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Meta-analyses

Meta-analysis of the efficacy and safety of structured triglyceride lipid emulsions in parenteral nutrition therapy in China

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SUMMARY

Background & aims: We performed a meta-analysis of data from recent studies to evaluate the safety and efficacy of parenteral nutrition (PN) with structured triglyceride (STG) lipid emulsions compared to medium-chain triglyceride (MCT)/long-chain triglyceride (LCT) lipid emulsions in Chinese patients.

Methods: PubMed, Embase, Cochrane Library, China National Knowledge Internet, Wanfang, and VIP were searched for randomized controlled trials comparing STGs with MCTs/LCTs published in English or Chinese between January 1987 and October 2017. Two independent investigators screened and selected studies according to prespecified selection criteria. Data were pooled and analysed using RevMan® version 5.3.

Results: Thirty-two studies comprising 1944 patients were included in the meta-analysis. Compared with MCT/LCT emulsions, STGs resulted in a shorter hospital length of stay (LOS) (weighted mean difference [WMD], −1.65 days; 95% confidence interval [CI]: −2.63, −0.67; P = 0.001) and lower adverse event rates (relative risk, 0.64; 95% CI: 0.48, 0.85; P = 0.002). STGs were associated with a significantly better cumulative nitrogen balance (WMD, 4.04 g/24 h; 95% CI: 3.10, 4.97; P < 0.0001) as well as higher concentrations of pre-albumin (WMD 35.20 mg/L; 95% CI: 26.59, 43.81; P < 0.0001) and albumin (WMD, 1.64 g/L; 95% CI: 1.17, 2.10; P < 0.0001) compared with MCTs/LCTs. In contrast, significantly lower concentrations of plasma triglycerides (WMD, −0.21 mmol/L; 95% CI: −0.30, −0.12; P < 0.0001), total cholesterol (WMD, −0.45 mmol/L; 95% CI: −0.60, −0.29; P < 0.0001), alanine aminotransferase (WMD, −7.68 IU/L; 95% CI: −9.68, −5.68; P < 0.0001) and aspartate aminotransferase (WMD, −10.27 IU/L; 95% CI: −16.05, −4.49; P = 0.0005) were observed in patients receiving STGs compared with MCT/LCTs. STGs were also associated with reduced inflammation and improved immunological function, as reflected by significantly lower C-reactive protein concentrations (WMD, −2.67 mg/L; 95% CI: −4.55, −0.79; P = 0.005) and increased concentrations of IgG (WMD, 2.11 g/L; 95% CI: 0.23, 3.99; P = 0.03), IgA (WMD, 0.21 g/L; 95% CI: 0.14, 0.28; P < 0.0001), CD3+ (WMD, 5.81%; 95% CI: 0.92, 10.70; P = 0.02), and CD4+/CD8+ (WMD, 0.12; 95% CI: 0.00, 0.24; P = 0.04) compared with MCT/LCTs.

Conclusions: Administration of STGs was shown to improve hepatic function, nutrition status, and immunological function and reduce inflammation, LOS, and adverse events compared with MCT/LCTs in Chinese patients receiving PN.

1. Introduction

Lipid emulsions are an important component of parenteral nutrition (PN), as they not only supply both energy and essential fatty acids, but also contribute to cell membrane structure and function, gene expression, and immune regulation [1–3]. The metabolism of lipid emulsions occurs predominantly in the liver [4]. For patients receiving PN, long-term fasting can have a negative effect on liver function, resulting in complications such as cholestasis [5]. Choosing the appropriate lipid emulsion not only helps to ensure that energy demands are met, but also reduces the risk of liver function impairment, which represents a major clinical goal in patients requiring PN.

Long chain triglycerides (LCTs), which contain more than 16 carbon atoms on each free fatty-acid chain, were the first lipid emulsions used for PN. LCTs remain the most widely used lipid emulsions in PN;

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Abbreviations

Alb	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHE	Cholinesterase
CRP	C-reactive protein
DBil	Direct bilirubin
Ig	Immunoglobulin
LCFA	Long-chain fatty acid
LCT	Long-chain triglyceride
LOS	Length of stay
MCFA	Medium-chain fatty acid
MCT	Medium-chain triglyceride
PA	Pre-albumin
PN	Parenteral nutrition
RCT	Randomized controlled trial
STG	Structured triglyceride
TBil	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
WMD	Weighted mean difference

however, the use of LCTs alone can induce immunological and metabolic side effects [6,7]. Medium chain triglycerides (MCTs), by contrast, are metabolized via a separate pathway that is partially independent of carnitine-mediated transport into the mitochondria. As a result, MCTs are hydrolyzed twice as fast as LCTs [8]. However, pure MCT emulsions may be associated with an increased risk of metabolic acidosis, neurological toxicity, increased energy expenditure, and essential fatty acid deficiencies [9].

Structured triglycerides (STGs) are novel synthetic lipid emulsions obtained by hydrolyzing MCTs and LCTs to long-chain fatty acids (LCFAs), medium-chain fatty acids (MCFAs), and glycerol. Mixed triglyceride molecules of both LCFA and MCFA bound to the same glycerol backbone are randomly formed after re-esterification [10,11]. Compared with traditional MCTs/LCTs, STGs exhibit more rapid clearance from the blood, supply more energy, and have less influence on hepatic function [12]. STGs have also been shown to have favorable effects on weight gain, nitrogen balance, and serum albumin concentration in the burned rat [13].

To date, several clinical trials evaluating STGs have been performed and four meta-analyses have reported findings on the efficacy and safety of STGs [14–17]. However, the most recent meta-analysis was limited to studies published prior to September 2015 [17]. Although another recent meta-analysis included studies published between January 2007 and March 2017, the population was limited to surgical patients with liver disease [18]. Several additional randomized controlled trials (RCTs) evaluating STGs have been conducted in mainland China, but most were published in Chinese journals without peer review, thus limiting the degree to which meaningful inferences may be drawn from the results. Therefore, we performed a meta-analysis to assess recent data on the efficacy and safety of STGs compared to MCT/LCTs in China and provide evidence for the reasonable application of STGs in PN therapy in Chinese patients.

2. Materials and methods

2.1. Search strategy

The following electronic databases were searched for published RCTs comparing STG-based lipid emulsions with MCT/LCT physical mixtures: PubMed, Cochrane Library, Embase, China National Knowledge Internet, VIP data, and Wanfang data. The last search was performed in October 2017. The following search terms were used: (structured triglyceride OR structured triacylglycerol OR structured lipid OR structural lipid OR STGs) AND (randomized controlled trial OR RCT). The search was limited to RCTs in humans being conducted in China published in Chinese or English between January 1987 and October 2017.

2.2. Study selection

Eligible studies met the following inclusion criteria: (1) RCT in surgical and/or critically ill patients receiving PN, (2) study compared outcomes in patients receiving STGs or MCT/LCTs as a lipid source, and (3) published data were adequate for analysis. The following studies were excluded: (1) non-RCTs, (2) studies with duplicate publications, (3) studies with unbalanced matching, and (4) studies for which only an abstract or incomplete data were available.

2.3. Data collection

Two independent investigators performed the screening and the studies were selected according to the pre-specified selection criteria. Disagreement was resolved by discussion. The following data were extracted: total cholesterol (TC), plasma triglycerides (TG), albumin (Alb), nitrogen balance, adverse event rates, total bilirubin (TBil), direct bilirubin (DBil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), pre-albumin (PA), hospital length of stay (LOS), immunoglobulin (Ig) G, IgM, IgA, CD3+, CD4+, CD8+, CD4+/CD8+, glucose, total protein, and cholinesterase (CHE).

2.4. Statistical analysis

Statistical analysis was performed using RevMan version 5.3 (The Cochrane Collaboration). The weighted mean difference (WMD) was used to characterize the effect size for continuous outcome parameters and relative risk (RR) was used to characterize the magnitude of effect for dichotomous outcome parameters. A fixed effects model was used when there was no heterogeneity of the data ($P > 0.10$, $I^2 \leq 50\%$); otherwise, a random effects model was used. The data are presented as the point estimate and 95% confidence interval (CI) for the comparison between STGs and LCT/MCTs; $P < 0.05$ was considered statistically significant.

2.5. Assessment of risk of bias in individual studies

The risk of bias of the individual studies was evaluated based on the Cochrane Collaboration's recommended tool, which was used to assess bias in six categories: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias according to the quality checklist recommended in the Cochrane Handbook.

2.6. Additional analysis

Beside the main analysis (all studies), a sensitivity analysis about published time and populations was carried out. For published time analysis, only studies published in 5 years (after 2013) were included. A population analysis was performed under a new search, the search strategy was the same as 2.1, the only difference was the

inclusion criteria did not limit the language and patient's population.

3. Results

3.1. Characteristics of the included studies, quality and risk of bias assessment

The original search retrieved 215 records. Among these, 32 RCTs including 1944 patients met the pre-specified selection criteria and were included in the meta-analysis. A flowchart summarizing the stages of study selection is shown in Fig. 1; detailed characteristics of the selected studies are presented in Table 1. The study population included either critically ill or postoperative patients in all studies and all studies reported outcomes in patients randomized to treatment with either STGs or MCT/LCTs. Figure 2 shows the results of the assessment of risk of bias.

3.2. Meta-analysis

The chi-square test detected heterogeneity ($P < 0.1$ and $I^2 > 50\%$) for all outcomes except adverse events, Alb, DBil, and IgA. Therefore, the random effects model was used in most analyses, while a fixed model was used in the analysis of adverse events, Alb, DBil, and IgA.

ALT and AST values were reported in 12 (n = 755) and 10 (n = 675) RCTs, respectively. Meta-analysis of data from these trials showed significant between-group differences in both measures, with lower values observed in the STG group compared with the MCT/LCT group (ALT: WMD, −7.68 IU/L; 95% CI: −9.68, −5.68; $P < 0.0001$; AST: −10.27 IU/L; 95% CI: −16.05, −4.49; $P = 0.0005$). However, there were no significant differences between groups in TBil or DBil (Fig. 3).

Pre-albumin (PA) and serum albumin (Alb) concentrations were reported in 17 (n = 990) and 11 (n = 807) studies, respectively. For both markers, the meta-analysis showed significantly higher values for the STG emulsion compared to MCT/LCTs (WMD, 35.20 mg/L; 95% CI: 26.59, 43.81; $P < 0.0001$ and 1.64 g/L; 95% CI: 1.17, 2.10; $P < 0.0001$, respectively; Fig. 4). Additionally, STG emulsions were associated with significantly lower plasma concentrations of triglycerides and total cholesterol (WMD, −0.21 mmol/L; 95% CI −0.30, −0.12; $P < 0.0001$ and −0.45 mmol/L; 95% CI: −0.60, −0.29; $P < 0.0001$, respectively; Fig. 5).

Cumulative nitrogen balance is widely used as an index of the effectiveness of nutritional support. Meta-analysis of data from the 10 studies (n = 576) reporting cumulative nitrogen balance showed a statistically significant difference favoring STGs over MCT/LCTs (WMD, 4.04 g/24 h; 95% CI: 3.10, 4.97; $P < 0.0001$; Fig. 6). As shown in Fig. 7, STGs were also associated with a significantly lower plasma concentration of CRP, a marker of systemic inflammation (WMD, −2.67 mg/L; 95% CI: −4.55, −0.79; $P = 0.005$).

Comparison of immune function parameters in the STG and MCT/LCT groups showed statistically significant differences in four parameters, each favoring treatment with STGs. Compared with MCT/LCTs, STGs resulted in significantly higher concentrations of IgG (WMD, 2.11 g/L; 95% CI: 0.23, 3.99; $P = 0.03$), IgA (WMD, 0.21 g/L; 95% CI: 0.14, 0.28; $P < 0.0001$), CD3+ (WMD, 6.41%; 95% CI: 2.92, 9.91; $P = 0.0003$) and CD4+/CD8+ (WMD, 0.12; 95% CI: 0.00, 0.24; $P = 0.04$) (Figs. 8 and 9). No significant differences were observed between groups in other laboratory parameters, including glucose, total protein and CHE (Additional file 1).

Six studies (n = 426) reported data on hospital LOS. Meta-analysis of pooled data from these studies showed a significantly shorter mean LOS in patients receiving STGs compared with MCT/LCTs (WMD, −1.65 days; 95% CI: −2.63, −0.67; $P = 0.001$). Due to the lack of available data for individual adverse events, the overall incidence of adverse events in each treatment group was analyzed. STGs were associated with a statistically significant reduction in the risk of experiencing an adverse event compared with MCT/LCTs (RR 0.64; 95% CI: 0.48, 0.85; $P = 0.002$; Fig. 10).

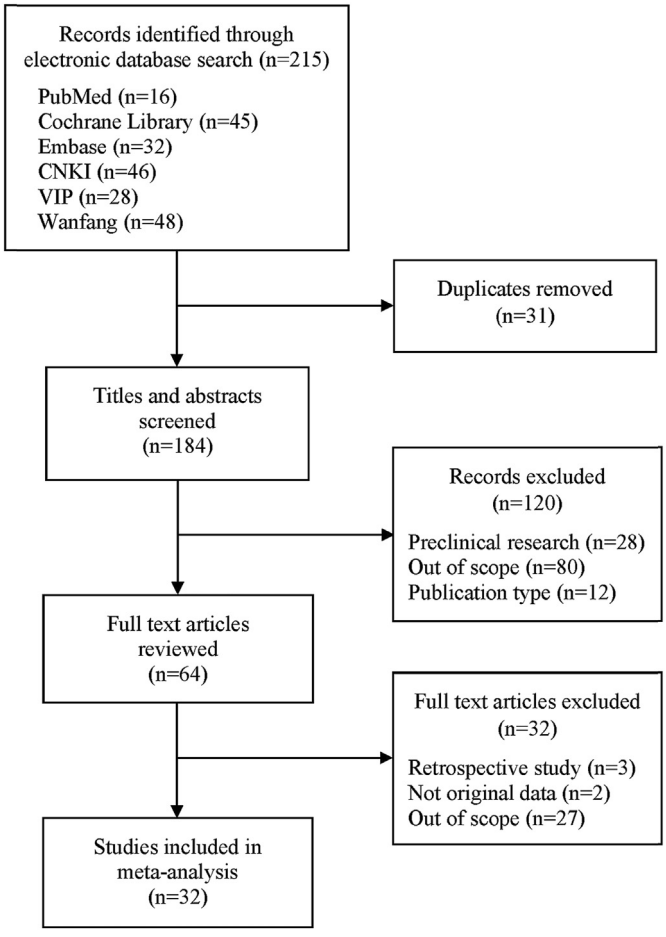

Fig. 1. Flow diagram of the stages of study selection.

3.3. Additional analyses

Only 4 RCT studies from France [51], Spain [52], Sweden [53] and Germany [54] were searched, and the effect estimated by population analysis is consistent with that of the main analysis (all studies) for nitrogen balance, AST, ALT, Alb and TBil (Additional file 1). For published time analysis, only studies published in 5 years (after 2013) were included, based on results, the administration of STGs provide similar benefit in both identified populations, except for AE, IgG and CD3+, in which the trend is maintained but the statistical significance is lost (Additional file 1).

4. Discussion

STGs are an alternative to physical MCT/LCT mixtures for patients who require PN treatment. Evidence from both animal studies and human trials shows that STGs are generally safe, well-tolerated, and associated with several potential advantages.

Lipid emulsions, which provide essential fatty acids and the energy to the body, are metabolized mainly in the liver. In addition to ensuring adequate nutrient provision, the preservation of liver function and lean body tissue are among the chief priorities in the

Table 1
Characteristics of the included studies.

Author, year	Population	Age, mean (SD)	Design	ITT	Control	Observation index	Considered outcomes
Bai L, 2009 [19]	Patients with gastrointestinal tumor and colorectal tumor	60.25 (9.05)	Randomized, blind, controlled	48	MCT/LCT	POD 1–6	TC, TG, N balance, PA, LOS
Bai X, 2015 [20]	Elderly patients after gastrointestinal tumor surgery	81.5 (10.3)	Randomized, controlled	68	MCT/LCT	POD 1–6	TP, ALB, PA, TC, TG, G, ALT, AST, TBil, DBil, CRP, CD3+, CD4+, CD8+, CD4+/CD8+
Bi XL, 2013 [21][a]	Patients with gastrointestinal tumor, Postoperative PN	61.5	Randomized, controlled	64	MCT/LCT	POD 1–6	N balance, CRP
Cai JP, 2017 [22]	Patients with pancreaticoduodenectomy	60.5 (20.3)	Randomized, controlled	70	MCT/LCT	POD 0–7	AST, ALT, AEs, TBil, PA, CD3+, TP
Chen HZ, 2013 [23][a]	Critically ill ICU patients	68 (6.8)	Randomized, controlled	80	MCT/LCT	Day 0–5	AST, ALT, ALP, TBil, TG, TC, AEs
Chen J, 2013 [24][a]	ICU patients with severe sepsis	71 (7.4)	Randomized, controlled	64	MCT/LCT	Day 1–7	AST, ALT, TG, PA, Alb, TC, G, LOS
Cao YQ, 2014 [25]	Patients with malignant obstructive jaundice	55.75 (5)	Controlled	63	MCT/LCT	Day 0–9	ALT, CHE, TBil, TG, TC, Alb, PA, IgA, IgG, IgM, CD4+, CD8+, CD4+/CD8+
Hao LW, 2015 [26]	Patients with severe bedsores	65.83 (13.98)	Randomized, controlled	24	MCT/LCT	Day 0–5	N balance
Jing K, 2010 [27][a]	Patients undergoing hepatectomy	49.9 (8.6)	Randomized, double-blind, controlled	125	MCT/LCT	POD 1–3/5	AST, ALT, TBil, Alb, TC, LOS
Li QX, 2014 [28]	Patients with severe craniocerebral injury	40 (5)	Randomized, controlled	80	MCT/LCT	Day 1/7	CRP, IgA, IgG, IgM, CD3+, CD4+, CD8+, CD4+/CD8+
Li YH, 2011 [29][a]	Critical ill ICU patients	38–68	Randomized, controlled	40	MCT/LCT	Day 0–6	AST, ALT, TG, PA, TC
Li Z, 2015 [30]	Elderly patients with acute biliary tract	80–95	Randomized, controlled	62	MCT/LCT	Day 0–7	TBil, DBil, TG, TC, G, N balance
Lu M, 2012 [31][a]	ICU patients requiring PN	55.1 (7.9)	Randomized, controlled	61	MCT/LCT	Day 0–5	TG, PA, Alb, TC, G, AEs
Luo HL, 2011 [32][a]	Patient with major abdominal surgery	60 (16)	Randomized, controlled	40	MCT/LCT	Day 0–5	TG, AST, ALT, AEs
Lu QQ, 2012 [33][a]	Patient with gastrointestinal cancer surgery	49.3 (8.5)	Randomized, double-blind, controlled	80	MCT/LCT	Day 0–7	AEs, LOS, IgA, IgG, IgM, CD3+, CD4+, CD8+
Lu QQ, 2014 [34]	Patient with gastrointestinal cancer surgery	54.7 (10.1)	Randomized, double-blind, controlled	80	MCT/LCT	Day 0–7	Alb, PA, CRP
Mao XL, 2010 [35][a]	Patients with gastrointestinal tumor	49.3 (8.5)	Randomized, double-blind, controlled	80	MCT/LCT	POD 1–7	N balance, PA, Alb, AEs
Peng N, 2017 [36]	Liver Carcinoma Patients after Hepatectomy	53.9 (7.9)	Randomized, controlled	100	MCT/LCT	Day 0–7	TC, AST, ALT, Alb, TG, TBil, CRP, PA, LOS
Shi XL, 2015 [37]	patients with primary liver cancer after hepatectomy	56	Randomized, double-blind, controlled	80	MCT/LCT	POD 0–7	ALT, AST, TBil, DBil, TP, Alb, PA, CRP, CHE, IgA, IgG, IgM, CD4+, CD8+, CD4+/CD8+
Shi YM, 2006 [38][a]	Patients with gastrointestinal surgery	55.9 (9.2)	Randomized, blind, controlled	60	MCT/LCT	POD 1–6	TG, PA, TC
Su MS, 2012 [39][a]	Patients with blood loss > 3000 mL before or during surgery	54.5 (9.1)	Randomized, controlled	20	MCT/LCT	POD 2–5/7	ALT, TBil, TG, PA
Tang C, 2015 [40]	Patients with gastrointestinal cancer	61.53 (4.32)	Randomized, controlled	82	MCT/LCT	POD 1–6	N balance, CRP
Tian N, 2014 [41]	Patients with multiple organ dysfunction syndrome	60 (11)	Randomized, double-blind, controlled	40	MCT/LCT	Day 0/1/3/7	N balance, PA, LOS
Wang XY, 2005 [42][a]	Patients with abdominal surgery	44 (17)	Randomized, controlled	24	MCT/LCT	POD 1–6	N balance, PA, LOS
Wang XY, 2006 [43][a]	Patients with abdominal surgery	48 (15)	Randomized, blind, controlled	40	MCT/LCT	Before and after injection at 2nd PN day	TG, TC
Wu ZS, 2013 [44][a]	Surgical patients with liver cancer	49.1 (1.8)	Randomized, controlled	66	MCT/LCT	POD 0–7	N balance, AST, ALT, TBil, PA, Alb, AEs
Yuan Y, 2012 [45][a]	Cirrhotic patients	59.3 (14.2)	controlled	26	MCT/LCT	Day 1–6	N balance, AST, ALT, TBil, PA, Alb, AEs
Yu YH, 2008 [46][a]	Patients with abdominal surgery	(N/A)	Randomized, controlled	50	MCT/LCT	POD 5	AST, ALT, AEs
Zhang GL, 2010 [47]	Patients with hematopoietic stem cell transplantation	32	Randomized, controlled	32	MCT/LCT	Day 14	AEs
Zhang Y, 2016 [48]	Patients with severe craniocerebral injury	40.7 (5.8)	Randomized, controlled	60	MCT/LCT	Day 0/7	CRP, IgA, IgG, IgM, CD3+, CD4+, CD8+, CD4+/CD8+
Zhou J, 2011 [49]	Hepatectomy in patients with hepatocarcinoma	47.9 (12.6)	controlled	49	MCT/LCT	POD 1–5	ALT, AST, PA, CRP, AEs
Zhuo DQ, 2010 [50][a]	Hepatic surgery patients	50 (14)	Randomized, double-blind, controlled	86	MCT/LCT	POD 1–7	N balance, TBil, PA, Alb

AEs = adverse events, Alb = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHE = cholinesterase, CRP = C-reactive protein, DBil = direct bilirubin, G = glucose, ICU = intensive care unit, Ig = immunoglobulin, ITT = intention to treat, LCT = long-chain triglyceride, LOS = length of stay, MCT = medium-chain triglyceride, N = nitrogen, PA = pre-albumin, POD = post-operative day, SD = standard deviation, STG = structured triglyceride, TBil-albumin, TC = total cholesterol, TG = triglycerides, TP = total protein.

[a] Data included in the meta-analysis by Wu et al. [16].

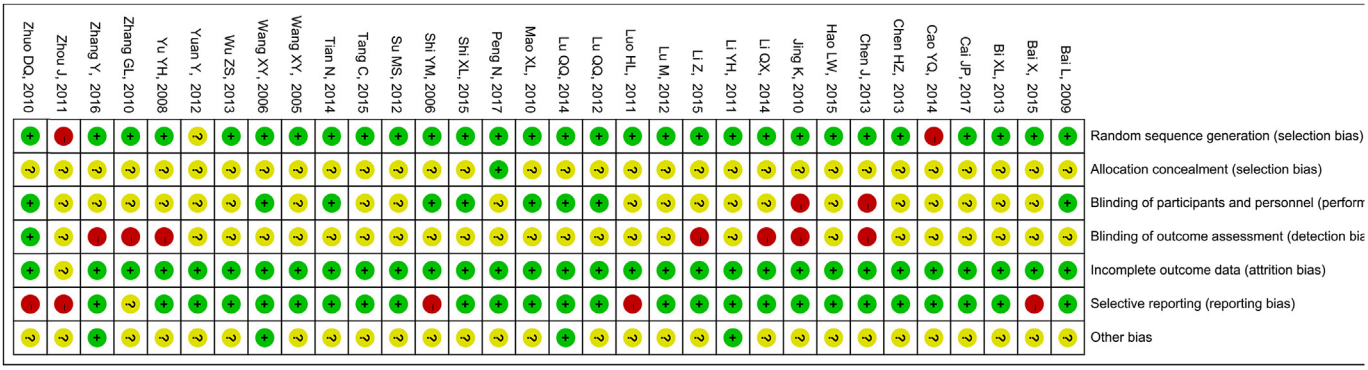

Fig. 2. Results of the assessment of risk of bias.

management of acutely ill patients requiring PN. The effect on measures of liver function and protein synthesis is therefore an important consideration in the administration of lipid emulsions. In the current study, we observed significant differences between STGs and MCT/LCTs in the effects on several measures of liver function and protein synthesis, including Alb, PA, AST, ALT, and cumulative nitrogen balance.

Alb and PA are both synthesized in the liver and serve as objective indicators of protein synthesis. The half-lives of Alb and PA are 20 days and 2–3 days, respectively; therefore, PA is a more sensitive indicator of acute changes in protein than Alb. Serum PA concentration is both a sensitive index for evaluating nutritional status and a true index of liver function [55,56]. Our findings showed that STG emulsions significantly increased the plasma concentrations of Alb and PA, indicating that STG emulsions decreased the burden on the liver and were beneficial in terms of inhibiting protein decomposition, reducing tissue consumption, and improving the metabolism of human body protein.

Several studies have shown that adverse events associated with lipid emulsions are closely related to the infusion rate and the specific pathways involved in the metabolism of the constituent lipids [57]. Although the LCFA and MCFA content of STGs and MCT/LCT mixtures is nearly the same, differences in the metabolic pathways can result in differences in the relative frequency of adverse events [4]. LCTs provide essential fatty acids, but long-term administration of LCTs is associated with a risk of metabolic complications and immune suppression [6,7]. Conversely, MCTs do not provide essential fatty acids; however, they are soluble in water and can be directly transported to the liver via the hepatic artery [8]. Additionally, MCTs are cleared more rapidly than LCTs and do not accumulate in the liver. Therefore, a physical mixture of MCTs and LCTs can provide complementary benefits and result in fewer side effects than single administration. Like MCT/LCT physical mixtures, STGs also combine the benefits of LCTs and MCTs; however, STGs are metabolized and cleared from the plasma more rapidly than MCT/LCT physical mixtures [2]. In the current meta-analysis, we found that the use of STGs resulted in significantly lower plasma TG and TC levels compared with MCT/LCTs. This finding is consistent with the more rapid clearance and hydrolysis of STGs into glycerol and fatty acids and suggests that STGs are likely to provide a more rapid source of calories than other lipid emulsions. Of note, significantly lower concentrations of AST and ALT were also seen in the STG group compared with the MCT/LCT group, further indicating that STGs did not increase the burden on the liver.

Another important consideration in the management of patients with critical illness or trauma is the systemic inflammatory response to acute stress which rapidly increases metabolic demands and accelerates proteolysis of lean tissue. [58,59] CRP is an acute phase protein that is elevated following traumatic stress and thus serves as a marker of systemic inflammation. Meta-analysis of data from seven RCTs in patients with clinical conditions associated with an acute inflammatory response showed significantly lower CRP levels in patients receiving an STG-based emulsion compared with an MCT/LCT mixture. To our knowledge, the current meta-analysis is the first to evaluate the relative effects of STGs and MCT/LCT mixtures on acute inflammation. Notably, the results suggest that STGs may attenuate the systemic inflammatory response to acute illness or surgical stress in patients requiring PN.

Surgical trauma also induces a state of stress that leads to disordered utilization of sugar and a negative nitrogen balance, which, in turn, exacerbates malnutrition and compromises immune function. Timely administration of adequate nitrogen and calories via PN can reverse the negative nitrogen balance in the immediate postoperative period and thus plays an important role in maintaining organ function and reducing surgical complications. [60] Meta-analysis of data from 10 trials in acutely ill and surgical patients showed a significant beneficial effect of STG administration on cumulative nitrogen balance compared to MCT/LCT mixtures, confirming observations from prior meta-analyses [14,16,17] and suggesting that treatment with STGs might induce a protein-sparing effect in both surgical and critically ill patients. Evidence from animal experiments suggest that the improved nitrogen balance associated with STGs might be attributable to the high oxidation rate, which results in a marked increase in the production of substrates required for protein synthesis, including ketone bodies [61,62].

Consistent with the observed effect on cumulative nitrogen balance, the meta-analysis also showed significant differences between the STG and MCT/LCT groups in several measures of immune function, including IgG, IgM, CD3+, and CD4+/CD8+. Among the T lymphocyte subgroups, CD3+ cells reflect the overall level of cellular immunity, whereas CD4+ T cells promote B cell differentiation to produce antibodies and secrete lymphatic factors, which in turn activate pro-inflammatory mediators. CD8+ T cells contribute to the adaptive immune response through the recognition and removal of intracellular pathogens, but can also inhibit antibody secretion and T-cell proliferation. Our analysis showed that both CD3+ and CD4+/CD8+ levels were significantly higher in the STG group compared with the MCT/LCT group, indicating that the reduction in the inflammatory response observed in the STG group was associated with recovery of immune function. Additionally, in contrast to prior reports suggesting that lipid emulsions can impair immune function [63], the higher concentrations of IgG,

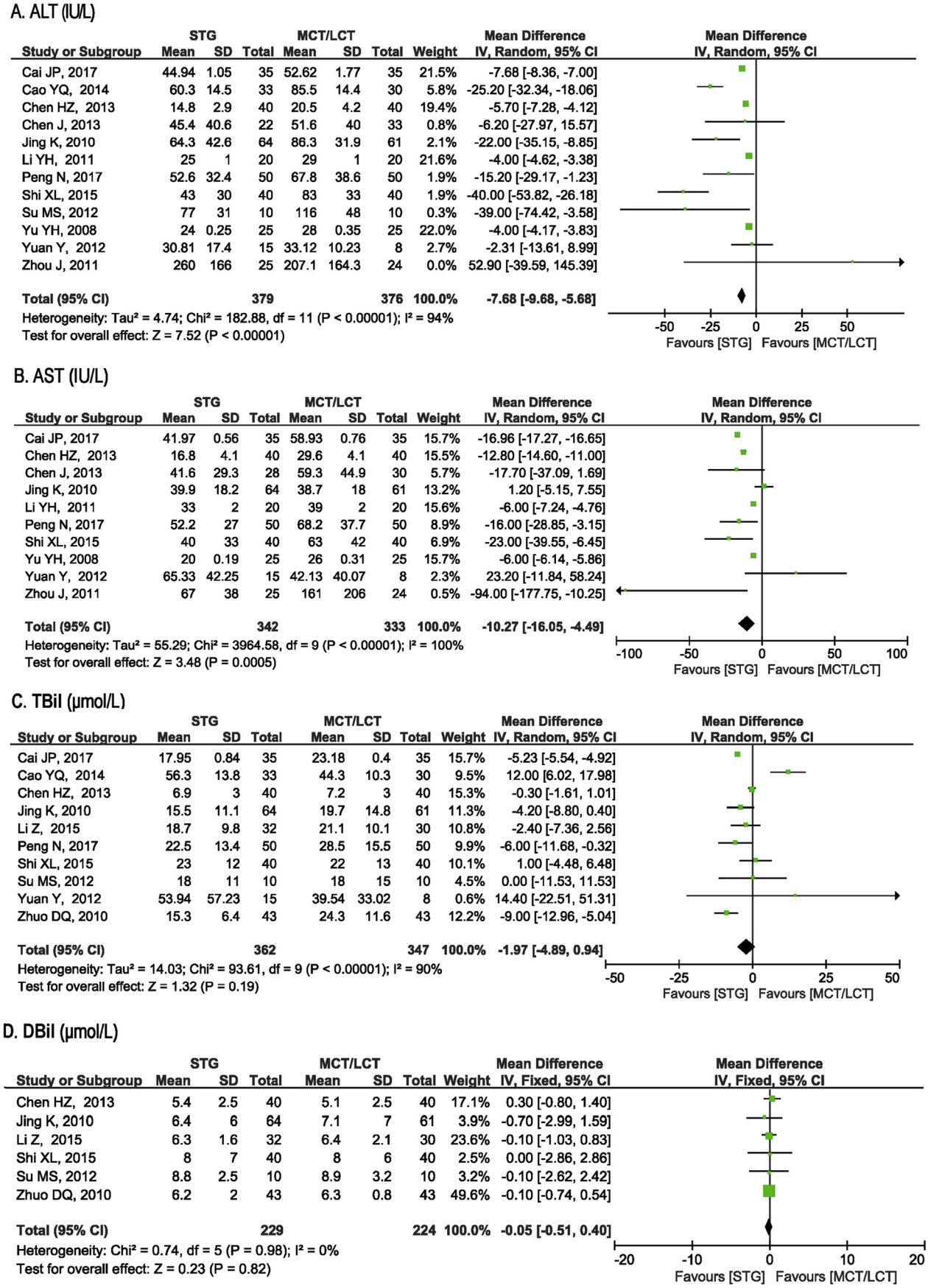

Fig. 3. Forest plots of the meta-analysis of the effect of STG versus MCT/LCT mixtures on ALT, AST, TBil, and DBil plasma concentration. ALT = alanine amino transferase, AST = aspartate aminotransferase, CI = confidence interval, DBil = direct bilirubin, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides, TBil = total bilirubin.

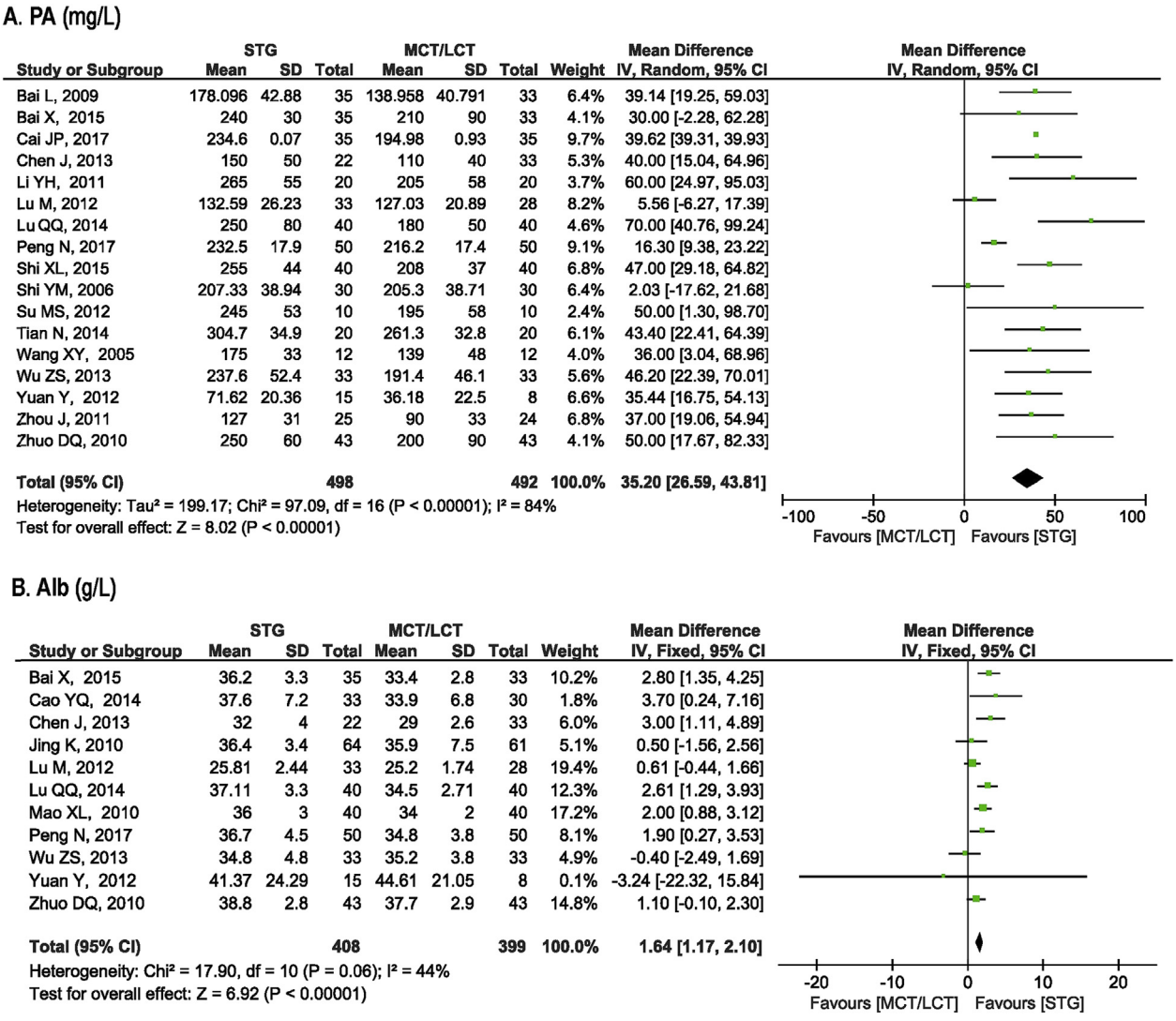

Fig. 4. Forest plots of the meta-analysis of the effect of STG versus MCT/LCT mixtures on plasma concentrations of PA and Alb. Alb = albumin; CI = confidence interval, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, PA = pre-albumin, SD = standard deviation, STG = structured triglycerides.

IgM, and CD3+ and CD4+/CD8+ cells observed in the STG group demonstrate that STGs can improve both cellular and humoral immune function.

Finally, meta-analysis of pooled data from trials evaluating hospital LOS and adverse events provided evidence that the beneficial effects of STGs on laboratory parameters translate into tangible clinical benefits. The mean LOS in the hospital was 1.65 days shorter and the risk of experiencing an adverse event was 36% lower among patients in the STG group compared with those in the MCT/LCT group. Based on a slightly smaller mean difference in LOS of −1.45 days in a prior meta-analysis, Wu et al. estimated that the use of STGs in Chinese critically ill and surgical patients is associated with a net cost benefit of ¥675 per patient compared with mixed MCT/LCT emulsions [17].

Our findings are generally consistent with previous meta-analyses evaluating STG-based lipid emulsions in Chinese patients [14,16,17]. Compared with the most recent meta-analysis by Wu et al. [17], the current analysis included an additional 5 RCTs and evaluated several additional parameters, including CRP, IgG, IgA, IgM, and CD3+, CD4+, CD8+ and CD4+/CD8+ cells. As a result, the current analysis yielded several new findings, including statistically significant benefits on measures of immunologic function and systemic inflammatory response in patients receiving STGs.

A limitation of the current study is that it only included RCTs performed in China; accordingly, the degree to which the findings are generalizable to other regions is unknown. To examine the influence of different literature criteria (selection bias) to the final results, a sensitivity analysis about published time and populations was carried out. If the results of the meta-analysis are reversed after changing the publishing time or patient populations, it should be warned if there is bias; if the changes are not significant, then the conclusion of the meta-analysis is more robust. We note, however, that STGs are mainly used in China and the current body of evidence is therefore largely based on studies conducted in Chinese populations. Additionally, heterogeneity ($P < 0.1$ and $I^2 > 50\%$) was found for most outcomes except adverse events, Alb, DBil, and IgA. The observed heterogeneity might be due to a variety of factors, including differences in study design, diagnosis, concomitant interventions, methods for controlling bias, and sample size.

In conclusion, based on the meta-analysis of data from RCTs, STG lipid emulsions appear to improve measures of hepatic function, nutrition status, and immunological function and reduce LOS and

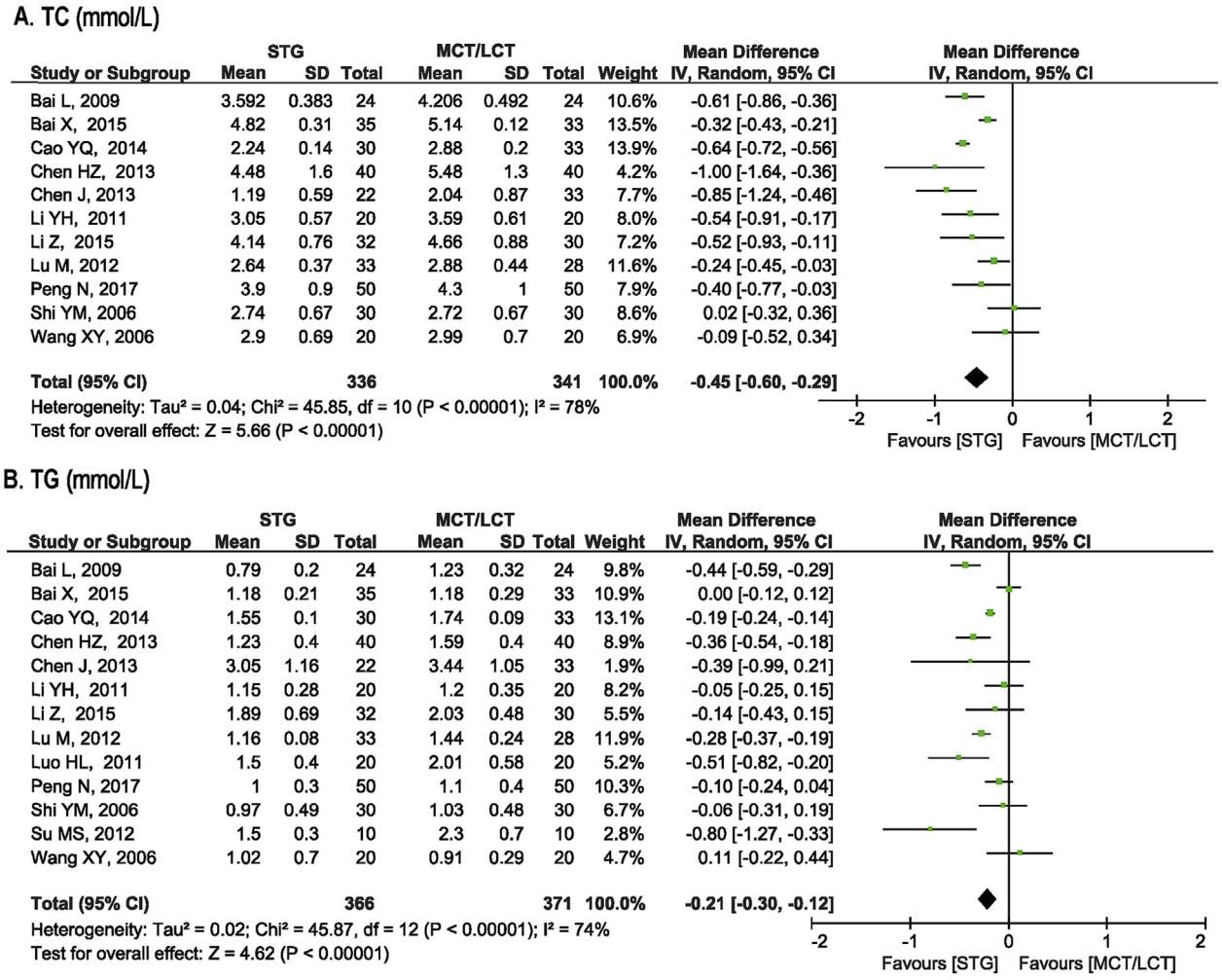

Fig. 5. Forest plots of the meta-analysis of the effect of STG versus MCT/LCT mixtures on plasma concentrations of TC and TG. CI = confidence interval, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides, TC = total cholesterol, TG = triglycerides.

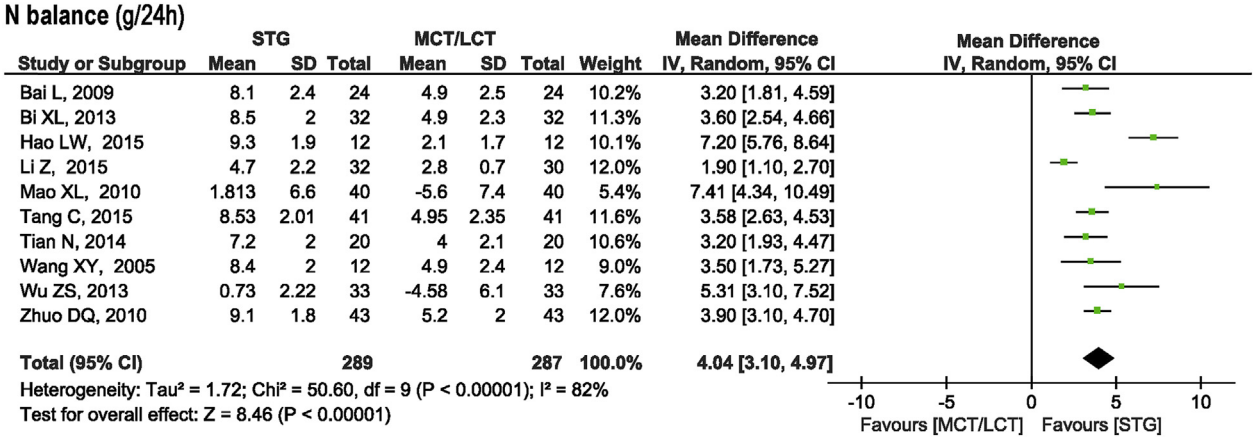

Fig. 6. Forest plot of the meta-analysis for the effect of STGs vs. MCT/LCT on nitrogen balance. CI = confidence interval, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides.

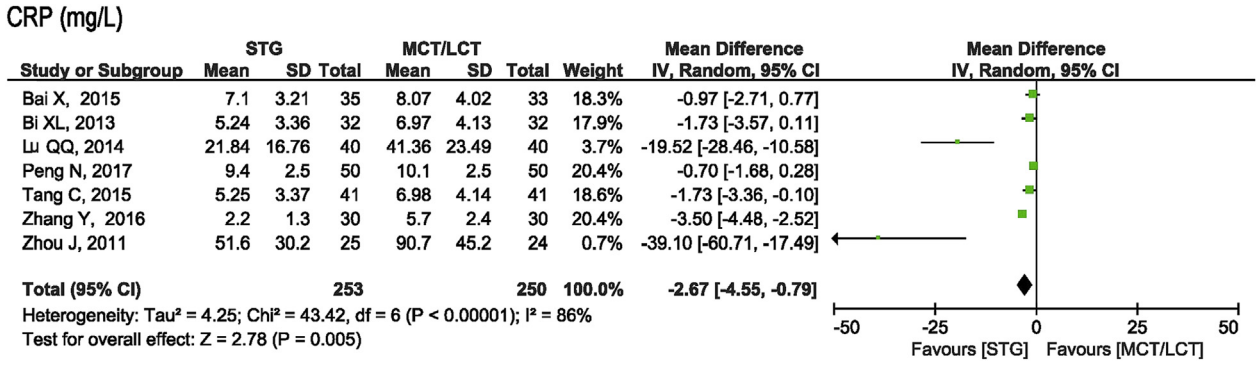

Fig. 7. Forest plot of the meta-analysis for the effect of STGs vs. MCT/LCT on the plasma concentration of CRP. CI = confidence interval, CRP = C-reactive protein, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides.

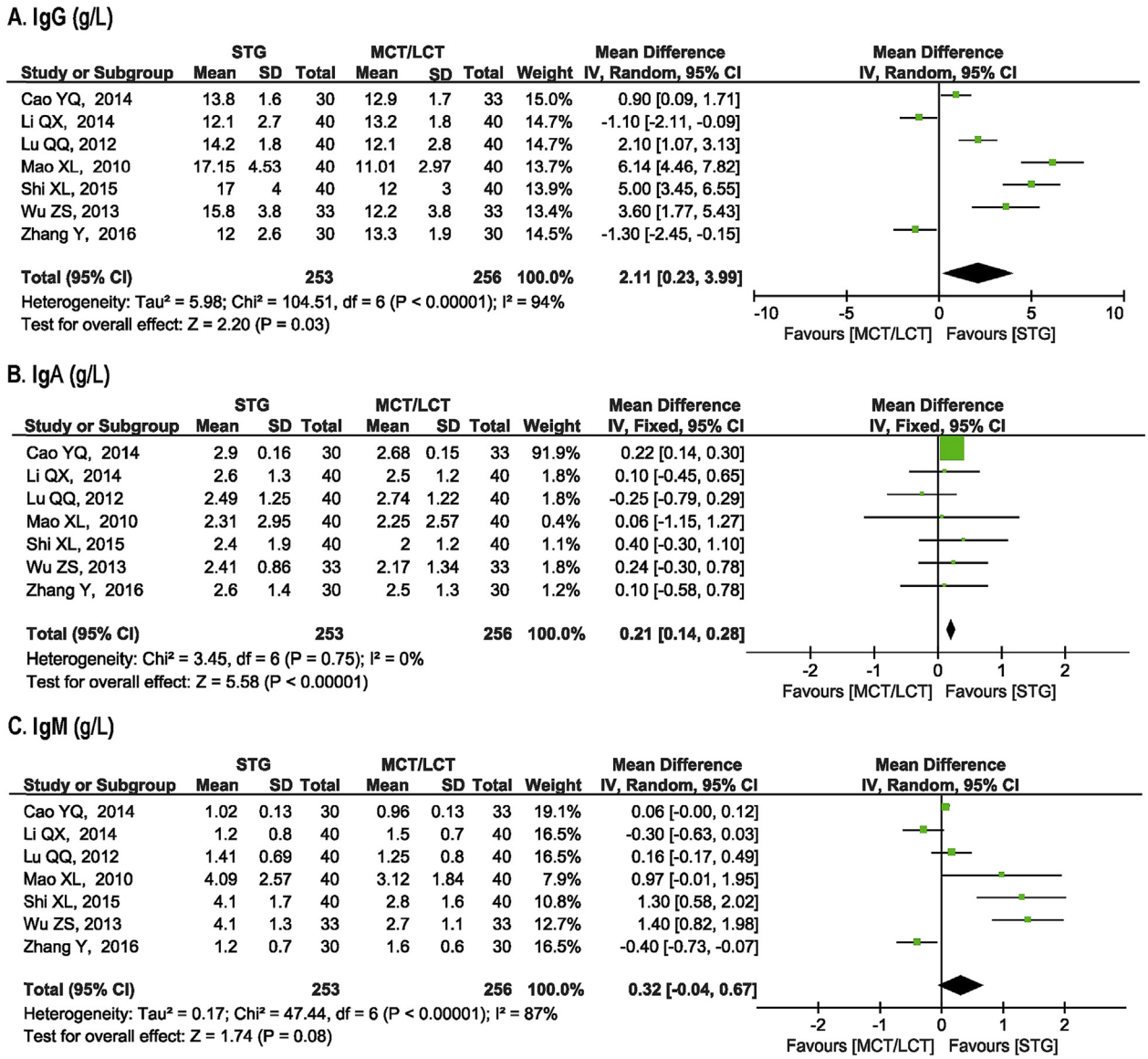

Fig. 8. Forest plots of the meta-analysis for the effect of STGs vs. MCT/LCT on (a) IgG, (b) IgA and (c) IgM. CI = confidence interval, Ig = immunoglobulin, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides.

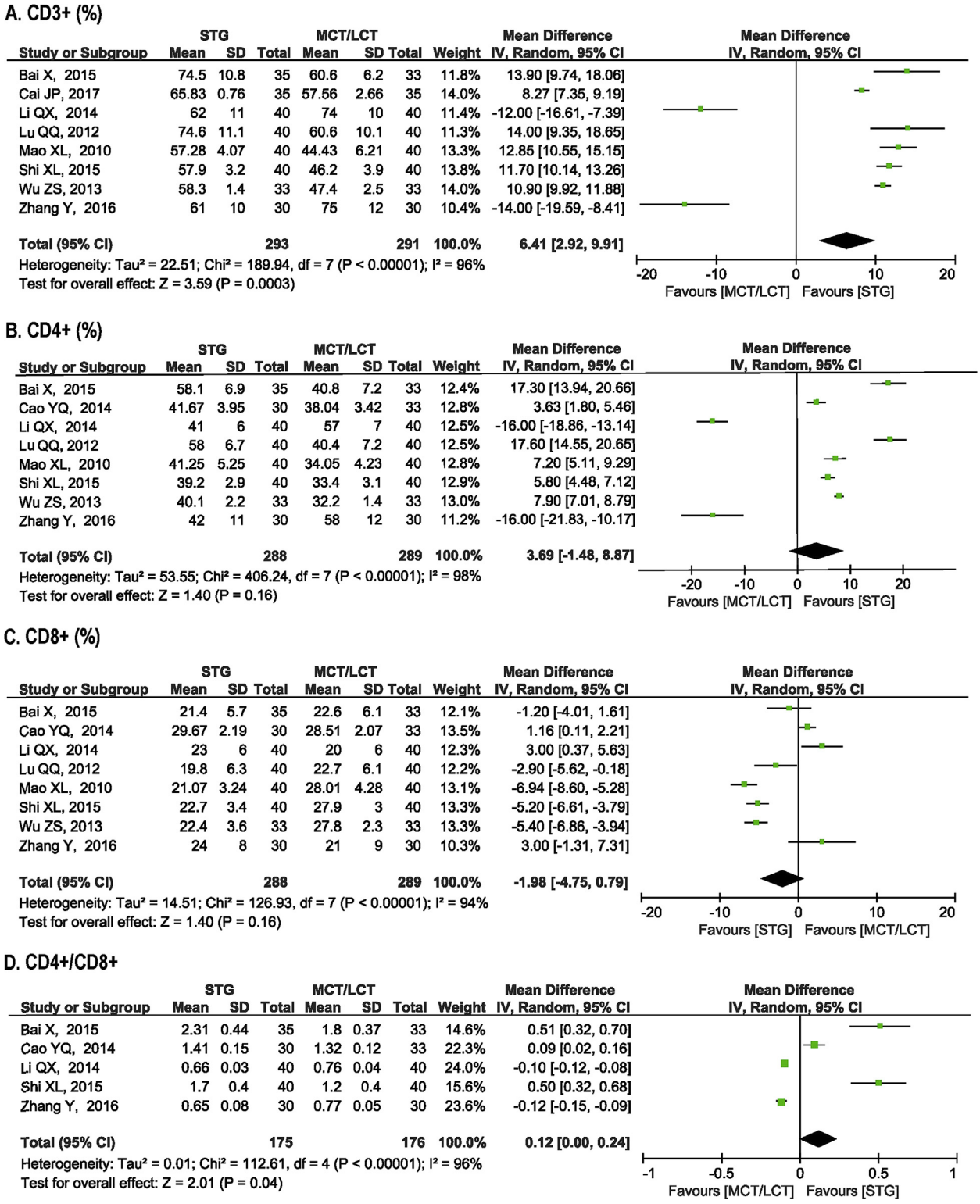

Fig. 9. Forest plots of the meta-analysis for the effect of STGs vs. MCT/LCT on (a) CD3+ cells, (b) CD4+ cells, (c) CD8+ cells, and (d) CD4+/CD8+ ratio. CI = confidence interval, LCT = long-chain triglycerides, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides.

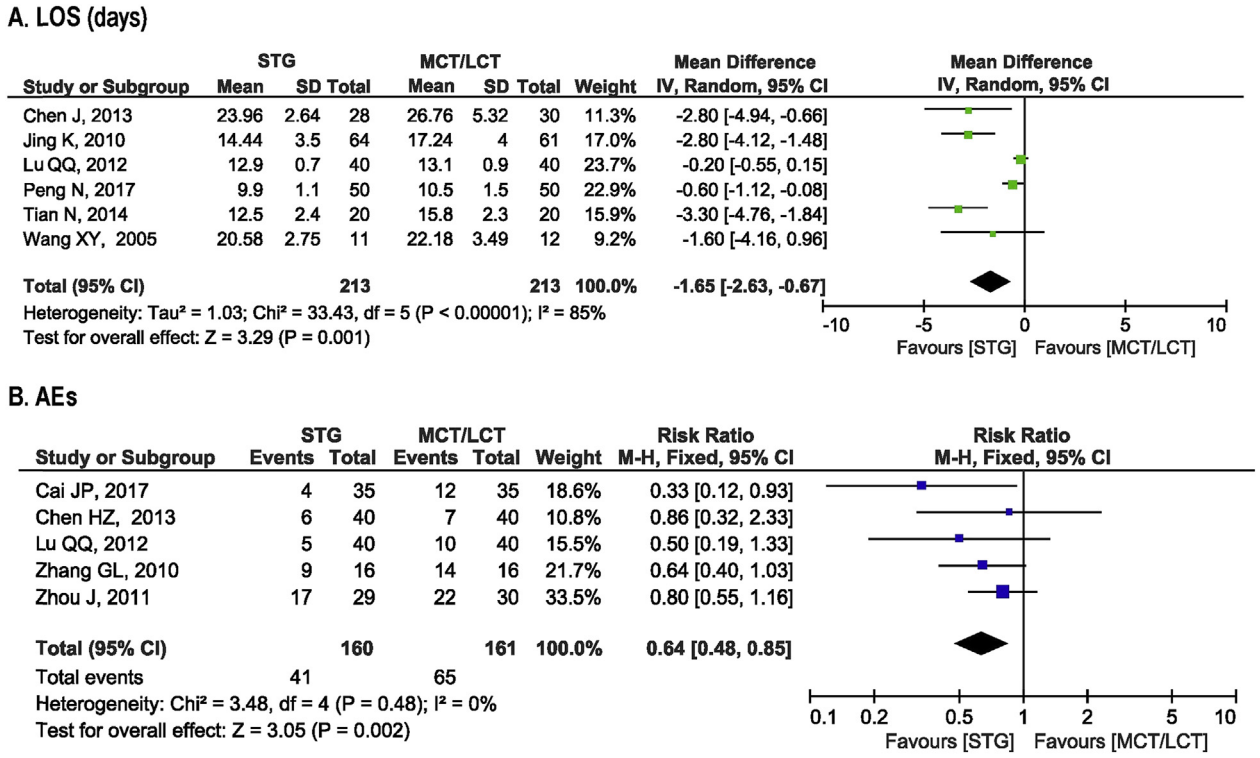

Fig. 10. Forest plots of the meta-analysis for the effect of STGs vs. MCT/LCT on clinical outcomes. AEs = adverse events, CI = confidence interval, LCT = long-chain triglycerides, LOS = length of stay, MCT = medium-chain triglycerides, SD = standard deviation, STG = structured triglycerides.

adverse events compared with MCT/LCT physical mixtures in Chinese patients requiring PN.

Author's contributions

The contributions of respective authors are as follows: Chao Li analyzed the data and drafted the manuscript; Qian Ni, Yi-Fang Pei, and Yi Ren searched and selected the studies and extracted data; Yu-Fei Feng directed the research. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.013.

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