with GI tumor in term of relevant biochemical indices, immune indices, and clinical outcomes.

Methods: Six databases were systematically searched to find eligible randomized controlled trials (RCTs) from 1966 to May 2014. When estimated the analysis indexes, the relative risk (RR) was used as the effect size of the categorical variable, while the weighted mean difference (MD) was used as the effect size of a continuous variable. Meta-analysis was conducted with Rev Man 5.2.

Results: Thirteen RCTs, involving 1034 patients, were included in the meta-analysis. The analysis showed that Gln enriched nutrition support was more effective in increasing serum albumin (MD: 0.10; 95% confidence interval [CI]: 0.02–0.18; $P < 0.05$), serum prealbumin (MD: 1.98; 95% CI: 1.40–2.55; $P < 0.05$) and serum transferring (MD: 0.35; 95% CI: 0.12–0.57; $P < 0.05$), concentration of IgG (MD: 1.26; 95% CI: 0.90–1.63; $P < 0.05$), IgM (MD: 0.18; 95% CI: 0.11–0.25; $P < 0.05$), IgA (MD: 0.22; 95% CI: 0.10–0.33; $P < 0.05$), $CD3^+$ (MD: 3.71; 95% CI: 2.57–4.85; $P < 0.05$) and CD4/CD8 ratio (MD: 0.27; 95% CI: 0.12–0.42; $P < 0.05$). Meanwhile, it was more significant in decreasing the incidence of infectious complications (RR: 0.67; 95% CI: 0.50–0.90; $P < 0.05$) and shortening the length of hospital stay (MD: −1.72; 95% CI: −3.31–−0.13; $P < 0.05$).

Conclusions: Glutamine enriched nutrition support was superior in improving immune function, reducing the incidence of infectious complications and shortening the length of hospital stay, playing an important role in the rehabilitation of surgical GI cancer patients.

Key words: Gastrointestinal Tumor; Glutamine; Immune; Meta-analysis; Postoperation

Introduction

Glutamine (Gln) is the most abundant naturally occurring, nonessential amino acid in the human body and one of the few amino acids that can directly cross the blood-brain barrier.[1] It is a major energy source of the cells of intestines, activated immune cells and many cancer cells with an average serum concentration of 0.6–0.9 mmol/L.[2-4] Normally, animals and humans would be rarely lack of Gln, but the serum concentration of Gln decreases significantly in the tumor-bearing state and severe traumatic stress condition, then Gln supplements become essential to meet the body's needs.[5] A series of *in vivo* studies showed that Gln could effectively improve the nutritional status, promote the body's immune function and to some extent, inhibit tumor growth. Austgen *et al*.[6] found that Gln-enriched total parenteral nutrition (TPN) did not stimulate tumor growth or tumor Gln metabolism. Kew *et al*.[7] proved that increasing the oral availability of Gln could promote the T-cell-mediated immune response. Yoshida *et al*.[8] demonstrated that Gln supplementation could attenuate loss of protein in the muscle in tumor-bearing animals, and protect immune and gut-barrier function during the radiochemotherapy in patients with advanced cancer. However, some results of vitro tests were on the contrary. Eagle and Piez[9] proved there was a significantly growth and proliferation of Hela cells with the addition of Gln in culture media. With studies on six different human solid tumor cell lines, Wasa *et al*.[10] discovered that some cancers may be better suited to survive and proliferation in a low Gln environment than others. Therefore, associations between Gln enriched nutrition support and surgical patients with gastrointestinal (GI)

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tumor remain controversy. The aim of this study was to review systematically and meta-analysis all randomized controlled trials (RCTs) thus investigating the effects of Gln enriched nutrition support on surgical patients with GI tumor published from 1966 to May 2014, to provide further evidence for rational clinical application of Gln.

Methods

Study selection

We systematically searched 6 databases (PubMed [http://www.pubmed.com], EMBASE [http://www.embase.com], Web of Science [http://apps.webofknowledge.com], The Cochrane Library [http://www.thecochranelibrary.com]), China National Knowledge Infrastructure (CNKI, http://www.cnki.net/), VIP (http://www.cqvip.com/) for all RCTs investigating the effects of Gln enriched nutrition support ("nutritional support," "nutrition supplement," "enteral nutrition," "parenteral nutrition (PN)," "TPN" and their variants) on postoperative ("surgery," "operative," "operation," "preoperative," "preoperation," "perioperative," "perioperation," "postoperative," "postoperation," "resection," "gastrectomy," "enterectomy" and their variants) patients of GI tumor ("GI," "upper GI," "lower GI," "digestive tract," "gastric," "colon," "colorectal," "cancer," "neoplasms" and their variants) published from 1966 to May 2014. References from the extracted articles and reviews were also consulted to complete the data bank. When multiple articles for a single study were present, we used the latest publication and supplemented it, if necessary, with data from the most complete or updated publication.

Studies were included if (i) they were the RCTs with parallel controlled design; (ii) the objects of study were surgical patients with GI tumor; (iii) the supplementation of Gln was the only difference between the treatment group and the control group; (iv) specific outcomes were mentioned, including relevant biochemical indices (serum total protein, serum albumin, serum prealbumin and serum transferrin), immune indices (concentration of IgG, IgM, IgA, $CD3^+$, $CD4^+$, $CD8^+$, CD4/CD8 ratio and tumor necrosis factor alpha [TNF-α]) and clinical outcomes (infectious complication, noninfectious complication [Table 1] and length of hospital stay); and (v) data related to supplementation of were available. And we excluded studies if (i) they were not randomized designs; (ii) they did not report an adequate statistical analysis; and (iii) reviews or case reports.

Data extraction

From each study, we extracted information on first author, publication year, country of origin, sample size, age, sex, type of diseases, average study follow-up time, number of subjects, type of nutrition support, duration of Gln enriched nutrition support, daily dose of Gln, disease outcome, method of outcome ascertainment, unit of measurement, and corresponding 95% confidence interval (CI), standard deviation (SD), or exact *P* value. Because differences in study populations and design might cause variations in results, study-quality score was made by methodology quality assessment.[11] A study-quality score was calculated for each of included traits ranged from 0 to 5. Studies were categorized into those with a high study quality score (3–5 points) and those with a low study-quality score (1–2 points), and no RCTs (0 point).

Table 1: Classification of complications in the included trials

Infectious complications	Noninfectious complications
Pneumonia	Anastomotic leak
Abdominal abscess	Wound dehiscence
Fasciitis	Gastrointestinal bleeding
Bacteremia	Gastrointestinal perforation, obstruction and ischemia
Septic shock	Pancreatitis
Septic coagulopathy	Myocardial infarction
Wound infections	Cardiogenic shock
Urinary tract infections	Cardiopulmonary arrest
Central venous catheter infectious	Stroke
	Pulmonary embolus
	Hemoperitoneum
	Pulmonary failure
	Renal failure
	Pleural effusion
	Hepatic dysfunction

Data analysis

Data pooling was performed with the use of classical meta-analytic methodology, using the RevMan 5.2 Copenhagen: The Nordie Cochrane Centre, The Cochrane Collaboration, 2012 http://ims.cochrane.org/revman/). $P < 0.05$ was considered statistically significant. Data were extracted from the text, tables and figures of the original published papers. To include data from as many trials as possible, missing SD data for one trial were imputed from SD data from all other trials using the same measure.[12] When estimated the analysis indexes, the relative risk (RR) was used as the effect size of the categorical variable, while the weighted mean difference (MD) was used as the effect size of a continuous variable. 95% CIs were calculated for each investigation and for each outcome variable. Before calculating the standardized mean effect for all trials, statistical heterogeneity test was evaluated by using the I^2 statistic ($\alpha = 0.05$), which assessed the appropriateness of pooling the individual study results. The I^2 value provided an estimate of the amount of variance across studies because of heterogeneity rather than chance.[13] And I^2 values of 25%, 50%, and 75% corresponded to low, moderate, and high levels of heterogeneity, respectively. If $P \geq 0.05$, the heterogeneity was not substantial, there was low heterogeneity between the trials. Thus, fixed-effects models were used, with Mantel-Haenszel method weighting for combined statistics. If $P < 0.05$, however, the heterogeneity was considered substantial, there was high heterogeneity between the trials. In this situation, subgroup analysis would be performed. If subgroup analysis could not remove the heterogeneity,

combined results were conducted with random-effects models, which were inversed variance weighting or DerSimonian-Laird method based on fixed-effects models. Moreover, a *priori* potential sources of heterogeneity were publication bias. Possible publication bias was investigated by drawing a funnel plot to look for funnel plot asymmetry and meta-regression based on study size.[14]

Results

Characteristics of the studies

The initial search yielded 776 potentially relevant references. After removing duplicates, reviews, animal trials and papers that were less related according to the titles and abstracts, there were 59 studies left. Then reading the full text of these studies and excluding the studies that were less related, 13 trials[15-27] met the inclusion criteria and were selected as appropriate for inclusion in this meta-analysis [Figure 1]. The included trials were published between 1966 to May 2014. The sample size varied from 11 to 428, reaching a total of 1034. The characteristics of the selected trials are presented in Table 2.

Relevant biochemical indices

Serum total protein

Totally 122 participants from three studies[18,24,27] were enrolled to evaluate the change of serum total protein (g/L), the heterogeneity of which (I^2 = 58%; P = 0.09; Chi-square = 4.81) was acceptable, so the fixed-effects model was used. The analysis showed that there was no statistically significant difference between the Gln and control group (MD: 0.86; 95% CI: −0.28–1.99; P > 0.05), from which we could draw the conclusion that Gln enriched nutrition support had no more difference in changing the serum total protein than control group [Figure 2a].

Serum albumin

A total of 356 participants from six studies[18,20,21,23,26,27] were enrolled in the serum albumin (g/dl) analysis, the heterogeneity of which (I^2 = 51%; P = 0.07; Chi-square = 10.15) was acceptable, so the fixed-effects model was used. There was statistically significant difference between Gln and control group (MD: 0.10; 95% CI: 0.02–0.18; P < 0.05) [Figure 2b].

Serum prealbumin

Six studies[17,18,21,23,24,26] with 324 subjects mentioned the data of serum prealbumin (mg/dl). The fixed-effects model was used, for the heterogeneity was acceptable (I^2 = 38%; P = 0.15; Chi-square = 8.06). The analysis suggested that Gln enriched nutrition support performed more effective in increasing serum prealbumin (MD: 1.98; 95% CI: 1.40–2.55; P < 0.05) than control [Figure 2c].

Serum transferring

There were five studies[17,18,23,24,26] with 274 subjects that mentioned the change of serum transferring (g/L) between the Gln and control group, but the heterogeneity among them was significant (I^2 = 76%; P < 0.05; Chi-square = 16.45). Thus, we performed a subgroup analysis according to

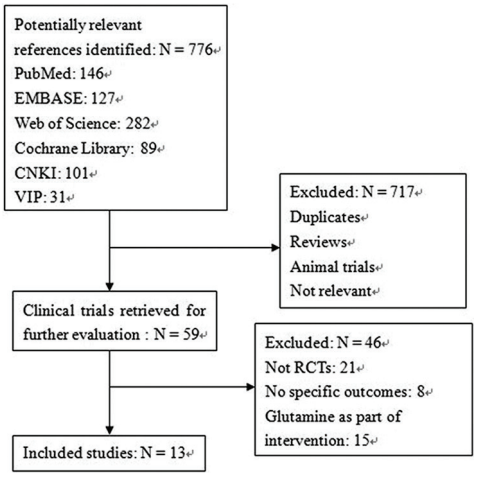

Figure 1: Flow diagram of trial selection process resulting from systematic search.

Table 2: Characteristics of the trials included in the meta-analysis, by year of publication*

Author	Year	Country	Type of diseases	Age (years)	Sex (male/female)	Number of subjects (treatment/control)	Type of nutrition support	Daily dose of glutamine	Duration (days)	Design	Study-quality score
Aosasa *et al.*[15]	1999	Japan	Colorectal cancer	63.8 ± 10.7	7/4	11 (6/5)	TPN	30 g/kg	≥5	R, PC	3
Dai *et al.*[17]	2001	China	Gastrointestinal cancer	61.2	11/9	20 (10/10)	TPN	20 g/kg	8	R, PC	3
Erdem *et al.*[18]	2002	Turkey	Gastrointestinal cancer	26 - 70	16/16	32 (16/16)	EN	0.2 g/kg	17	R, PC	3
Huang *et al.*[20]	2002	China	Colorectal carcinoma	41 - 70	16/6	22 (11/11)	PN	0.2 g/kg	6	R, PC	3
Weng *et al.*[24]	2006	China	Gastric cancer	67.8 ± 4.1	23/7	30 (15/15)	PN	0.2 g/kg	7	R, PC	3
Xia *et al.*[25]	2006	China	Gastrointestinal cancer	60.4 ± 11.1	21/19	40 (20/20)	TPN	0.3 g/kg	10	R, PC	3
Oguz *et al.*[22]	2007	Turkey	Colorectal cancer	57 ± 17	71/38	109 (57/52)	EN	1 g/kg	5 - 8	R, PC	3
Wang and Che[23]	2007	China	Gastrointestinal cancer	35 - 62	32/28	60 (30/30)	PN	0.4 g/kg	7	R, PC	3
Yang *et al.*[26]	2008	China	Digestive tract cancer	63 ± 10	87/45	132 (70/62)	EN	0.5 g/kg	7	R, PC	3
Gianotti *et al.*[19]	2009	Italy	Major gastrointestinal cancer	>18	260/168	428 (212/216)	PN	0.4 g/kg	≥6	R, PC	3
Cui *et al.*[16]	2011	China	Colon cancer	35 - 75	23/17	40 (20/20)	PN	0.5 g/kg	2	R, PC	3
Lu *et al.*[21]	2011	China	Gastrointestinal cancer	66.8 ± 14.9	34/16	50 (25/25)	TPN	0.3 g/kg	7	R, PC	3
Zhao *et al.*[27]	2012	China	Gastric cancer	58.2 ± 12.5	35/25	60 (30/30)	PN	0.4 g/kg	10	R, B, PC	4

*EN: Enteral nutrition; PN: Parenteral nutrition; TPN: Total parenteral nutrition; B: Blind; PC: Parallel-controlled; R: Randomized.

different countries and regions. I^2 between subgroups was 0% ($P = 0.36$; Chi-square = 0.85), but the total heterogeneity was still large. In this case, we used a random-effects model to analyze the data. There was significantly increase of serum transferring in Gln group (MD: 0.35; 95% CI: 0.12–0.57; $P < 0.05$) [Figure 2d]. Moreover, the symmetry funnel plot suggested scarcely any publication bias existed between studies mentioned change of serum transferring [Figure 3].

Relevant immune indices

Concentration of IgG, IgM and IgA

There were six studies[17,20,23,24,26,27] with 324 subjects that mentioned the compare of relevant immune globulin between two groups. The fixed-effects model was used, for the heterogeneity of three variables was acceptable [Figure 4a-c]. The analysis suggested that Gln could improving the immune function with higher concentration of IgG (MD: 1.26; 95% CI: 0.90–1.63; $P < 0.05$), IgM (MD: 0.18; 95% CI: 0.11–0.25; $P < 0.05$) and IgA (MD: 0.22; 95% CI: 0.10–0.33; $P < 0.05$).

Change of CD3+, CD4+, CD8+ T-cell and CD4/CD8 ratio

There are five studies[23-27] with 322 subjects that mentioned the change of $CD3^+$, $CD4^+$, $CD8^+$ T-cell and CD4/CD8 ratio. The heterogeneity of $CD3^+$ and $CD8^+$ T-cell was acceptable, so the fixed-effects model was used [Figure 5a and c].

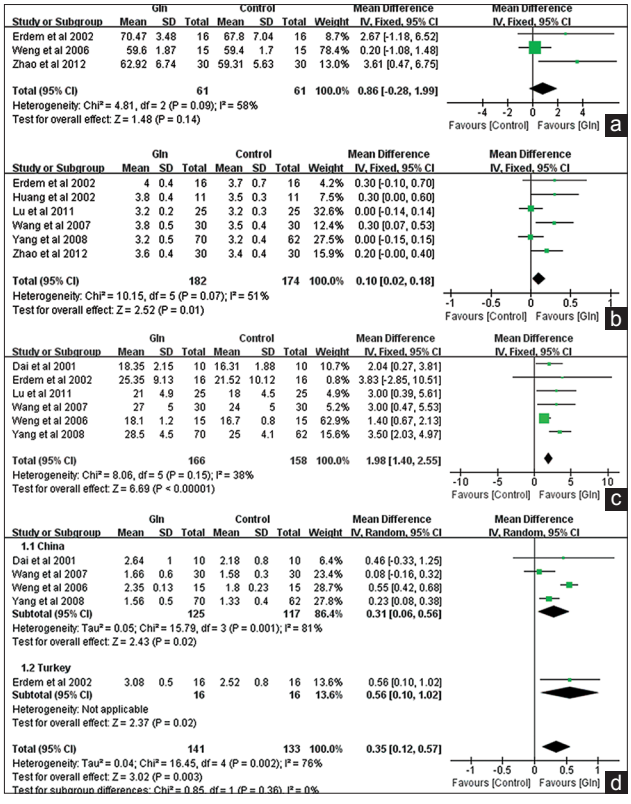

Figure 2: Forest plot of relevant biochemical indices between Glutamine and control group. (a) Change of serum total protein between glutamine and control group: Fixed-effects model. (b) Change of serum albumin between glutamine and control group: Fixed-effects model. (c) Change of serum prealbumin between glutamine and control group: Fixed-effects model. (d) Change of serum transferrin between glutamine and control group: Subgroup analysis with random-effects model.

While the heterogeneity among $CD4^+$ T-cell and CD4/CD8 ratio was significant, so the random-effects model was used [Figure 5b and d]. Analysis suggested Gln enriched nutrition support could effectively increase postoperative $CD3^+$ T-cell (MD: 3.71; 95% CI: 2.57–4.85; $P < 0.05$) and CD4/CD8 ratio (MD: 0.27; 95% CI: 0.12–0.42; $P < 0.05$) of GI cancer patients. But changes between $CD4^+$ (MD: 4.11; 95% CI: −0.82–9.04; $P > 0.05$) and $CD8^+$ (MD: −0.37; 95% CI: −1.12–0.38; $P > 0.05$) T-cell were not statistically significant.

Concentration of tumor necrosis factor alpha

In the analysis for concentration of TNF-α (pg/ml), 101 patients in three studies[15,16,21] were extracted. The heterogeneity among them was significant (I^2 = 89%; $P < 0.05$; Chi-square = 17.77), thus we used a random-effects model to analyze the data. The change of concentration of TNF-α was not statistically significant (MD: −7.34; 95% CI: −18.15–3.47; $P > 0.05$) [Figure 6].

Relevant clinical outcomes

Infectious complications

Eight studies,[19-22,24-27] 872 subjects included, evaluated the effect of Gln enriched nutrition support on infectious complications, and the analysis showed a trend towards a reduction of postoperative infectious complications (RR: 0.67; 95% CI: 0.50–0.90; $P < 0.05$) in GI cancer patients [Figure 7a]. Moreover, the fixed-effects model was used with acceptable heterogeneity (I^2 = 49%; P = 0.06; Chi-square = 13.61).

Noninfectious complications

From three studies[19,20,22] 559 participants were enrolled to evaluate the incidence of noninfectious complications, the heterogeneity of which (I^2 = 17%; P = 0.28; Chi-square = 10.87) was acceptable, so the fixed-effects model was used. However, there was no statistically significant difference between the two groups (RR: 0.80; 95% CI: 0.53–1.21; $P > 0.05$), from which we could draw

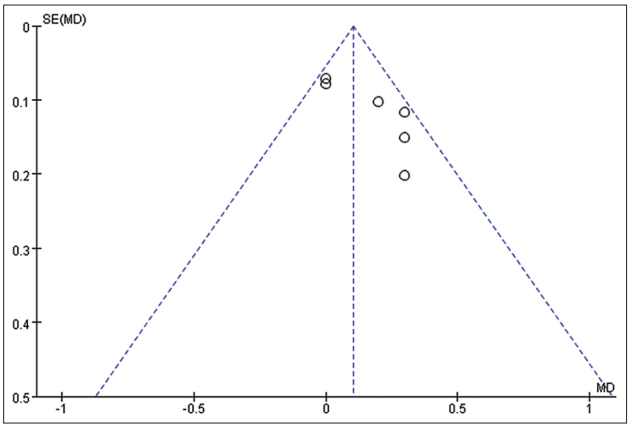

Figure 3: Funnel plot of studies mentioned change of relevant biochemical indices between glutamine and control group. Dotted lines are pseudo 95% confidence intervals. The asymmetry funnel plot suggested possible publication bias existed, which was associated with the significant heterogeneity of studies mentioned change of serum transferrin.

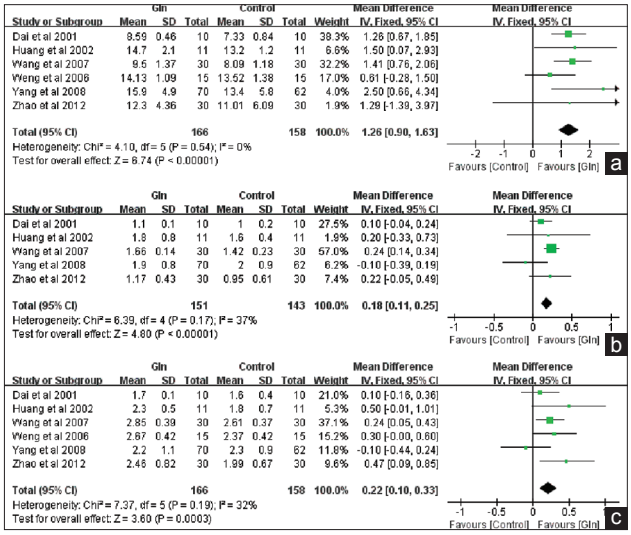

Figure 4: Forest plot of relevant immune globulin between glutamine and control group. (a) Change of concentration of IgG between glutamine and control group: Fixed-effects model. (b) Change of concentration of IgM between glutamine and control group: Fixed-effects model. (c) Change of concentration of IgA between glutamine and control group: Fixed-effects model.

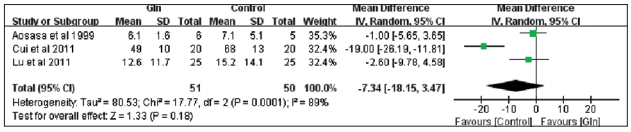

Figure 6: Forest plot of change of concentration of tumor necrosis factor-α; between glutamine and control group: Random-effects model.

the conclusion that Gln enriched nutrition support had no more difference in changing the incidence of noninfectious complications than standard nutrition [Figure 7b].

Length of hospital stay

Four studies[19,22,26,27] with 729 subjects mentioned the length of hospital stay. I^2 between studies was 91% ($P < 0.05$; Chi-square = 32.53), thus a random-effects model was used. Analysis showed that nutrition support was more effective in shortening the length of hospital stay than control group (MD: −1.72; 95% CI: −3.31–−0.13; $P < 0.05$) [Figure 7c].

Discussion

Gastrointestinal cancer patients often accompanied by malnutrition and immune dysfunction, thereby slowing the recovery after surgical trauma and increasing mortality.[28,29] During surgical stress, the consumption of Gln exceeds the synthesis, resulting in depletion of Gln stores.[30] Moreover, the limited intestinal reserves and surgical fasting period would further aggravating relative lack of Gln. In that situation, supplement of Gln became necessary. Gln has various physiological functions in the body. Above all, the oxidation of Gln was the nitrogen source for other amino acids and protein, which in turn preventing muscle degradation and increasing protein synthesis.[31,32] In this meta-analysis, although the Gln enriched nutrition support had no significant effect on change of serum total protein,

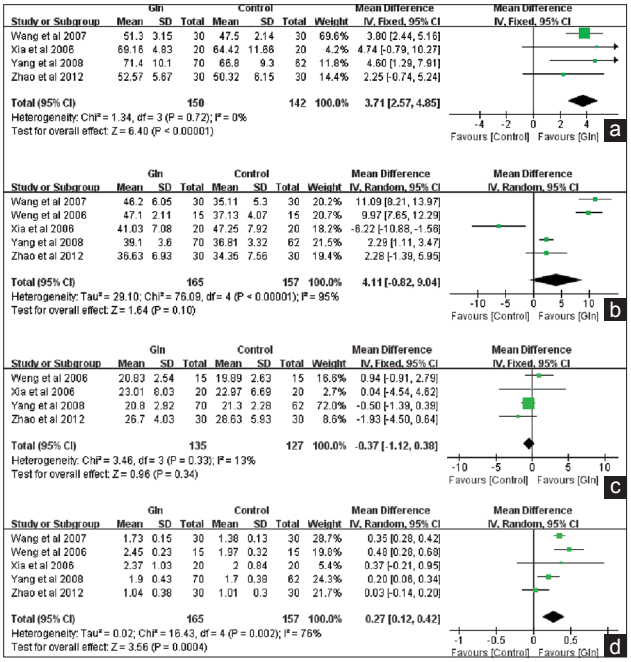

Figure 5: Forest plot of relevant immune indices between glutamine and control group. (a) Change of $CD3^+$ T-cell between glutamine and control group: Fixed-effects model. (b) Change of $CD4^+$ T-cell between glutamine and control group: Random-effects model. (c) Change of $CD8^+$ T-cell between glutamine and control group: Fixed-effects model. (d) Change of CD4/CD8 ratio between glutamine and control group: Random-effects model.

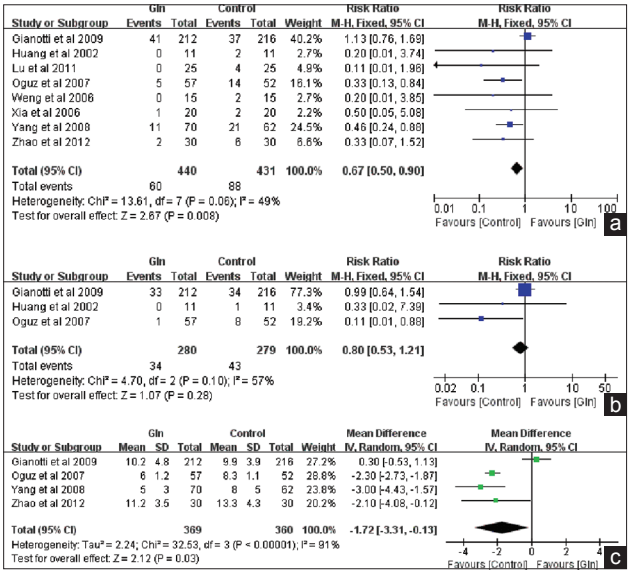

Figure 7: Forest plot of relevant clinical outcomes between glutamine and control group. (a) Change of infectious complications between glutamine and control group: Fixed-effects model. M-H: Mantel-Haenszel test. (b) Change of noninfectious complications between glutamine and control group: Fixed-effects model. M-H: Mantel-Haenszel test. (c) Change of length of hospital stay between glutamine and control group: Random-effects model.

levels of serum albumin, prealbumin and transferring were increased significantly, suggesting Gln enhanced nutritional support benefited protein synthesis for surgical patients with GI tumor.

Furthermore, Gln is an indispensable material for the proliferation of immune cell. It is avidly consumed by rapidly dividing cells, such as immune cells, intestinal mucosal cells, fibroblasts and tumor cells.[33-35] The high efficiency of Gln in many immune cells has a strong association with the functional activity of thses cells, such as cell proliferation, antigen presentation, cytokine synthesis, nitric oxide and superoxide production and phagocytosis.[36,37] Our anylysis showed that Gln could increase the postoperative concentration of $CD3^+$ T-cell and raised CD4/CD8 ratio of patients, suggesting that Gln could promote the proliferation of lymphocytes to some extent, thus enhancing body's cellular immune function.

Additionally, as the main energy source of the intestinal tract, Gln is the most important nutrient for intestinal repair, preventing mucosal atrophy process via PN.[38] Due to the complexity of intestinal immune system, many cells are involved in the immune function of gut, such as macrophages, natural killer cells and lymphocytes, of which the salivary IgA (S-IgA) secreted by plasmocyte could effectively prevent bacterial adhesion to the intestinal mucosa.[39,40] Study found that Gln can promote the secretion of intestinal S-IgA that further increase coated rate of bacteria, reduce bacterial adhesion, improve the quantity of $CD3^+$, $CD4^+$, $CD8^+$ lymphocytes, and then prevent bacterial translocation.[41] Moreover, bacterial translocation is closely related to a decrease of adenosine triphosphate level in intestinal epithelial cells. However, as an acute depletion of Gln, the bacterial translocation induced by cytokine is a process across the cell rather than through the cell gap.[42,43] Therefore, Gln plays a critical role in the protection of the intestinal immune barrier and the resistance of microbe, as the energy substrate of intestinal epithelial cells. In this meta-analysis, patients in Gln group had a significant higher concentration of IgG, IgM and IgA, lower incidence of infectious complications and shorter length of hospital stay. Gln could improve the body's immune globulin, and reduce the inflammatory response and the risk of postoperative infection, thus promote postoperative recovery.

Tumor necrosis factor alpha, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, inflammation and to inhibit tumorigenesis and viral replication.[44,45] Dysregulation of TNF-α production has been implicated in a variety of human diseases including Alzheimer's disease,[46] cancer[47] and inflammatory bowel disease.[48] Moreover, the concentrations of serum TNF-α has been postulated as a biochemical marker of tissue injury, which is a major reactive mediator during inflammation.[49] TNF-α is also a proinflammatory cytokine, despite it not being reduced significantly in our meta-analysis. As shown in the study of Yaqoob and Calder,[50] Gln had a smaller effect on T-cell-drived TNF-α production and dose not influence monocyte-derived TNF-α generation.

This meta-analysis systematically reviewed the effects of Gln enriched nutrition support on surgical patients with GI tumor from the aspects of relevant biochemical indices, immune indices and clinical outcomes. However, it also exists some limitations. Firstly, a large proportion of included studies came from China, literatures of other areas were relatively few, which may brought selection bias. Secondly, the thirteen included trials all mentioned randomization and parallel control, but did not about blind, which making some trials' study-quality score lower relatively. Thirdly, the study-quality score of Gianotti *et al*.[19] was three but the number of enrolled subjects was large, which will bring uncertainty biases to the final result of the meta-analysis. Fourthly, statistically significant results were not equal to the effective clinical significance, which provided clinical evidence for the effectiveness and the rational application of Gln to clinicians. Overall, more large-sample and multicenter RCTs are still needed to verification in the future.

Glutamine enriched nutrition support was superior in improving immune function, reducing the incidence of infectious complications and shortening the length of hospital stay, playing an important role in the rehabilitation of surgical GI cancer patients.

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