Efficacy of enteral nutrition for patients with acute pancreatitis: A systematic review and meta-analysis of 17 studies

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Abstract. Nutrition support is a key method to treat acute pancreatitis (AP). Enteral nutrition (EN) has a role in treating AP, but the time point for EN initiation remains unclear. The present systematic review and meta-analysis aimed to assess the efficacy of early EN (EEN) and delayed EN (DEN) based on different time points (24, 48 and 72 h). The relevant databases including Pubmed, Web of Science, Embase and Cochrane library were searched until Dec 1, 2022. Studies comparing EEN and DEN in AP were included. The relative risk (RR) was used for comparing categorical variables, while standard mean difference (SMD) was used for continuous variables, both reported with 95% CI. A total of 17 studies with 1,637 patients with AP was included in the present systematic review and meta-analysis. The patients in the DEN group showed a significantly higher risk of mortality compared with the EEN group (RR=1.95; 95% CI, 1.21-3.14; P=0.006). In subgroup analysis, when using 48 h as the cut-off time to distinguish EEN and DEN, the risk of mortality was 3.89-fold higher in the DEN group compared with that in the EN group (95% CI, 1.25-12.17; P=0.019). DEN also increased the occurrence of sepsis in patients with AP (RR=2.82; 95% CI, 1.10-7.18; P=0.03) and duration of hospital stay (P<0.001). The present systematic review and meta-analysis suggested that EEN decreased associated complications, length of hospitalization and mortality in patients with AP and therefore provided a safe approach to improve recovery but there is still controversy around the time point for EEN.

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Abbreviations: SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; PN, parenteral nutrition; EEN, early enteral nutrition; DEN, delayed EN; NOS, Newcastle-Ottawa Quality Assessment Scale; ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; RR, relative risk; SMD, standard mean difference

Key words: acute pancreatitis, early enteral nutrition, edema, systemic inflammatory response syndrome

Introduction

Acute pancreatitis (AP) is characterized by activation of pancreatic enzymes in the pancreas by a variety of causes such as hypertriglyceridemia and cholelithiasis, followed by local inflammatory reactions such as autodigestion, edema, hemorrhage and necrosis in the pancreatic tissue as the main pathological changes, with or without other disease characterized by changes in the organ function. The common causes include biliary stones, hyperlipidemia, alcohol (long-term heavy use), hypercalcemia, drug use, surgery or trauma and tumors (1). Severe AP (SAP) is one of the most common critical illnesses in surgery and intensive care unit. The pathophysiological process with complex pathogenesis and multiple risk factors not only causes local damage to the pancreas but also induces systemic inflammatory response syndrome (SIRS). The initial stage of the disease is accompanied by lung, kidney and liver damage, and multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF) (2). SAP is associated with numerous complications with a mortality rate of 20-30%. Previous studies have showed that the high mortality rate may be due to the significant correlation between infectious complications and MODS during the development of the disease (3,4).

Nutritional support is a key method to treat SAP (4). On the one hand, it can provide enough nutrition for the body in a high energy consumption state. On the other hand, nutritional support effectively blocks progression of SAP, such as intestinal mucosal barrier damage, bacterial migration, large amounts of endotoxin absorption, gastrointestinal dysfunction and serious pathological processes, so as to gain sufficient time for further clinical treatment (5,6). In the earlier view of nutrition support for AP, parenteral nutrition (PN) should be adopted first, especially for SAP, because PN provides sufficient nutrients for metabolism and minimizes stimulation of pancreatic secretion (7). However, the adverse effects in of PN treatment of SAP have attracted attention (8). First, PN increases the risk of infection. Second, long-term

fasting causes intestinal dysfunction, changes in mucosal permeability, immune function decline and intestinal bacterial growth; release of a large number of immune mediators leads to SIRS or MODS (9).

Compared with PN, enteral nutrition (EN) is more in line with the physiological process of the body and has more advantages in terms of affordability. EN is more conducive to protecting the intestinal mucosa, maintaining normal function of the intestine and avoiding the shift of flora caused by long-term fasting (7). Based on this, EN has gradually been recognized and has been used in the clinical treatment of SAP with good results (8). EN initiation time given by the Society for SAP is 48 or 72 h after receiving treatment (10). However, a consensus on the best cut-off time for early EN (EEN) has not yet been reached due to concerns about its effect on the complication such as infection and sepsis . The present systematic review and meta-analysis aimed to analyze and compare the complications and hospital stay in patients receiving EEN or delayed EN (DEN).

Materials and methods

Ethics. The present study was performed following the preferred reporting items for systematic review and meta-analysis guidelines (11). Due to the study design, the requirement for ethical approval was waived by Ethical Committee of 900 Hospital of The Joint Logistics Team.

Search strategy. The present systematic review and meta-analysis was designed to compare EEN and DEN in treating AP. Pubmed (pubmed.ncbi.nlm.nih.gov/), Web of Science (webofknowledge.com/), Embase (embase.com/) and Cochrane library (cochranelibrary.com/) were searched until Dec 1, 2022. The grey literature was searched by Google Scholar (scholar.google.com). An additional literature search was performed by reviewing the reference lists. These studies were typically meta-analyses or reviews that were identified during the literature search process and may cite articles that may be missed by the key words search. The key words and medical sub-headings terms included 'acute pancreatitis' and 'enteral nutrition'. All studies were downloaded and imported into Endnote X7 (Thomson Reuters) to delete duplications and for further literature screening.

Selection criteria. Studies were included if they satisfied the following criteria: i) Study included patients diagnosed with AP; ii) all patients received EN and iii) patients receiving EN were divided and compared based on different EN time.

Study exclusion criteria were: i) No patients with AP were involved; ii) no comparison between EEN and DEN; iii) study was a review, comment or case report and iv) studies not published in English.

Literature screening, quality assessment and data extraction. Two investigators (YL and ZW) independently screened titles and abstracts according to the inclusion and exclusion criteria. Full-texts were further evaluated if the inclusion could not be determined via abstract and data could not be extracted. A third investigator (DL) was responsible for checking the results of the other investigator and resolving discrepancies by discussing with the other two investigators and repeating the literature review.

In addition, two investigators (YL and DL) independently assess the quality of the papers based on the Newcastle-Ottawa Quality Assessment Scale (NOS); high quality was indicated by a score of 6-9, whereas low quality scored 0-5 (12).

Two investigators (YL and DL) also independently extracted the data from the original studies and the extracted data were recorded in an Excel (Microsoft Corporation). The data extracted included: i) Study characteristics such as author, year of publication, institutions, recruitment periods, country and study type; ii) patient characteristics, such as median age, sex, the severity of AP, enteral route, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II score and number of patients; iii) associated complications such as sepsis, necrotic collection, walled-off pancreatic necrosis, acute respiratory distress syndrome (ARDS), MODS, SIRS and mortality in either EEN or DEN group. Mortality was defined as the number of deaths caused by AP or associated complications.

Statistical analysis. The relative risk (RR) was used for statistical analysis of categorical variables, while standard mean difference (SMD) was used for continuous variables. Both results were reported with 95% CI. $P<0.05$ was considered to indicate a statistically significant difference. Data provided as median and range (or interquartile range) were converted to mean ± standard deviation using the formula provided by Hozo *et al* (13). Data heterogeneity was evaluated using the I^2 statistic and χ^2 test was used for statistical analysis. When heterogeneity was found ($I^2 \geq 50\%$), the random-effects model was used; otherwise the fixed-effect model was used. Finally, forest plots were drawn and the funnel plots were used for evaluating publication bias. To assess the risk of bias due to missing results in a data synthesis, the metabias module of STATA software version 15.0 (StataCorp LP) was used to perform Egger's test, where $P<0.05$ was considered to indicate a significant publication bias. The funnel plot for identifying underreported articles was constructed using the metafunnel module of STATA to display the results of reporting bias assessment. To explore the potential heterogeneity, meta-regression was performed using the metareg module of the STATA software. Baseline factors such as EN route and start time, study location and design, severity of AP, APACHE II index and patient age were analyzed to explore potential source of heterogeneity.

Results

Literature screening. A total of 1,212 studies was identified through a database search and 988 studies were screened by titles and abstracts. After excluding irrelevant studies, 160 studies were screened by full-text analysis and 17 studies were included in the present systematic review and meta-analysis based on the aforementioned inclusion and exclusion criteria (Fig. 1) (3,8,14-28).

Characteristics of included studies. The characteristics of the included studies are shown in Tables I and II. The year of publication ranged from 1997-2017, with recruitment

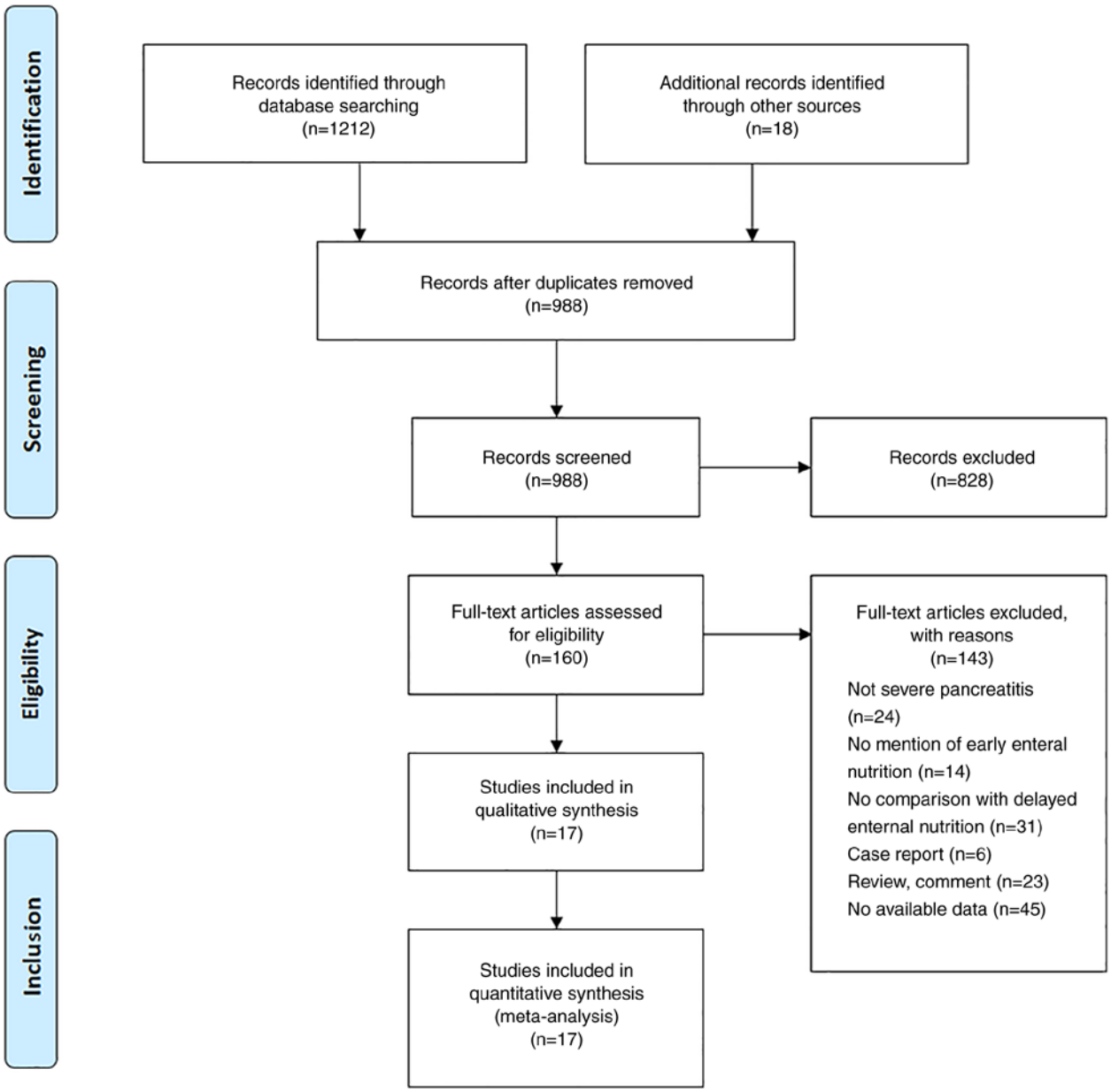

Figure 1. Flowchart of literature screening. Records were identified via databases (n=1,162) and other methods (n=18). After screening, a total of 17 records was considered eligible for inclusion in the present meta-analysis.

between 1990 and 2016. The present study included data from 12 countries, including China, Croatia, Netherlands, New Zealand, Poland, Russia, Sweden, Canada, the United Kingdom, Hungary, Greece and the United States. The majority of studies (15/17) were designed as randomized control trials (RCTs). Routes of administration were either nasojejunal or nasogastric tube. Of the included studies, three, nine and five studies initiated EEN support at 24, 48 and 72 h, respectively (Table I)

A total of 1,637 patients with AP was included in the present study (Table II). Of these, 831 patients received EEN, while 806 patients received DEN. The median proportion of male patients was 58.4 and 55.0% in the EEN and DEN groups, respectively. The median age was 53.2 (range, 41-71) and 54.8 (range, 43.8-72) years in the EEN and DEN groups, respectively. Median BMI and APACHE II scores were similar between the two groups.

The majority of studies were assessed as high quality with a score >7; however Gupta *et al* (17) was assessed with NOS score of 6.

Clinical outcome between EEN and DEN groups. Overall mortality of patients with AP between EEN and DEN groups is shown in Fig. 2. A total of 10 studies reported mortality data; in the study by Qin *et al*, (21) the mortality in both EEN and DEN groups was zero. Thus, only nine studies reported valid data on mortality with a total of 28 patients with AP-associated death. Patients in the DEN group had a higher risk for mortality compared with the EEN group (RR=1.95; 95% CI, 1.21-3.14; P=0.006; I^2=0.8%; fixed effect model).

The comparison of necrotic collection, walled-off pancreatic necrosis and sepsis is shown in Fig. 3. Patients with AP in the DEN group had a higher probability of sepsis compared with that in the EEN group (RR=2.82; 95% CI, 1.10-7.18;

Table I. Characteristics of included studies.

First author, year	Recruitment period	Country	Study type	Severity of AP	EN route	EN start time, h	NOS score	(Refs.)
Jin *et al*, 2017	2013-2016	China	Retrospective	Moderate and severe	NJ	<72	8	(28)
Stimac *et al*, 2016	2007-2012	Croatia	RCT	Moderate and severe	NJ	<72	8	(27)
Zou *et al*, 2014	2008-2013	China	RCT	Not stated	NJ	<72	8	(26)
Bakker *et al*, 2014	ND	Netherlands	RCT	Severe	NJ	<48	9	(3)
Wereszczynska-Siemiatkowska *et al*, 2013	2001-2010	Poland	RCT	Severe	NJ	<48	8	(25)
Sun *et al*, 2013	2010-2011	China	RCT	Severe	NJ	<48	8	(24)
Petrov *et al*, 2013	2010-2011	New Zealand	RCT	AP	NG	<72	8	(23)
Bakker *et al*, 2009	ND	Netherlands	Retrospective	Severe	NJ	<48	7	(22)
Qin *et al*, 2008	2002-2006	China	RCT	Severe	NJ	<48	7	(21)
Petrov *et al*, 2006	2002-2004	Russia	RCT	Severe	NJ	<24	8	(20)
Eckerwall *et al*, 2006	2002-2004	Sweden	RCT	Severe	NG	<24	7	(19)
Louie *et al*, 2005	ND	Canada	RCT	Severe	NJ	<24	7	(18)
Gupta *et al*, 2003	1996-1998	UK	RCT	Severe	NJ	<48	6	(17)
Olah *et al*, 2002	1995-1996	Hungary	RCT	AP	NJ	<48	7	(16)
Abou-Assi *et al*, 2002	2000	USA	RCT	AP	NJ	<72	8	(8)
McClave *et al*, 1997	ND	USA	RCT	Moderate	NJ	<48	7	(15)
Kalfarentzos *et al*, 1997	1990-1995	Greece	RCT	Severe	NJ	<48	7	(14)

ND, no data; RCT, randomized control trial; AP, acute pancreatitis; NJ, neojejunal; NG, neogastric; EN, enteral nutrition; NOS, Newcastle-Ottawa quality assessment scale.

P=0.03; I^2=0%; fixed effect model); however, there was no significance in terms of necrotic collection and walled-off pancreatic necrosis between the two groups (RR=1.074 and 1.342, respectively; all P>0.05).

ARDS, MODS and SIRS are shown in Fig. 4. No statistical differences were found in these complications of AP (RR=1.01, 1.27 and 1.07, respectively; all P>0.05).

The comparison of hospital stay is shown in Fig. 5. The median duration of hospital stay was significantly shorter in the EEN group compared with that in the DEN group (17.4 vs. 20.0 days; SMD=-0.93; 95% CI, -1.57- -0.29; P<0.001; I^2=90.4%; randomized effect model).

Publication bias analysis. Egger's test for the comparisons of mortality, necrotic collection, walled-off pancreatic necrosis, sepsis, ARDS, MODS, SIRS and hospital stay showed no significant difference (P>0.05; data not shown). The funnel plots of these comparisons showed favorable symmetry (Fig. 6), indicating no significant publication bias for these comparisons.

Subgroup analysis. The comparison of complications between EEN and DEN at different cut-off times is shown in Table III. DEN was associated with a 3.89-fold increase in risk of mortality compared with that in the EEN group with a cut-off of 48 h (95% CI, 1.25-12.17; P=0.019). Although there was a higher risk of complications such as walled-off pancreatic necrosis, sepsis, ARDS, MODS and SIRS in patients with DEN, there was no significant difference due to small sample size.

Heterogeneity of the comparison of hospital stays. The heterogeneity of the comparison of hospital stays was considerable (Fig. 5. Therefore, meta-regression was performed. Of baseline factors, only the severity of AP showed a significant impact on the outcome (Coefficient=0.903; P=0.025; Table IV). The difference in hospital stay was more significant in patients with AP compared with that in patients with SAP/moderate AP; this contributed to the heterogeneity of hospital stays.

Discussion

The present study is an up-to-date systematic review and meta-analysis of studies comparing the complications observed in patients with AP and supported with EEN or DEN. The present meta-analysis showed that patients with AP and supported with EEN have a lower risk of mortality and sepsis, and therefore have a shorter hospital stay.

SAP is a disease with rapid onset and progression and high mortality (10). At present, several conservative medical treatments are performed in the early stage of the disease (18,28). In addition to early fluid resuscitation and organ function

Table II. Patient data from the included studies.

	ENN group					DEN group					
First author, year	Sample size, n	Male, %	Age, years, mean ±SD/ median (range)	BMI, kg/m^2	APACHE II	Sample size	Male, %	Age, years, mean ±SD/ median (range)	BMI, kg/m^2	APACHE II	(Refs.)
Jin et al, 2017	35	23 (66)	43.7±15.6	26.3±3.7	10.8±5.6	52	45 (87)	45.7±14.4	26.2±3.5	11.4±7.2	(28)
Stimac *et al*, 2016	107	64 (60)	69.0 (28.0-88.0)	ND	9.84±3.26	107	57 (53)	72.0 (26.0-90.0)	ND	9.8±3.2	(27)
Zou *et al*, 2014	46	26 (56)	46.5 (34.6-59.3)	25.8 (22.5-26.9)	6.0 (3.0–9.0)	47	26 (55)	48.0 (34.0-60.0)	24.5 (21.9-26.1)	8.0 (5.0-10.0)	(26)
Bakker *et al*, 2014	101	55 (54)	65.0±160	ND	11.0±4.0	104	45 (43)	65.0±15.0	ND	11.0±5.0	(3)
Wereszczynska-Siemiatkowska *et al*, 2013	97	72 (74)	49.0 (39.0-56.0)	ND	4.0 (2.0-7.0)	100	61 (61)	50.0 (41.0-62.5)	ND	5.0 (2.0-7.5)	(25)
Sun *et al*, 2013	30	18 (60)	43.0 (34.5-51.0)	24.6 (23.5-26.8)	9.5 (8.5-11)	30	20 (67)	45.0 (35.0-52.0)	25.8 (23.9-28.8)	10.0 (8.0-11.5)	(24)
Petrov *et al*, 2013	17	10 (59)	41.0 (34.0-60.0)	26.0 (24.0-30.0)	6.0 (2.0-9.0)	18	8 (44)	55.0 (36.0-70.0)	25.0 (23.0-28.0)	6.0 (3.0-11.0)	(23)
Bakker *et al*, 2009	184	ND	ND	ND	ND	112	ND	ND	ND	ND	(22)
Qin *et al*, 2008	36	11 (31)	54.3±13.1	21.1±2.3	8.8±0.5	38	12 (32)	58.4 (19.1)	22.7±1.8	8.9±0.7	(21)
Petrov *et al*, 2006	35	27 (77)	51.0 (42.0-67.0)	ND	12 (10-14)	34	24 (71)	52.0 (41.0-70.0)	ND	12.5 (11.0-16.0)	(20)
Eckerwall *et al*, 2006	24	10 (42)	71.0 (58.0-80.0)	27.0 (25.0-30.0)	9.0 (8.0-10.0)	26	14 (54)	68.0 (60.0-80.0)	28.0 (27.0-30.0)	10.0 (8.0-13.0)	(19)
Louie *et al*, 2005	10	ND	ND	ND	ND	18	ND	ND	ND	ND	(18)
Gupta *et al*, 2003	8	4 (50)	65.0 (56.0-89.0)	ND	8.0 (6.0-12.0)	9	3 (33)	57.0 (38.0-86.0)	ND	10.0 (7.0-14.0)	(17)
Olah *et al*, 2002	41	33 (80)	42.0	ND	ND	48	42 (88)	43.8	ND	ND	(16)
Abou-Assi *et al*, 2002	26	16 (62)	48.0±3.0	26.6±1.3	ND	27	13 (48)	50.0±3.0	25.7±1.6	ND	(8)
McClave *et al*, 1997	16	ND	47.6±4.0	ND	17.5±4.1	16	ND	45.1±4.2	ND	22.4±5.0	(15)
Kalfarentzos *et al*, 1997	18	8 (44)	63.0±10.7	ND	12.7±2.6	20	7 (35)	67.2±8.9	ND	11.8±1.9	(14)

ND, no data; EEN, early enteral nutrition; DEN, delayed EN; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation.

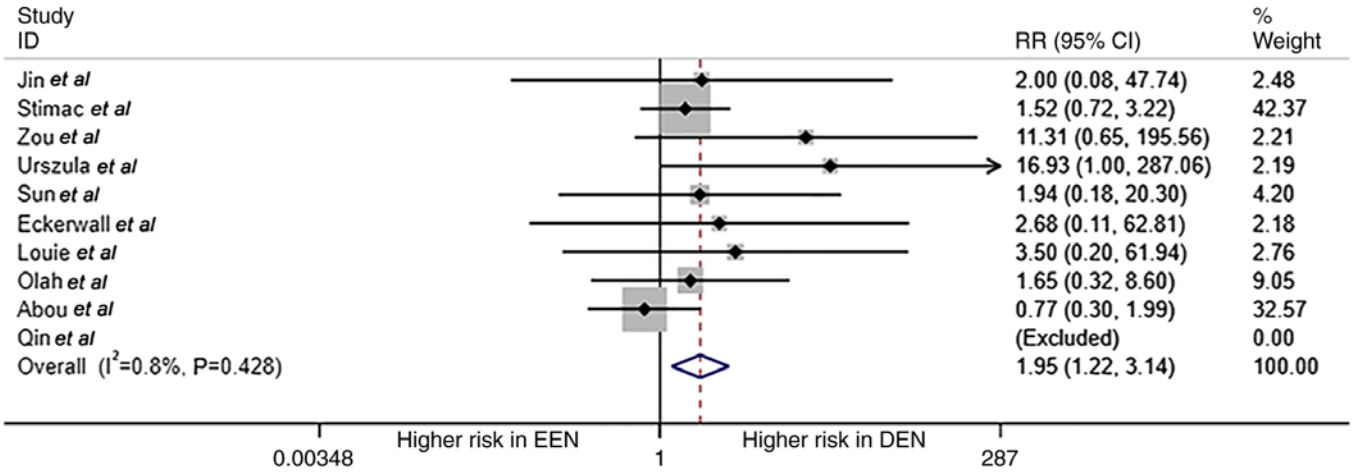

Figure 2. Overall mortality for EEN and DEN. The forest plot shows the relative risk of overall mortality of EEN vs. DEN. EEN, early enteral nutrition; DEN, delayed EN; RR, relative risk.

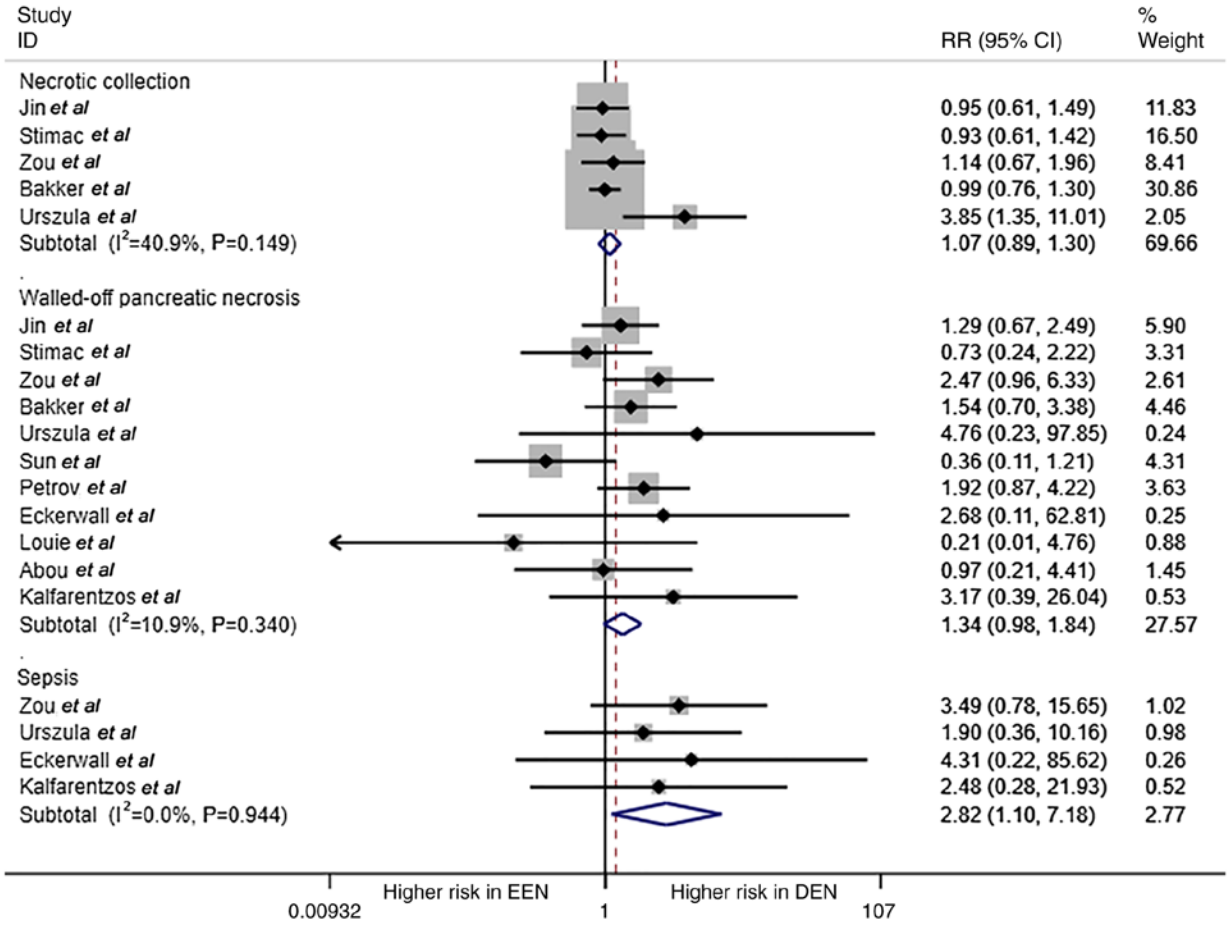

Figure 3. Necrotic collection, walled-off pancreatic necrosis and sepsis for EEN and DEN. RR of necrotic collection, walled-off pancreatic necrosis and sepsis of EEN vs. DEN. EEN, early enteral nutrition; DEN, delayed EN; RR, relative risk.

support, nutritional support treatment is a key example of conservative medical treatment (4,6). Patients with SAP are mostly in a state of high catabolism with severe negative nitrogen balance coupled with prolonged gastrointestinal decompression and often suffer from water and electrolyte imbalances and malnutrition, which cause complications such as arhythmia and affect the prognosis of the disease (29,30). In the case of patients with high metabolism, it is important to provide adequate energy support. The sequential pathological processes of SAP include acute reaction, systemic infection and residual infection period. The acute stage of SAP is characterized by a 'cascade of inflammation' (10). In theory, EN improves inflammation-associated intestinal wall, pancreatic edema and peripancreatic effusion and can

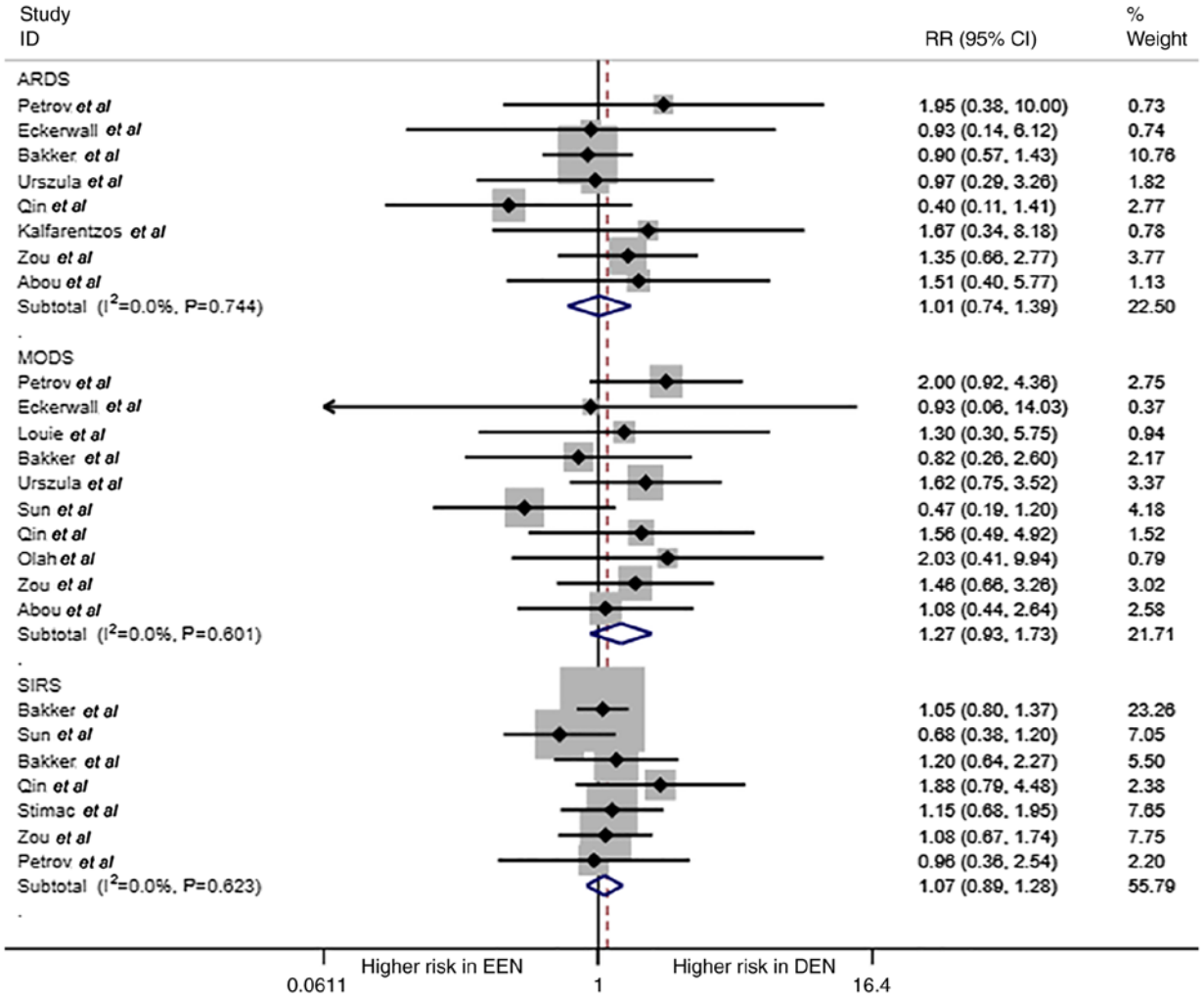

Figure 4. ARDS, MODS, SIRS for EEN and DEN. The forest plot shows the RR of ARDS, MODS, SIRS of EEN vs. control treatment (DEN). ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; EEN, early enteral nutrition; DEN, delayed EN; RR, relative risk.

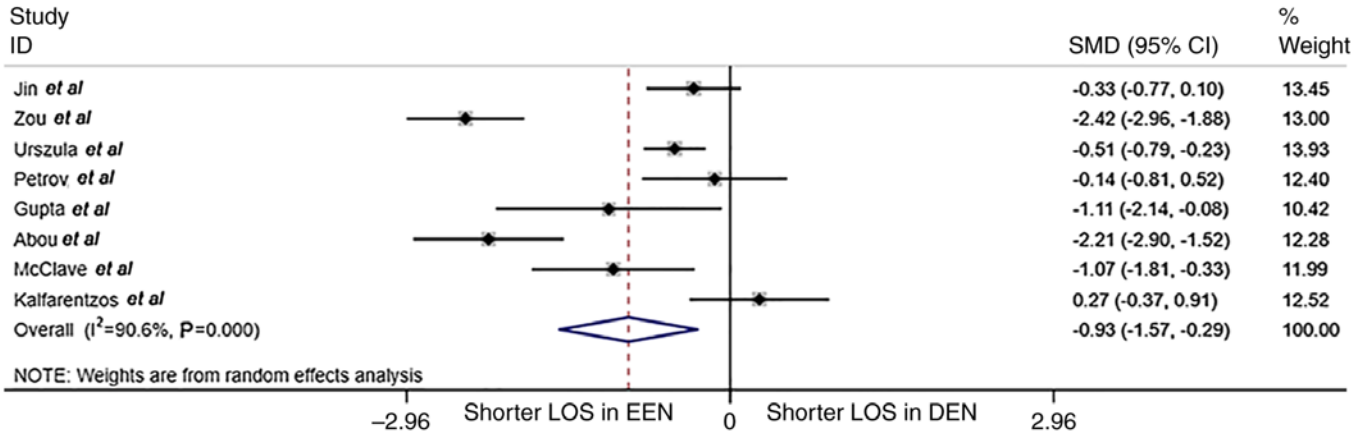

Figure 5. Hospital stay for EEN and DEN. LOS, length of stay; EEN, early enteral nutrition; DEN, delayed EN; SMD, standard mean difference.

reduce intra-abdominal pressure (31). At SAP onset, the intestinal mucosa undergoes cell shedding and apoptosis of villi, the height of villi and thickness of the intestinal mucosa are significantly reduced, the tight junctions between cells loosen, the morphology and function of the intestinal mucosa are damaged and the intestinal flora is shifted (31). Secondary systemic infection and local necrotic tissue infection may also occur (32); therefore, intestinal barrier function is very important in the occurrence and development of SAP. It is reported that 80% of patients with SAP

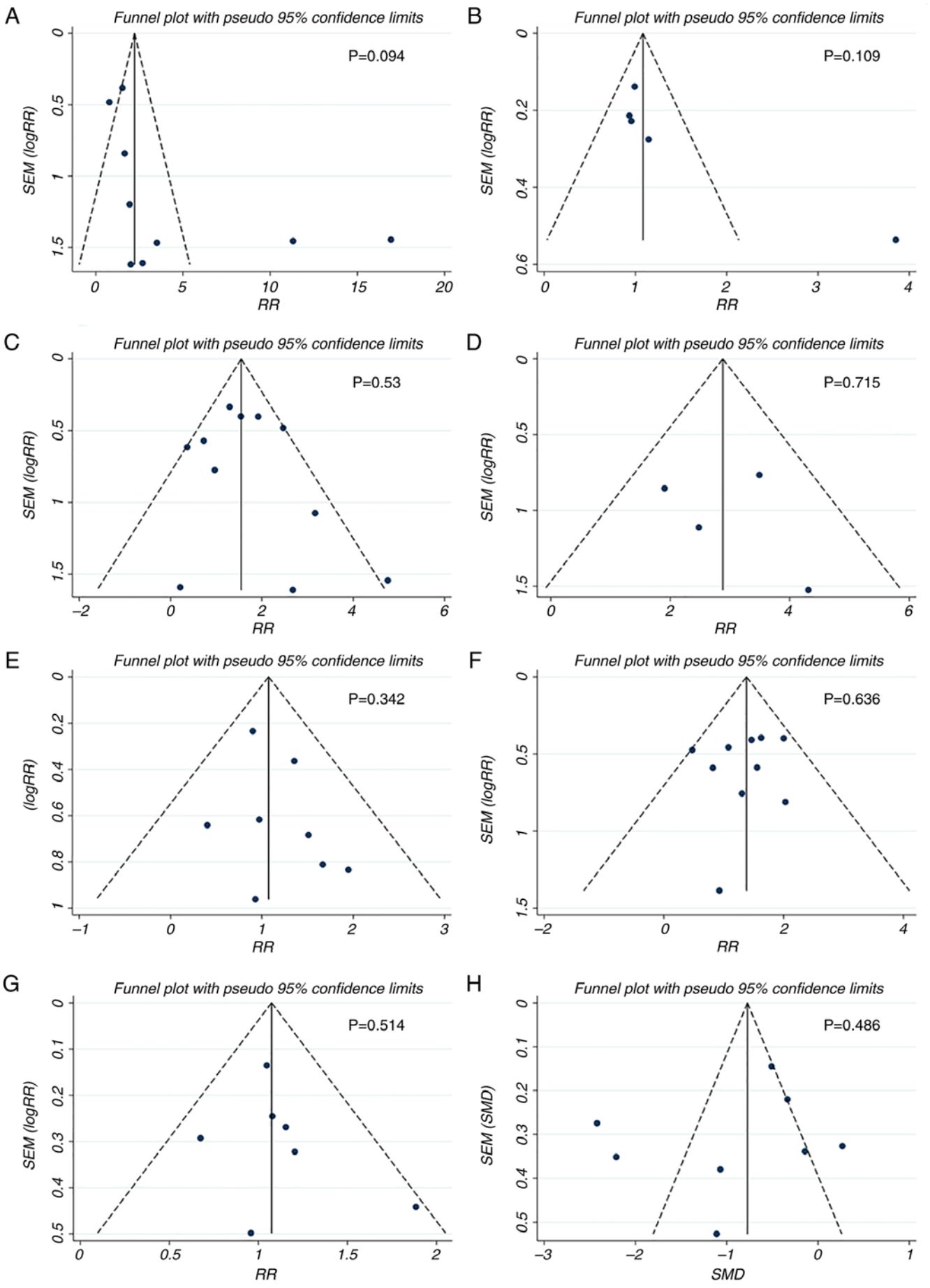

Figure 6. Funnel plots for publication bias assessment. (A) Mortality. (B) Necrotic collection. (C) Walled-off pancreatic necrosis. (D) Sepsis. (E) Acute respiratory distress syndrome. (F) Multiple organ dysfunction syndrome. (G) Systemic inflammatory response syndrome. (H) Hospital stay. RR, relative risk.

Table III. Subgroup analysis of complications at different time points.

	Enteral nutrition time point, h								
	<24			<48			<72		
Outcome	Number of studies	RR (95% CI)	P-value	Number of study	RR (95% CI)	P-value	Number of study, n	RR (95% CI)	P-value
Mortality	2	3.14 (0.37-26.34)	0.29	4	3.89 (1.25-12.17)	0.02	4	1.50 (0.87-2.59)	0.14
Walled-off pancreatic necrosis	3	1.64 (0.86-3.36)	0.17	4	1.18 (0.67-2.09)	0.57	4	1.35 (0.86-2.12)	0.20
Sepsis	1	4.31 (0.21-85.61)	0.34	2	2.1 (0.56-7.92)	0.27	1	3.49 (0.78-15.65)	0.10
Necrotic collection	NA	-	-	2	1.17 (0.90-1.52)	0.24	3	0.98 (0.6-1.29)	0.93
Acute respiratory distress syndrome	2	1.43 (0.42-4.83)	0.56	4	0.86 (0.58-1.27)	0.45	2	1.39 (0.74-2.61)	0.35
Multiple organ dysfunction syndrome	3	1.74 (0.89-3.38)	0.10	5	1.09 (0.70-1.71)	0.68	2	1.28 (0.71-2.33)	0.41
Systemic inflammatory response syndrome	NA	-	-	4	1.01 (0.85-1.21)	0.64	3	1.10 (0.91-1.54)	0.59

RR>1 indicates that DEN is a risk factor as compared with EEN. NA, not applicable; RR, relative risk; -, no data due to limited number of studies.

Table IV. Meta-regression.

Variable	Coef.	Standard error	P-value	Lower 95% CI	Upper 95% CI
EN route	0.901	1.071	0.432	-1.720	3.523
EN start time	-0.691	0.689	0.355	-2.377	0.995
Study location	0.076	0.203	0.721	-0.421	0.573
Study design	-0.689	1.066	0.542	-3.298	1.919
Severity of acute pancreatitis	0.903	0.302	0.025	0.161	1.643
Acute Physiology and Chronic Health Evaluation II index	0.032	0.084	0.716	-0.183	0.248
Patient age	0.019	0.045	0.683	-0.092	0.131

EN, enteral nutrition.

have secondary infections of the pancreas and peripancreatic tissue (7,10). The pathogens of secondary infection are mostly *Escherichia coli*, *Enterococcus* and certain anaerobic bacteria, all of which are intestinal-derived strains. After infection occurs, the stress response is aggravated, patient condition worsens and the occurrence of systemic complications is increased (33,34).

EN at the appropriate timepoint of SAP course is not only more aligned with the normal physiology of the human body but also decreases bacterial translocation, while ensuring that the intestine have sufficient rest time and preserving the integrity of intestinal mucosa function and structure, which can significantly decrease morbidity and mortality to benefit patients with SAP (5,7). While EN provides nutrients needed by the body, it also decreases occurrence of metabolic complications and catheter-associated infections. At the same time, it can effectively maintain functional integrity of gastrointestinal mucosa, decrease bacterial translocation and intestinal infection, promote gastrointestinal peristalsis, increase intestinal mucosal perfusion blood flow and decrease incidence and mortality of MODS (6,7,34). Therefore, early nutritional support is important in the treatment of SAP (35). The initiation of EN in patients with SAP is associated with gastrointestinal function. In the early stage of SAP, severe stress response and inflammatory stimulation lead to intestinal ischemia, hypoxia and increased permeability. Therefore, premature EN support not only fails to ensure good digestion but also leads to further damage to the intestine, thereby increasing the likelihood of endotoxin translocation of intestinal bacterial agents (36). Suitable EN support is beneficial to maintain integrity of intestinal mucosal cell structure and function, repair and maintain mechanical, biological, immune and chemical barrier function of the intestinal mucosa, decrease bacterial translocation and intestinal infection and improve the prognosis (6).

For patients with more severe AP, the clinician might delay the initiation of EN, and this might lead to patient selection bias. However, according to the RCT design of most included studies, the type of intervention (ENN or DNN) was not decided based on severity. The disease severity parameters in ENN and DNN groups were comparable among the included studies. Therefore, the selection bias was not present.

For patients with SAP who are considered for EN treatment, the optimal time to initiate EN remains unclear. European Society for Parenteral Enteral Nutrition recommends that EN should be started within 24 h of hospital admission (37), while the American Society for Parenteral Enteral Nutrition clinical guidelines recommend that EN be started within 48 h (38). Moreover, certain studies consider it safe and feasible to start EN within 3 days (39), while others have indicated that the best time to start EN is when the internal bowel function starts to recover 3-5 days after jejunostomy or conservative treatment for 3-5 days (40). Pontell *et al* (41) showed that following intestinal ischemia-reperfusion, intestinal peristalsis is weakened and longitudinal muscles of the intestine are severely damaged, which may aggravate destruction of the intestinal barrier and cause bacteria shifting. In clinical practice, it is not easy to start EN within 48 h so it is important to record and evaluate EN. Reperfusion is performed following intestinal mucosal blood loss in patients with SAP at the initial stage, which induces activation of inflammatory factors and produces inflammatory response syndrome, resulting in MODS (5,10). European Society for Parenteral Enteral Nutrition (37) has discussed the needs of PN and EN and concluded that EN should be administered within 24 h of admission to obtain the best treatment effect. Relevant studies have proved that EN can only be applied in a relatively narrow 'diagnostic window' to achieve the expected treatment efficacy (14,15). Within 48 h of admission, EN can be used to control the inflammatory response, decrease bacterial translocation and protect the gastrointestinal mucosal barrier (3,24). A number of studies have also confirmed that the initiation of EN in patients with SAP 48 h after admission significantly increases incidence of pancreatic infection, MODS and mortality compared with EN started within 48 h (25). The present data analysis further confirmed that it is more appropriate to initiate EN within 48 h, while it is more harmful to start it >48 h after hospital admission. Hegazi *et al* (42) demonstrated that initial nutritional support can significantly decrease patient mortality and optimize the prognosis of patients with SAP. The most appropriate mode of nutrition for the human body is digestion and absorption of nutrients via intestinal nutrition, which not only effectively decrease intestinal infections and bacterial translocation, but also encourages patients to restore body nutrition support as soon as possible (10). A meta-analysis by Qi *et al* (43) investigated EEN (defined as EN initiated within 24 h of hospital admission) and DEN. Their analysis included eight studies and found no significant difference in risk of

mortality, infectious complications and pancreatic-associated infection but MOF was less common in patients treated with EEN. By contrast, the present meta-analysis included 17 studies and explored EEN (defined as EN initiated at 24, 48 or 72 h after hospital admission) and DEN. The present analysis showed that starting EN at 48 h significantly decreased mortality, sepsis and length of hospital stay. In light of the previously published meta-analysis (43), the present results indicated that, as the time point for EEN start, 48 h may be more beneficial to decrease disease-related mortality.

The present meta-analysis had limitations. Firstly, due to the lack of peer-reviewed topical studies, the subgroup analysis did not find the best time point for EEN. Secondly, heterogeneity in hospital stay data may be present and the hospital stay should be further investigated in future studies.

The present systematic review suggested that EEN decreased complication in patients with AP and therefore provides a safe approach to improve recovery. The best time point for EEN is still debated but 24-72 h are safe time points for EEN.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL and DL contributed to the study conception and design. YL, DL and ZW wrote the manuscript and analyzed and interpreted data. YL and DL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Requirement for ethical approval of the present study was waived by Ethical Committee of 900 Hospital of The Joint Logistics Team.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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