Surgical Oncology 21 (2012) e87–e95

Contents lists available at SciVerse ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Perioperative immunonutrition for gastrointestinal cancer: A systematic review of randomized controlled trials

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ARTICLE INFO

Article history:
Accepted 10 January 2012

Keywords:
Immunonutrition
Gastrointestinal cancer
Randomized controlled trials
Meta-analysis

ABSTRACT

Background: To improve the clinical outcome, immunonutrition (IN) was usually used in the patients undergoing elective gastrointestinal caner surgery. However, its effectiveness remains uncertain.
Methods: Randomized controlled trials (RCTs) published between 1995 and 2011 were identified and extracted by two reviewers independently from electronic databases, including PubMed, EMBASE, and Cochrane Library. The quality of included trials was assessed according to the handbook for Cochrane reviewer (V5.0.1). Statistical analysis was carried out with RevMan software.
Results: Nineteen RCTs involving a total of 2331 patients were included in our meta-analysis. The results showed perioperative IN significantly reduced length of hospital stay (WMD, −2.62; 95% CI, −3.26 to −1.97; $P < 0.01$) and morbidity of postoperative infectious complication (RR, 0.44; 95% CI, 0.32 to 0.60; $P < 0.01$) compared with standard diet. Moreover, perioperative IN also significantly decreased morbidity of postoperative non-infectious complication in comparison with standard diet (RR, 0.72; 95% CI, 0.54 to 0.97; $P = 0.03$).
Conclusion: Perioperative IN is effective and safe to reduce postoperative infection, non-infection complication and length of hospital stay.

Contents

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doi:10.1016/j.suronc.2012.01.002

Introduction

Patients undergoing elective gastrointestinal cancer surgery are at high risk of developing postoperative infection due to several factors, such as malnutrition, tumor-induced immune suppression, surgical stress, and blood infusion, etc [1]. Among them, malnutrition is the most important factor, and has negative impact on clinical outcome [2].

Recently, several reports have demonstrated immunonutrition (IN) may be a good choice to decrease infection risk in patients who underwent gastrointestinal operation. For example, enteral nutrition with supplemental arginine, ω-3 polyunsaturated fatty acids (ω-3 PUFA), glutamine (Glu) or ribonucleic acid (RNA) has been proved to enhance immune function compared with standard diet [3–5]. But the clinical effects reported by these studies are inconsistent, and the optimal period of IN administration is still unclear.

Meta-analysis has been applied in medical research to improve statistical efficiency and subsequently draw reliable conclusions from studies with similar topic and methodology but reporting inconsistent results. In addition, a meta-analysis can provide promising direction for future research and guideline for clinical treatment [5]. The purpose of this study was to assess the effects of IN on postoperative complications and length of hospital stay through a meta-analysis based on randomized controlled trials (RCTs).

Materials and methods

Inclusion criteria

Inclusion criteria of this study were: 1) Type of study: we only considered randomized controlled trials (RCTs) with or without blinding method; 2) Eligible patients: patients with digestive system malignancy and undergoing elective surgery were considered; 3) Interventions: The trials compared perioperative IN diet with standard diet. IN diet included at least two of following nutrients: arginine, glutamine, ω-3 PUFA or RNA. IN administration was performed at three periods, including pre-operation period, both pre- and post-operation period, or post-operation period; 4) Outcome measurements: Postoperative complications (including infectious and non-infectious complications) and length of hospital stay.

Search strategy

A computerized literature search was applied to the following electronic databases: PubMed (1995–2011.4), EMBASE (1995–2011.4), the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (1995–2011.4). Medical subject heading (MeSH) terms were used for searching PubMed. ((“Esophageal Cancer”) OR (“Gastric cancer”) OR (“Hepatic cancer”) OR (“Colon cancer”) OR (“Rectal cancer”) OR (“Pancreatic cancer”) OR (“Digestive System Neoplasms”) OR (“gastrointestinal cancer”) OR (“colorectal cancer”) OR (“bile duct cancer”) OR (“Gallbladder cancer”)) AND ((immunonutrition OR Arginine OR (“omega-3 fatty acid”) OR Glutamine OR RNA)) AND ((“diet supplementation”) OR (“nutritional support”) OR (“Parenteral nutrition”) OR (“Enteral nutrition”) OR (“enteric feeding”) OR “diet therapy”)) AND (postoperative OR perioperative OR preoperative OR surgery) were used as keywords. Excerpta Medica Tree (EMTREE) was used for searching EMBASE with identical keywords as used in PubMed. The researching words were immunonutrition for Cochrane database. In addition, electronic links to related

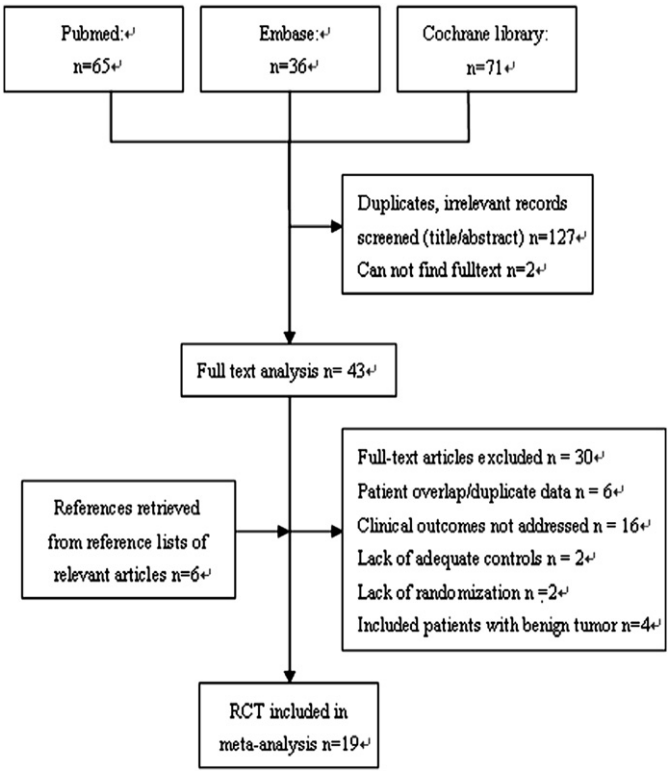

Figure 1. Flow chart showed detail information for article inclusion and exclusion.

Table 1
Characteristics of included randomized trials.

Trials	Yr	Country	Procedure	Baseline (IN: Control)	Surgical variables (IN: Control)	Antibiotic prophylaxis
Daly	1995	USA	UGI	NS	NS	Before surgery and 1 d after surgery
Schilling	1996	Switzerland	UGI, LGI	NS	NS	During induction of anesthesia
Heslin	1997	USA	UGI	NS	Anesthesia time: IN > control	Not stated
Senkal	1997	Germany	UGI	NS	NS	Before surgery
Gianotti	1997	Italy	UGI	NS	NS	During induction of anesthesia, the 2nd dose if >4 h
Braga	1998	Italy	UGI	NS	NS	During induction of anesthesia, the 2nd dose if >4 h
Braga	1999	Italy	UGI, LGI	NS	NS	30 min before surgery, the 2nd dose if >4 h
Di Carlo	1999	Italy	UGI	NS	NS	During induction of anesthesia, the 2nd dose if >4 h
Senkal	1999	Germany	UGI	NS	NS	before the surgery
Braga	2002	Italy	UGI, LGI	NS	NS	30 min before surgery, the 2nd dose if >4 h
Braga-2	2002	Italy	LGI	NS	NS	30 min before surgery, the 2nd dose if >4 h
Gianotti	2002	Italy	UGI, LGI	NS	NS	30 min before surgery, the 2nd dose if >4 h
Farreras	2005	Spain	UGI	concentration of protein: IN > control, age: IN < control, weight: IN > control	NS	Before surgery
Xu	2006	China	UGI, LGI	NS	NS	30 min before surgery, the 2nd dose if >4 h
Klek	2008	Poland	UGI	NS	NS	Postoperative period.
Gunerhan	2009	Turkey	UGI, LGI	NS	NS	Not stated
Okamoto	2009	Japan	UGI	NS	Operative time: IN > control	During induction of anesthesia, the 2nd dose if >4 h
Suzuki	2010	Japan	UGI	NS	NS	During induction of anesthesia, the 2nd dose if >4 h, post 3 d
Klek	2010	Poland	UGI	NS	NS	Not stated

IN, immunonutrition; UGI, upper gastrointestinal surgery; LGI, lower gastrointestinal surgery; NS, not significant.

articles and references of selected articles were hand-searched. Only articles written in English were considered to be eligible.

Quality assessment

The quality of included RCTs was assessed by two reviewers independently according to the handbook for Cochrane reviewer (V5.0.1) [6], such as: Randomized method (YES, NO, UNCLEAR), Allocation sequence concealment (YES, NO, UNCLEAR), Blinding (YES, NO, UNCLEAR), Incomplete outcome data (YES, NO, UNCLEAR), Selective outcome reporting (YES, NO, UNCLEAR), and other sources of bias (YES, NO, UNCLEAR). Disagreements were resolved by consensus with a third reviewer.

Statistical analysis

Statistical analysis was performed with Cochrane Collaboration's RevMan5.0.2 software. $P < 0.05$ was considered statistically significant. Heterogeneity was measured through χ^2 and I^2 test. If between-study heterogeneity existed ($I^2 > 50\%$), random-effect model was used; otherwise, meta-analysis was done with fixed-effect model. The intervention effect was expressed with odds ratio (OR) for the dichotomous variable and weighted mean difference (WMD) for the continuous variable, with 95% confidence

Table 2
Characteristics of included randomized trials.

Trials	Yr	Patient (groups analyzed)	Group		Immunonutrition		
			Study	Control	Contents	Dose (4 days after operation)	Preop./postop duration (days)
Daly	1995	60 (30/30)	Postop.	ICN	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/open
Schilling	1996	45 (14/14/13)	post	IC, IV	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/open
Heslin	1997	195 (81/83)	Postop	IVF	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/open
Senkal	1997	164(77/77)	Postop	IC	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/5
Gianotti	1997	260(87/87/86)	postop	ICN, TPN	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/7
Braga	1998	166(55/55/56)	postop	ICN, TPN	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/8
Braga	1999	206(85/86)	periop	ICN	Arg, *n*−3FA, RNA	1 l/1.5 l	7/7
Di Carlo	1999	100(33/35/32)	postop	ICN, TPN	Arg, *n*−3FA, RNA	25 kcal/kg/day	-/open
Senkal	1999	178 (78/76)	Periop	ICN	Arg, *n*−3FA, RNA	1 l/(25 kcal/kg/day)	5/5
Braga	2002	150(50/50/50)	peri, pre	ICN	Arg, *n*−3FA, RNA	1 l/(28 kcal/kg/day)	7/7
Braga-2	2002	200(50/50/50/50)	peri, pre	ICN, RD	Arg, *n*−3FA, RNA	1 l/1.5 l	5/open
Gianotti	2002	305(101/102/102)	peri, pre	IV + RD	Arg, *n*−3FA, RNA	1 l/1.5 l	5/open
Farreras	2005	66(30/30)	Post	ICN	Arg, *n*−3FA, RNA	Harris-Benedict formula	-/7
Xu	2006	60(30/30)	pre	ICN	Arg, *n*−3FA, RNA	25 kcal/kg/day	7/-
Klek	2008	205(52/51/53/49)	Post	ICN	Arg, *n*−3FA, Glu,	75 ml/h	-/7
Gunerhan	2009	56 (13/11/9)	pre	IC, RD	Arg, *n*−3FA, RNA	Harris-Benedict formula	7/-
Okamoto	2009	60 (30/30)	pre	IC	Arg, *n*−3FA, RNA	750 ml/d	7/-
Suzuki	2010	30(10/10/10)	peri, post	TPN	Arg, *n*−3FA, RNA	750 ml/(25 kcal/kg/day)	5/7
Klek	2010	305(152/153)	Post	ICN	Arg, *n*−3FA, Glu	75 ml/h	-/7

preop, preoperative IN; postop, postoperative IN; periop, preoperative IN and postoperative IN combined; ICN, isocaloric and isonitrogenous; IC, isocaloric; TPN, total parenteral nutrition; IV, intravenous glucose or saline solution; RD, regular diet; Arg, arginine; *n*-3 FA, omega-3 fatty acids (unsaturated); Glu, glutamine.

intervals (95% CI). If the included trials have the clinical heterogeneity, we would only describe their characteristics. If necessary, sensitivity analysis was performed to test the stability of our results.

Results

Study characteristics

The electronic literature search yielded 172 studies potentially fitting for exclusion inclusion. Of these studies, 127 studies were excluded because of obvious irrelevance to our topic by reviewing the titles and abstracts. Two studies without full-text were thus excluded. Thirty studies with full texts were further excluded, because: i) six trails had overlapping dates, ii) sixteen trails did not address clinical outcomes, iii) two trails were lacking of adequate controls, iv) two trails were lacking of randomization and v) four trials contained some patients with benign tumor (Fig. 1). Ultimately, nineteen RCTs with 2331 patients met the specified inclusion criteria [3,7–24]. Characteristics of included RCTs presented in Table 1 and Table 2. Three out of nineteen trials showed significantly different outcomes between IN and control treatment. Nine trials were done to compare postoperative IN with standard diet, 2 trials were for comparing perioperative IN with standard diet, one trial was for comparing postoperative and perioperative IN with standard diet, 3 trials were for comparing perioperative and preoperative IN with standard diet, 4 trials were for comparing preoperative IN with standard diet. Dates of the clinical outcome were listed in Table 3.

Table 3
Outcome measures of included randomized trials.

Trials	Yr	Group	LOS	Infectious complication	Non-infectious complication
*Daly	1995	postop	16 ± 0.9	1/30	2/30
		ICN	22 ± 2.9	8/28	7/28
Schilling	1996	Postop	14.5 ± 8	3/14	–
		IC	14 ± 19	6/14	–
		IV	14 ± 10.3	6/13	–
Heslin	1997	postop	11 (5–41)	14/81	–
		IV	10 (6–75)	16/83	–
Senkal	1997	postop	27 ± 2.3*	14/77	7/77
		IC	30.6 ± 3.1*	19/77	10/77
Gianotti	1997	postop	16.1 ± 6.2	13/87	–
		ICN	19.2 ± 7.9	20/87	–
		TPN	21.6 ± 8.9	24/86	–
Braga	1998	postop	13.7 ± 4.8	9/55	9/55
		ICN	16.1 ± 5.9	13/55	7/55
		TPN	17.5 ± 6.1	16/56	13/56
*Braga	1999	periop	11.1 ± 4.4	9/85	7/85
		ICN	12.9 ± 4.6	21/86	8/86
*Di Carlo	1999	postop	16.3 ± 6.2	3/33	8/33
		ICN	17.8 ± 6.9	6/35	8/35
		TPN	19.3 ± 8.0	8/32	11/32
*Senkal	1999	periop	22.2 ± 4.1*	9/78	3/78
		ICN	25.8 ± 3.8*	14/76	9/76
Braga	2002	periop	12.0 ± 3.8	6/50	12/50
		preop	13.2 ± 3.5	10/50	16/50
		ICN	15.3 ± 4.1	13/50	19/50
Braga-2	2002	periop	9.8 ± 3.1	5/50	5/50
		preop	9.5 ± 2.9	6/50	4/50
		ICN	12.0 ± 4.5	16/50	3/50
		RD	12.2 ± 3.9	15/50	4/50
Gianotti	2002	periop	12.2 ± 4.1	16/101	28/101
		preop	11.6 ± 4.7	14/102	30/102
		IV + RD	14.0 ± 7.7	31/102	36/102
Farreras	2005	postop	13 (11–22)*	2/30	0
		ICN	15 (10–22)*	9/30	8/30
Xu	2006	preop	9 ± 3.2	2/30	2/30
		ICN	12 ± 3.7	8/30	3/30
Klek	2008	Postop-EN	13.1 ± 4.1	13/52	–
		Postop-PN	12.5 ± 3.3	15/51	–
		ICN	12.4 ± 3.9	12/53	–
		TPN	12.9 ± 4.9	13/49	–
Gunerhan	2009	preop	16.54 ± 14.83	–	5/13
		IC	14.22 ± 9.12	–	2/11
		RD	12 ± 3.69	–	3/9
Okamoto	2009	preop	23.8 ± 16.6	2/30	4/30
		IC	25 ± 10.6	8/30	4/30
Suzuki	2010	periop	–	1/10	2/10
		Postop	–	6/10	7/10
		TPN	–	6/10	4/10
Klek	2010	postop	13.1 ± 13.8	43/152	–
		ICN	17.1 ± 12.2	60/153	–

LOS, length of postoperative hospital stay; "–" indicates no available date; "*" indicates length of hospital stay defined as time from admission to discharge.

Methodological quality of studies

The methodological qualities of included RCTs were comprehensively assessed, and results were shown in Table 4. Nine trials described how the random allocation sequence was generated, while in other ten trials the allocation was only said to be "randomized", and detailed method was not specified. Ten trials described the detail method used to conceal the allocation sequence. Twelve studies reported blinding of patients, the investigator or assessor.

Comparison between postoperative IN and standard diet

Eleven trials including 1246 patients were included in this meta-analysis. Six hundreds and twenty one patients and 625 patients were randomized to postoperative IN group and standard diet group respectively [7–12,14,19,21,23,24].

All trials reported postoperative infectious complication, but only two trials showed morbidity of postoperative infectious complication was lower in IN group than that in standard diet group. Through pooled analysis, statistically significant differences were present between the two groups (RR, 0.69; 95% CI, 0.57 to 0.84; $P < 0.01$) (Fig. 2A). Six trails documented the morbidity of postoperative non-infectious complication [7,10,12,14,19,23]. Farreras showed the rate of non-infectious complication was significantly reduced in the postoperative IN group than that in the standard diet group. However, no significant differences were observed between these two groups through pooled analysis (RR, 0.81; 95% CI, 0.41 to 1.59; $P = 0.54$) (Fig. 2B). Nine trails reported

Table 4
Methodologic quality assessment of included studies.

Trials	Yr	Randomization	Allocation concealment	Blinding	Lost to follow-up
Daly	1995	unclear	Adequate	Single blind	No lost
Schilling	1996	Unclear	unclear	No	stated
Heslin	1997	unclear	Adequate	Single blind	stated
Senkal	1997	Adequate	Adequate	Double blind	stated
Gianotti	1997	unclear	unclear	Single blind	No lost
Braga	1998	Unclear	unclear	Single blind	stated
Braga	1999	Unclear	Adequate	Double blind	stated
Di Carlo	1999	Unclear	unclear	No	stated
Senkal	1999	Adequate	Adequate	Double blind	stated
Braga	2002	Adequate	unclear	Single blind	stated
Braga-2	2002	Adequate	unclear	Single blind	stated
Gianotti	2002	Adequate	unclear	Single blind	stated
Farreras	2005	Adequate	Adequate	Double blind	stated
Xu	2006	Unclear	unclear	No	No lost
Klek	2008	Adequate	Adequate	No	stated
Gunerhan	2009	Unclear	unclear	No	stated
Okamoto	2009	Adequate	Adequate	Single blind	No lost
Suzuki	2010	Unclear	Adequate	No	No lost
Klek	2010	Adequate	Adequate	No	Stated

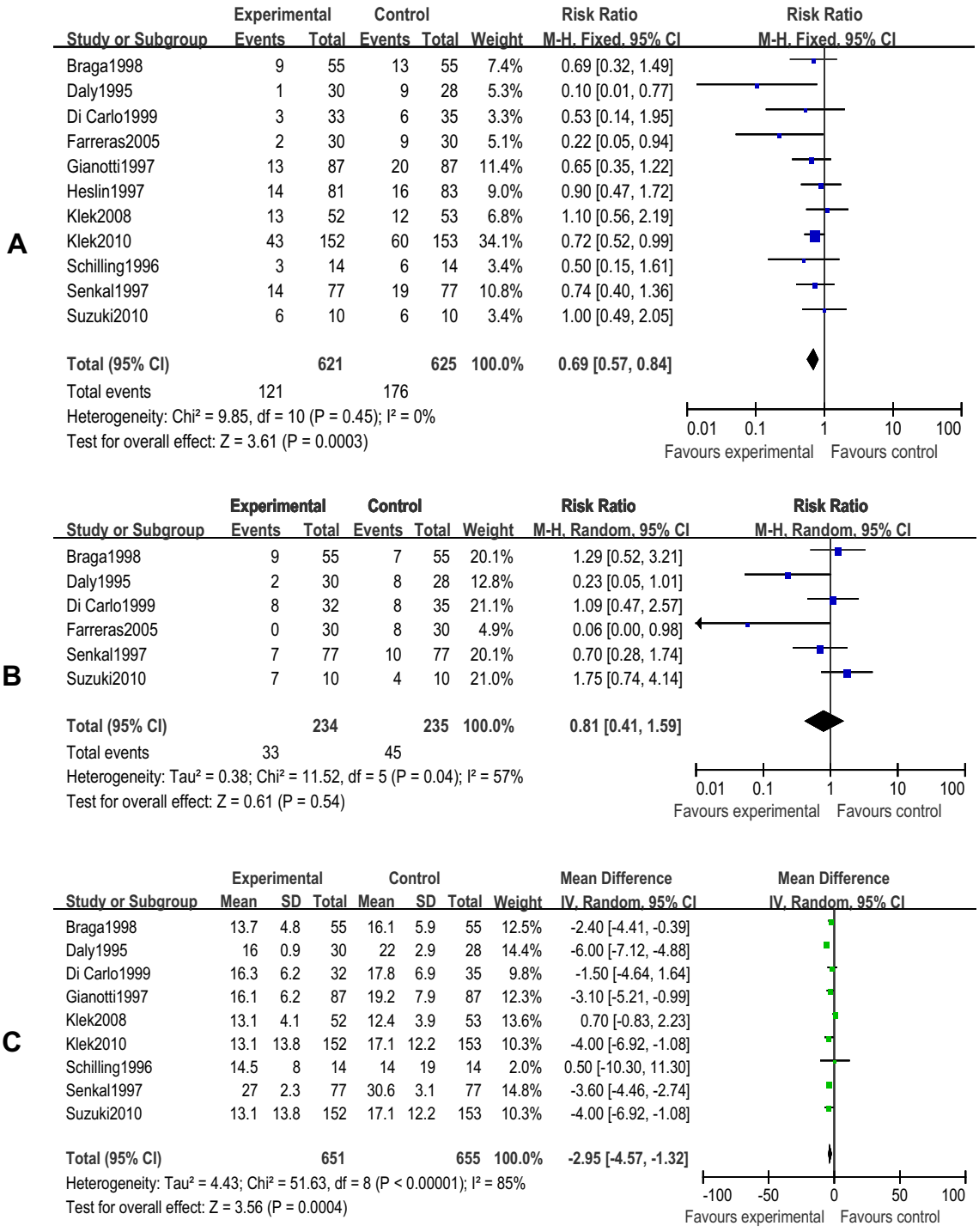

Figure 2. Compared effect of postoperative IN and standard diet on postoperative infectious, non-infection complication, and length of hospital stay. A: postoperative infectious complication; B: postoperative non-infectious complication; C: length of hospital stays.

the length of hospital stay [7,8,10–12,14,21,23,24]. Postoperative IN also had positive effect on length of hospital stay than that of standard diet group (WMD, −2.95; 95% CI, −4.57 to −1.32; $P < 0.01$) (Fig. 2C).

Comparison between preoperative IN and standard diet

Six trials with 548 patients were included, 275 patients and 273 patients were randomized to preoperative IN group and standard diet group respectively [3,16–18,20,22]. Of them, five trails [3,16–18,20] compared the effect of preoperative IN on postoperative infectious complication with standard diet. The pooled result indicated there were significant differences in risks of postoperative infectious complications between two groups (RR, 0.45; 95% CI, 0.31 to 0.65; $P < 0.01$) (Fig. 3A). Six trials reported the risk of postoperative non-infectious complication. Combined analysis showed there were no significant differences between IN and control group (RR, 0.90; 95% CI, 0.67 to 1.21; $P = 0.49$) (Fig. 3B).

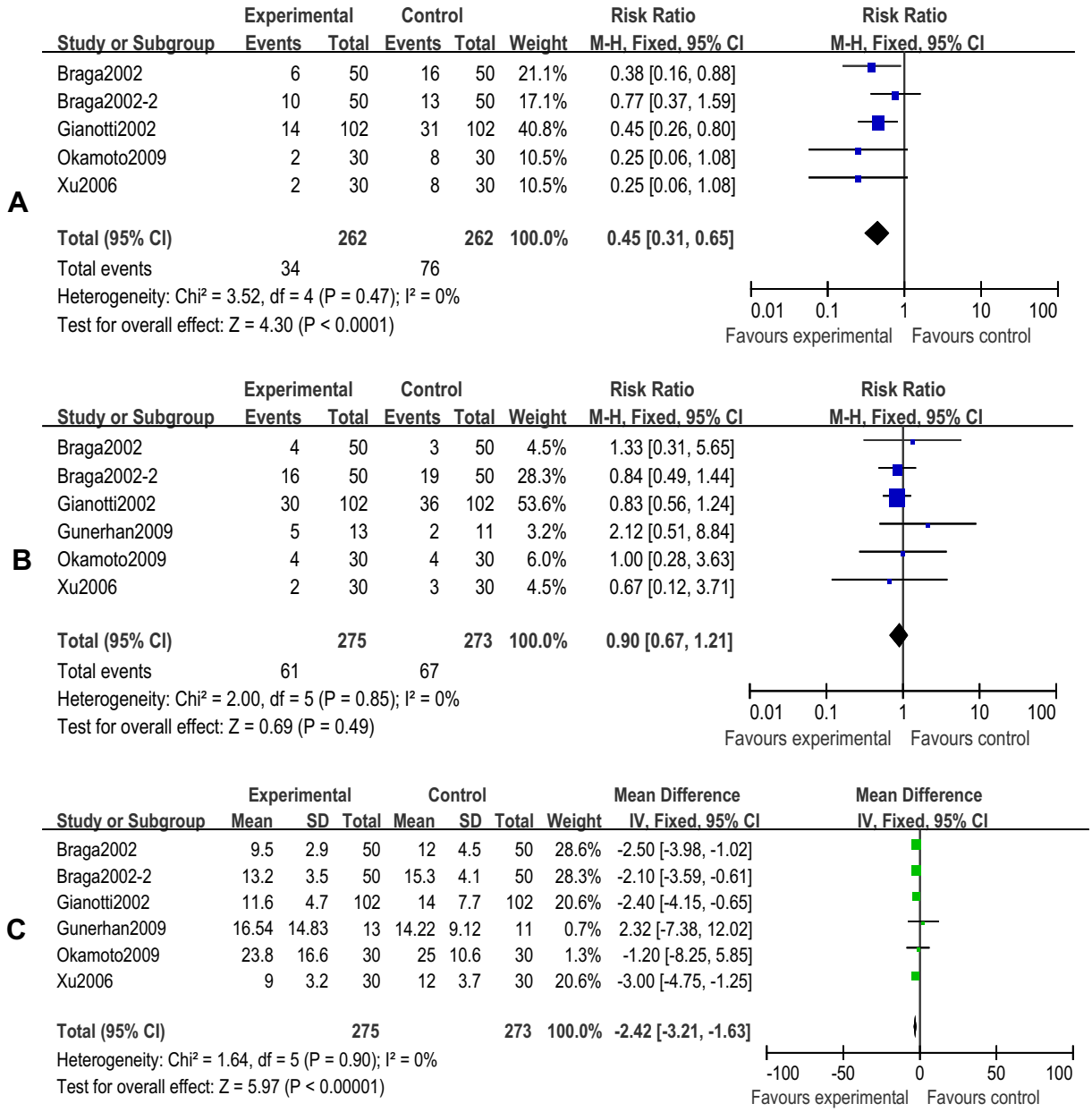

Figure 3. Compared effect of preoperative IN and standard diet on postoperative infectious, non-infection complication, and length of hospital stay. A: postoperative infectious complication; B: postoperative non-infectious complication; C: length of hospital stays.

However, significant differences of length of hospital stay have been observed between two groups (WMD, −2.95; 95% CI, −3.21 to −1.63; $P < 0.01$) (Fig. 3C).

Comparison between perioperative IN and standard diet

Six trials with a total of 748 patients were included in this subgroup analysis, and each group (IN group and standard diet group) had 374 patients [13,15–18,23]. The pooled results showed that significant effect on postoperative infectious complication could be obtained for perioperative IN group (RR, 0.44; 95% CI, 0.32 to 0.60; $P < 0.01$) (Fig. 4A).

All trials here [13,15–18] showed no statistical difference in postoperative non-infectious complication between perioperative IN and standard diet. But pooled result favored perioperative use of IN (RR, 0.72; 95% CI, 0.54 to 0.97; $P = 0.03$) (Fig. 4B). Five trials revealed that there were significant differences of length of hospital stay between two groups (WMD, −2.62; 95% CI, −3.26 to −1.97; $P < 0.01$) (Fig. 4C).

Comparison between preoperative IN and perioperative IN

Three trials with a total of 403 patients were included; of them, 202 patients were randomized to preoperative IN group, and 201 patients were randomized to perioperative IN group [16–18].

The pooled results showed that there were no statistical differences of postoperative infectious complication between two groups (RR, 1.12; 95% CI, 0.64 to 1.97; $P = 0.68$) (Fig. 5A). No benefit of postoperative non-infectious complication could be obtained for

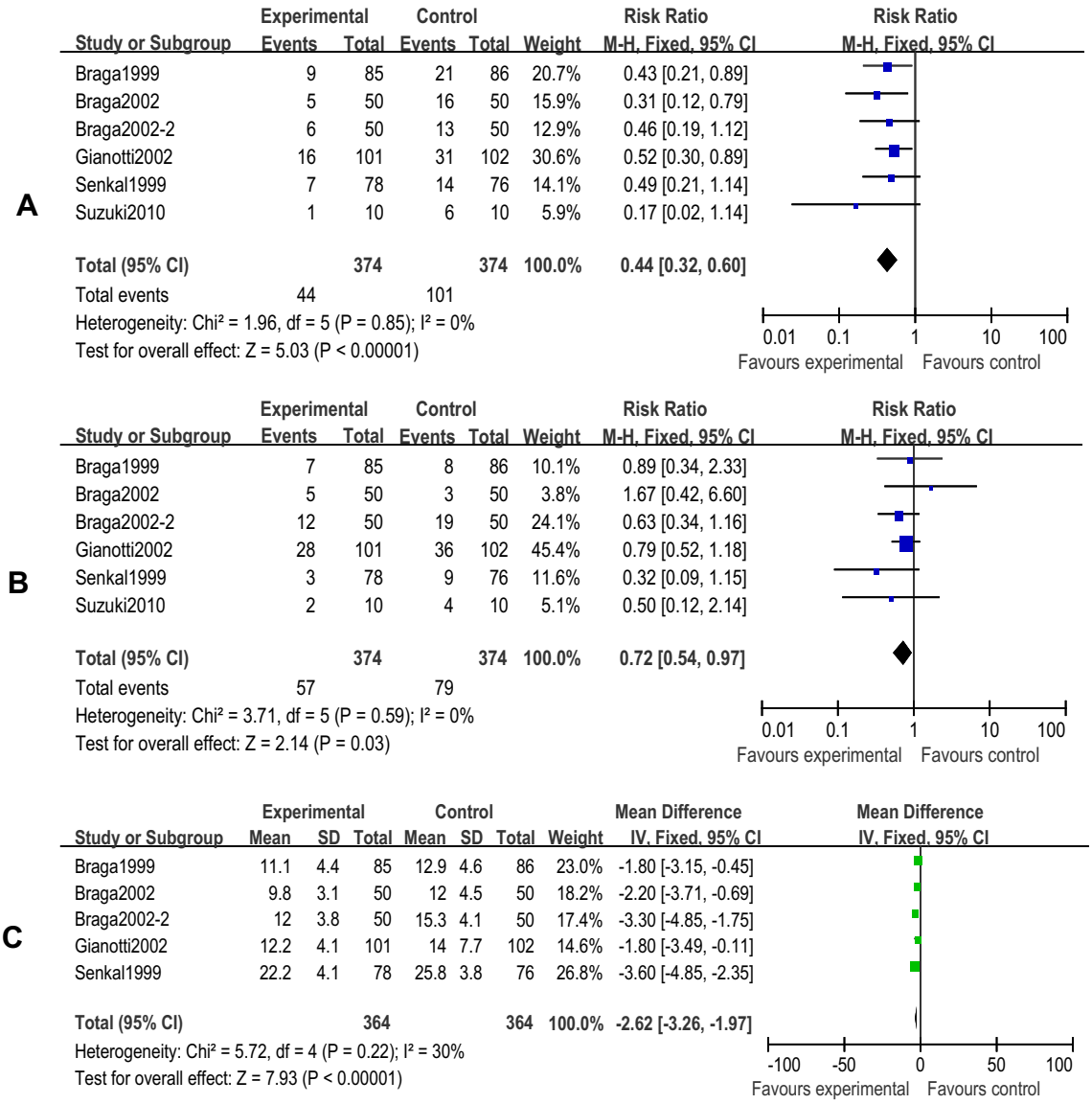

Figure 4. Compared effect of perioperative IN and standard diet on postoperative infectious, non-infection complication, and length of hospital stay. A: postoperative infectious complication; B: postoperative non-infectious complication; C: length of hospital stays.

use of IN (RR, 1.10; 95% CI, 0.78 to 1.56; $P = 0.57$) (Fig. 5B). Identically, there were no significant differences in the length of hospital stay in three trails (WMD, −0.02; 95% CI, −0.75 to 0.71; $P = 0.96$) (Fig. 5C).

Discussion

This systematic review based on 19 RCTs containing 2331 patients evaluated the impact of IN on postoperative infection, non-infection complication, and length of hospital stay. The salient results of our study were that IN significantly decreased postoperative infection complication risk and shorten hospital stay, either with preoperative, postoperative or combined preoperative and postoperative use. Moreover, perioperative IN also could reduce the postoperative non-infection complication risk.

Recently, IN application has been demonstrated to minimize tumor-induced and postsurgical immune suppression, reduce pro-inflammatory reaction and improve visceral microperfusion, ultimately reduce the morbidity of postoperative complication. For example, postoperative supplementation with IN could decrease the expression of PEG2, IL-6, and TNF-a, but increased IL-2R expression [7,11,25–32]. Gianotti et al. [33] showed, in first day after surgery, there was a significant increase of IL-2Rα in perioperative IN group compared with standard diet group. Ates et al. [34] manifested that Cortisol and CRP levels were significantly increased in perioperative IN group in first day after surgery, but they rapidly returned to (on POD1) preoperative level in IN group. Besides, XU et al [20] found TRF was significantly higher in preoperative IN group than that in postoperative IN group. Compared perioperative IN with postoperative IN, Braga et al. [35] found that perioperative IN could prevent the early postoperative impairment of phagocytosis, DHR, total number of lymphocytes, and CD4/CD8 ratio ($P < 0.05$ versus postoperative group). These studies suggested preoperative and perioperative IN might be superior to postoperative IN. In this study, we also found that there

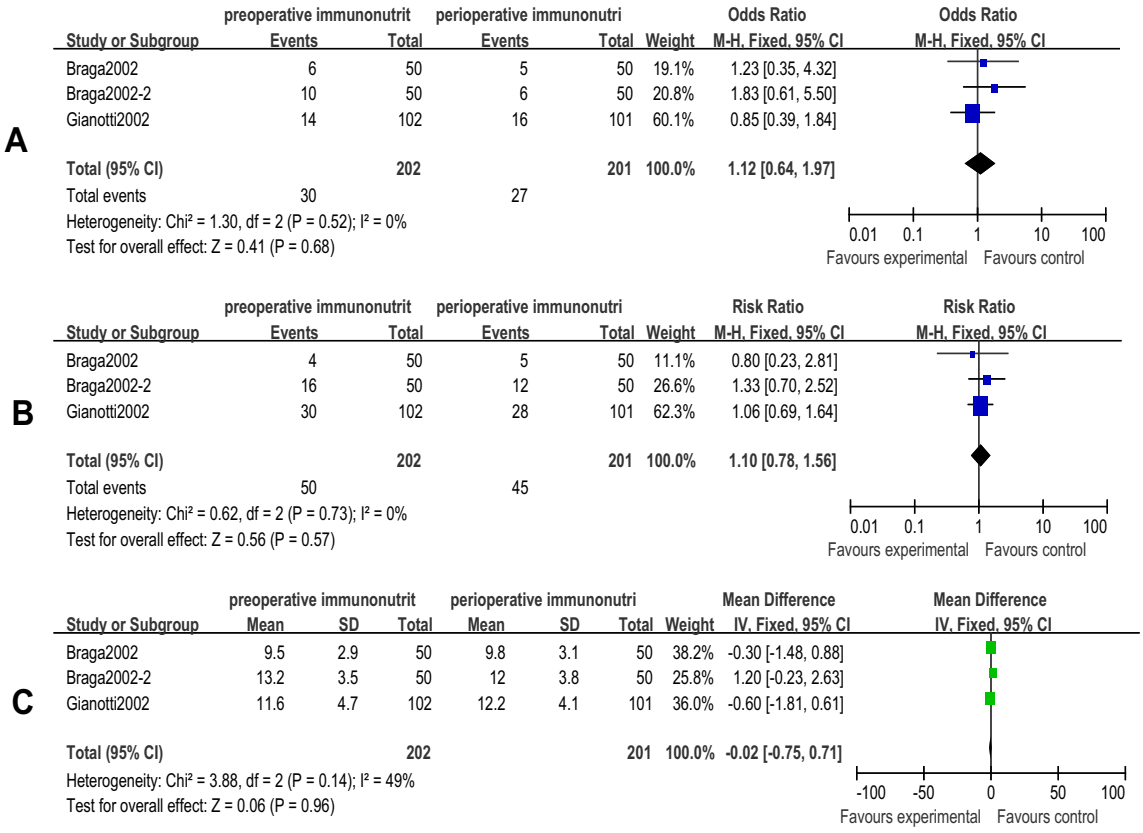

Figure 5. Compared effect of perioperative IN and preoperative IN on postoperative infectious, non-infection complication, and length of hospital stay. A: postoperative infectious complication; B: postoperative non-infectious complication; C: length of hospital stays.

were no significant differences in reducing postoperative infectious complication and length of hospital stay between preoperative and perioperative IN group. This seemed to be in accordance with previous reports. For example, Braga et al. [35] stated phagocytosis ability of patients receiving the perioperative IN did not decrease after surgery, and remained similar as the preoperative values. Importantly, we found that perioperative IN also could reduce the postoperative non-infection complication risk. It might be because that administration of immuonutrients before and after surgery could ameliorate splanchnic microperfusion and oxygenation, and increase immune response.

In conclusion, perioperative IN contributed to reducing postoperative morbidity of postoperative infectious and non-infection complication as well as length of hospital stay.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

Yan Zhang and Yuanhui Gu share first authorship of this article. The authors thank Stanislaw Klek for reviewing his publications for patient overlap. Yang Kehu and Ma Bin in Evidence Based Medicine Center of Lanzhou University provide help for the authors. The authors declare no conflict of interest.

Authorship statement

Guarantor of the integrity of the study: Hui Cai
Study concepts: Yan Zhang
Study design: Hui Cai
Literature research: Yuanhui Gu
Data acquisition: Yuanhui Gu
Data analysis: Yuanhui Gu
Statistical analysis: Yan Zhang
Manuscript preparation: Yan Zhang
Manuscript editing: Hui Cai
Manuscript review: Tiankang Guo, Yiping Li

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