

Effects of Early Versus Delayed Feeding in Patients With Acute Pancreatitis

A Systematic Review and Meta-analysis

Xi-Ying Liang, MD,*† Xin-An Wu, MB,† Ying Tian, MB,† Hang Gao, MB,†
Jing-Jing Chen, MB,† and Quan-Xin Feng MD, PhD†‡

Background: The aim of this study was to summarize the optimal strategy for early feeding in patients with acute pancreatitis.

Methods: The search was undertaken in electronic databases, which compared early with delayed feeding in acute pancreatitis. The primary outcome was the length of hospital stay (LOHS). The second outcomes were intolerance of refeeding, mortality, and total cost of each patient. This meta-analysis followed the “Preferred Reporting Items for Systematic Reviews and Meta-analyses” guideline. Research is registered by PROSPERO, CRD42020192133.

Results: A total of 20 trials involving 2168 patients were included, randomly assigned to the early feeding group (N = 1033) and delayed feeding group (N = 1135). The LOHS was significantly lower in the early feeding group than the delayed feeding group (mean difference: -2.35, 95% CI: -2.89 to -1.80; $P < 0.0001$), no matter the mild or severe subgroup ($P_{\text{int}} = 0.69$). The secondary outcome of feeding intolerance and mortality were no significant difference (risk ratio: 0.96, 0.40 to 2.16, $P = 0.87$ and 0.91, 0.57 to 1.46, $P = 0.69$; respectively). Moreover, the hospitalization cost was significantly less in the early feeding group, resulting in an average savings of 50%. In patients with severe pancreatitis, early feeding after 24 hours may be beneficial ($P_{\text{int}} = 0.001$).

Conclusion: Early oral feeding can significantly reduce the LOHS and hospitalization costs in patients with acute pancreatitis without increasing feeding intolerance or mortality. In patients with severe pancreatitis, early feeding after 24 hours may be beneficial.

Key Words: acute pancreatitis, early feeding, delayed feeding, nutrition

(*J Clin Gastroenterol* 2024;58:522–530)

Received for publication November 13, 2022; accepted May 22, 2023. From the *Department of Cardiology, The Second Affiliated Hospital of Xi'an Jiaotong University; †Pancreatic Disease Center, Xi'an Peoples Hospital; and ‡Intensive Care Unit of Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, Shaanxi, China.

Data availability statement: The data that support the findings of this study are openly available in published articles that come from electronic databases. All data generated during this study are included in this published article (Supplemental Information files, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>).

This work was supported by the Natural Science Basic Research Program of Shaanxi Province (2022JM-475).

The authors declare that they have nothing to disclose.

Address correspondence to: Quan-Xin Feng, MD, PhD, Pancreas Disease and Intestinal Fistula Center, Xi'an People's Hospital, No.155, Hangtian East Road, Hangxin City, Chang'an District, Xi'an, Shaanxi 710000, China (e-mails: fengquanxin2022@163.com; fengqx@fmmu.edu.cn).

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.jcge.com.

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/MCG.0000000000001886

Acute pancreatitis incidence has been increasing in recent years, with about 34 cases per 100,000 general population and 2.6 billion dollars cost per year in the United States.^{1,2} The previous “pancreas rest” theory has been disproved by several trials and meta-analyses a decade ago.^{3,4} Further studies confirmed that early feeding does not exacerbate parenchymal inflammation, facilitates recovery from acute pancreatitis, and is associated with lower mortality and infectious complications.^{3,5-7}

“Gut rousing” theory has emerged in recent years, which is based on the theory that gut function can influence the prognosis of patients with acute pancreatitis.⁸ Reducing pancreatic exocrine stimulation through fasting does not contribute to the recovery of intestinal function.⁸ Pathologic studies indicate that enteral nutrition can protect the intestinal mucosal barrier and reduce bacterial translocation, which can reduce the risk of pancreatic infection and necrosis around the pancreas.⁹ Therefore, early feeding has been recommended in clinical.

The safety of early feeding is verified in several trials and recommended by guidelines.¹⁰⁻¹³ However, the refeeding timing in trials is various, such as returning bowel sounds, hunger-based, or immediate oral feeding.^{12,14,15} In terms of oral refeeding material, such as the conventional stepwise refeeding from clear liquid, a low-fat solid diet, and normal solid foods were performed.¹⁴⁻¹⁶ Therefore, the optimal early feeding strategy for acute pancreatitis remains unclear, such as the best feeding time, material, and patterns. Although the guidelines urge early eating, they do not specifically recommend eating time.¹¹ In addition, a traditional stepwise from clear to solid diet was previously recommended, but studies have shown that a direct solid diet may be beneficial for patient recovery but increase the risk of feeding intolerance.⁴ Although there have been many previous meta-analyses on early feeding, most of them were focused on mild or moderate pancreatitis. In some trials of severe acute pancreatitis, some were predicated severe acute pancreatitis, and the prediction criteria were inconsistent.^{4,17} Therefore, the current conclusions are not widely applicable.

Based on the previous views, a meta-analysis of randomized controlled trials (RCTs) was performed, which included patients with mild, moderate, or severe acute pancreatitis. And trials were stratified by disease severity, feeding time, and pattern, to comprehensively evaluate the better feeding strategy in patients with acute pancreatitis, including refeeding timing, pattern, and material. We assume that early feeding is safe, effective, and cost-effective, and intend to analyze the optimal feeding strategy (CRD42022296576).

METHODS

The PRISMA statement was used to perform the meta-analysis.¹⁸ This study is based on published trials and the ethics declaration is not required. The electronic literature search was undertaken in PubMed, Embase, Web of Science, the Cochrane Library, and China National Knowledge Internet. The search was performed from inception to February 19, 2022, without language restriction, compared to the early and delayed feeding in patients with acute pancreatitis. The search terms were with the following keywords: “early feeding,” “delayed feeding,” “AP,” “acute pancreatitis,” “enteral nutrition,” “oral feeding,” “randomized controlled trial,” or “RCT”. All studies were screened by 2 researchers independently. Any disagreement was consultation with the third party. The inclusion criteria were as follows: (1) compared early and delayed feeding in adult patients with acute pancreatitis and (2) the studies were RCTs. Exclusion criteria were as follows: (1) meta-analysis, case-control study, or editorials were excluded, (2) they compare parenteral and enteral nutrition, (3) compared different enteral nutrition materials, (4) primary outcomes were not reported, and (5) they were duplicates or involved in the same trial. Two reviewers independently screened the titles, abstracts, and full texts using the inclusion and exclusion criteria. Discrepancies were resolved by the third part. Studies quality was assessed according to the Cochrane risk of bias tool.¹⁹

Two investigators independently extracted baseline characteristics of trials and patients and the outcome data. Discrepancies were resolved through negotiation. Continuous variables were summarized with means or medians, and categorical variables were summarized with percentages. The primary outcome was the length of hospital stay (LOHS). Secondary endpoints included mortality, feeding intolerance, and hospital cost. Subgroup analysis and stratification analysis were also performed.

Statistical Analyses

Continuous data were pooled to obtain mean differences and dichotomous data were pooled to obtain risk ratio (RR) with a 95% CI. Heterogeneity was assessed using the Q and I^2 statistic. I^2 score $> 50\%$ was considered as moderate heterogeneity. In case of I^2 score $> 50\%$, a random-effect model would be used, otherwise, the fixed-effects model would be used. The P value < 0.05 was considered statistically significant. Funnel plot and Begg's test were performed to test the publication bias. Sensitivity analysis was conducted by eliminating studies one by one to explore the effect of single studies on outcomes. The effects of feeding pattern, severity, material, type, and feeding timing on clinical outcomes were investigated in a predetermined subgroup analysis. The feeding pattern was separated into oral and tube feeding groups. Severity was grouped according to information provided in the original article and the Computed Tomography Severity Index, in which a score of 4 or higher was considered severe pancreatitis. And stratified analysis was performed based on disease severity. Review Manager Version 5.3 software (The Nordic Cochrane Center) was used for meta-analysis.

RESULTS

During the preliminary search, a total of 430 publications were found. After screening the title and abstract, 80 articles were screened out and 20 RCTs were included for final analysis by reading the full text (Fig. 1).^{4,12–17,20–32}

Twelve trials included mild acute pancreatitis (MAP) patients and 8 trials included moderate, severe, or predicted severe acute pancreatitis patients. The Computed Tomography Severity Index were only reported in 7 studies, 3 of them were considered as severe pancreatitis. In terms of feeding pattern, 6 trials used tube feeding (including 1 nasogastric tube and 5 nasojejunal tube feeding), and the remaining 14 trials were oral feeding. The timings of start feeding were various. The study design and trial characteristics are listed in Table 1. The baseline characteristics of patients were shown in Table 2. There are 2169 patients included. The mean age is 55.5 years old, and more than half of the patients were males. Biliary pancreatitis was the most reason for pancreatitis, accounting for 54.5%. The level of serum amylase, lipase, leukocytes, and C-creative protein in 2 groups was also listed. For invasive procedures, 6 of the 20 trials were reported and only 3 trials were reported in detail. For early feeding groups, the rate of invasive procedures was 0% to 20%, among these; endoscopic retrograde cholangiopancreatography accounted for 0% to 10%. In the control group, the rate of the invasive procedure was slightly higher than experiment group, was 5% to 46%, and endoscopic retrograde cholangiopancreatography was 1.6% to 20% (details in Supplemental Table S1, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>).

The Cochrane Risk Assessment Tool was used to evaluate the quality of the included studies. Since most of the trials were single-blind or open-label, there were significant performance bias and detection bias. A slight selection bias was observed, due to some studies did not declare the random methods. Results were shown in Supplemental Figure S1 (Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>).

The Primary Outcomes

All of the trials reported the primary outcome of LOHS in both groups. The pooled analysis demonstrates that the LOHS of the early feeding group was significantly lower than that of the delayed feeding group, with a significant bias (mean difference = -2.35 , 95% CI: -2.89 to 1.80 ; $P < 0.0001$, $I^2 = 72\%$) (Fig. 2). Funnel plot shown slight asymmetry in this outcome, result shown in Supplemental Figure S2 (Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>). Further, Begg's tests were performed, showing no potential publication bias ($P = 0.87$). Sensitivity analysis showed that one study deviated significantly from the combined effect (Supplemental Fig. S3, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>). However, heterogeneity did not change significantly after the study was removed.

The Secondary Outcomes

Seven of 20 trials reported the feeding intolerance outcome. Meta-analysis showed that no significant difference in feeding intolerance in early and delayed feeding groups (RR = 0.96, 95% CI 0.40 to 2.16, $P = 0.87$, $I^2 = 70\%$), shown in Fig. 3 (A). For the mortality outcomes, there is no significant difference between the two groups (RR = 0.91, 95% CI 0.57 to 1.46, $P = 0.69$, $I^2 = 0\%$), shown in Fig. 3 (B). Three studies reported hospital costs, which were significantly less in the early feeding group than in the delayed feeding group, with an average savings of 57.7% in medical costs (Table 3).

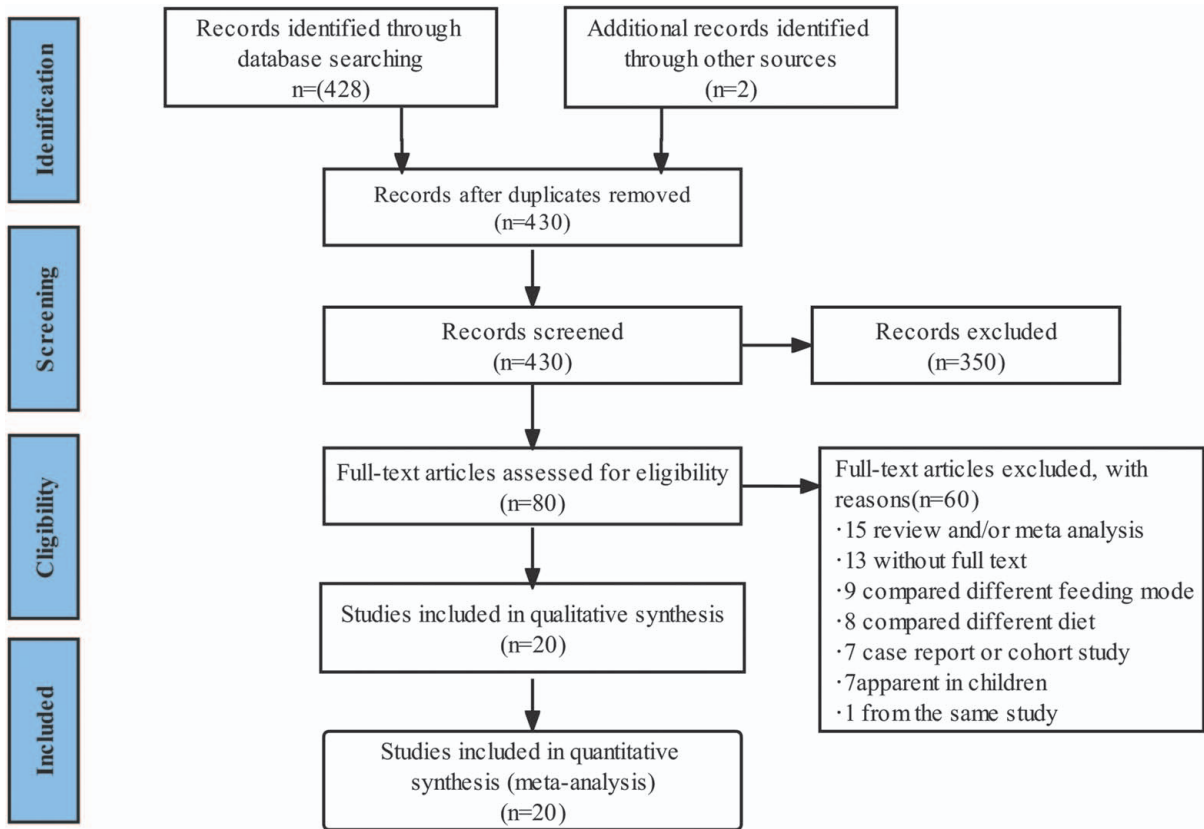


FIGURE 1. Flowchart of meta-analysis.

Subgroup Analysis

Subgroup analysis was performed based on the preset subgroup in the protocol. For the feeding pattern subgroup, 14 of 20 trials were early oral feeding, and the other 6 trials

were tube feeding. Analysis has shown that there was a significant difference in the LOHS between oral feeding and tube feeding subgroups ($P_{int} = 0.04$, Supplemental Fig. S4, Supplemental Digital Content 1, <http://links.lww.com/JCG/>

TABLE 1. Characteristics of RCTs Included

Study, year	Country	Severity	Refeeding time	Refeeding material	Feeding mode
Ramirez-Maldonado, 2021 ¹²	Spain*	MAP, MSAP	Immediately upon hospital admission	Low-fat diet	Oral feeding
Yang, 2018 ³²	China	MAP	Immediately upon hospital admission	Clear liquid diet	Oral feeding
Wu, 2009 ³¹	China	MAP	Immediately upon hospital admission	Low-fat diet	Oral feeding
Esmer, 2021 ²⁰	Mexico	MAP, MSAP	Within 8 h after treatment	Nutrition drinks	Tube feeding
Khan, 2017 ²³	Pakistan	MAP	Within 12 h	—	Oral feeding
Li, 2013 ²⁴	China	MAP	Felt hungry	Clear liquid diet	Oral feeding
Lozada-Hernández, 2020 ²⁵	Mexico	MAP	During 16 to 24 h	Soft diet	Oral feeding
Eckerwall, 2007 ⁴	Sweden	MAP	Immediately upon hospital admission	Eat and drink freely	Oral feeding
Horibe, 2020 ²¹	Japan	MAP	Within 24 h of diagnosis	Low-fat food	Oral feeding
Stimac, 2016 ¹³	Croatia	Predicted SAP	Within 24 h of admission	Nutrition drinks	Nasojejunal
Lariño-Noia, 2014 ¹⁵	Spain	MAP	Bowel sounds are present.	Normal solid foods	Oral feeding
Petrov, 2013 ²⁶	New Zealand	MAP, MSAP	Within 24 h of hospital admission	Nutrition drinks	Nasogastric
Teich, 2010 ²⁹	Germany	MAP	Self-selection	Low-fat diet	Tube feeding
Rai, 2022 ¹⁴	India	MSAP, SAP	Felt hungry	Clear liquid diet	Tube feeding
Jin, 2020 ²²	China*	MSAP, SAP	Within 48 h after admission	Nutrition drinks	Nasojejunal
Sun, 2013 ²⁸	China	SAP	Within 48 h after admission	Nutrition drinks	Nasojejunal
Tong, 2019 ³⁰	China	MSAP	Felt hungry	Low-fat diet	Oral feeding
Zhao, 2015 ¹⁶	China	MSAP, SAP	Felt hungry	Clear liquid diet	Oral feeding
Bakker, 2014 ¹⁷	Netherlands*	Predicted SAP	Within 24 h after admission	Nutrition drinks	Nasojejunal
Powell, 2000 ²⁷	United Kingdom	Predicted SAP	Early enteral nutrition	Nutrition drinks	Nasojejunal

*Multicenter study.

MAP indicates mild acute pancreatitis; MSAP, moderate-severe acute pancreatitis; RCT, randomized controlled trial; SAP, severe acute pancreatitis.

TABLE 2. The Baseline Characteristics of Patients in This Meta-analysis

Study, year	group	n	Age, mean	Male, n	Etiology				Hours from onset to admission	Serum amylase	Serum lipase	Leukocytes	CRP
					Biliary	Alcoholic	Hyperlipidemia	Miscellaneous					
Ramírez-Maldonado, 2021 ¹²	Exp	71	70.2	37	54	6	0	11	24	1339.9	4182.5	9.4	10.5
	Con	60	64.9	30	42	10	0	8	24	1527.6	5259.7	9.2	9.4
Rai, 2022 ¹⁴	Exp	56	38	56	0	54	0	2	—	755.1 (721)	—	—	—
	Con	54	37.9	48	3	47	0	4	—	800.7 (545)	—	—	—
Esmer, 2021 ²⁰	Exp	29	37	3	29	0	0	0	35.7 (22.7)	1523 (587)	1024 (315)	8.3 (3.99)	—
	Con	30	38	5	30	0	0	0	51.4 (34.3)	1357 (689)	945 (358)	8.9 (4.3)	—
Lozada-Hernández, 2020 ²⁵	Exp	61	45.3	15	61	0	0	0	20 (2.6)	—	540.2 (111.1)	10.2 (1.4)	—
	Con	59	50	18	59	0	0	0	22.3 (1.9)	—	531.6 (130.1)	10.4 (1.3)	—
Jin, 2020 ²²	Exp	91	48	57	60	17	11	3	—	—	—	—	142.4 (45.9)
	Con	196	46	121	120	39	25	12	—	—	—	—	117.1 (36.5)
Horibe, 2020 ²¹	Exp	13	50.1	10	0	7	0	6	21.6 (21.6)	—	—	—	—
	Con	13	60.8	8	2	4	1	6	16.8 (21.6)	—	—	—	—
Tong, 2019 ³⁰	Exp	60	48.5	32	—	—	—	—	—	304 (402)	358 (435)	14.2 (7.6)	—
	Con	60	49.3	31	—	—	—	—	—	139 (151)	253 (198)	9.1 (4.8)	—
Yang, 2018 ³²	Exp	42	44.3	23	30	1	5	6	—	—	—	—	—
	Con	42	44.7	20	25	2	7	8	—	—	—	—	—
Khan, 2017 ²³	Exp	30	—	—	—	—	—	—	—	—	—	—	—
	Con	30	—	—	—	—	—	—	—	—	—	—	—
Stimac, 2016 ¹³	Exp	107	68	44	68	17	5	16	—	—	—	—	—
	Con	107	71	57	64	23	1	19	—	—	—	—	—
Zhao, 2015 ¹⁶	Exp	67	51	43	13	12	33	9	40.8 (31.2)	1523 (584)	1024 (315)	12.8 (5.9)	—
	Con	71	48	43	16	14	29	12	36 (28.8)	1357 (689)	945 (358)	12.9 (3.5)	—
Lariño-Noia, 2014 ¹⁵	Exp	37	—	18	20	9	3	5	17.5 (20.8)	—	6084.5 (4056.1)	—	—
	Con	35	—	15	20	7	1	6	16.4 (16.7)	—	5514.2 (3061.2)	—	—
Bakker, 2014 ¹⁷	Exp	101	65	55	59	14	0	28	12.5 (4.6)	—	—	—	73.3 (31.6)
	Con	104	65	59	56	23	0	28	13.6 (5.8)	—	—	—	77.7 (35.4)
Sun, 2013 ²⁸	Exp	30	45	20	19	4	6	1	—	—	—	—	197 (21.2)
	Con	30	43	18	17	3	8	2	—	—	—	—	207.5 (15.9)
Petrov, 2013 ²⁶	Exp	17	42	10	10	3	0	4	—	947 (527)	—	10 (1.3)	57 (44.8)
	Con	18	54	8	10	5	0	3	—	839 (177)	—	12 (2.2)	70 (35.4)
Li, 2013 ²⁴	Exp	75	49	53	41	19	0	15	20.1 (17.2)	3247 (689)	2021 (732)	14.6 (4.3)	—
	Con	74	48	47	37	19	0	18	23.7 (12.9)	3326 (657)	2143 (568)	13.9 (4.9)	—
Teich, 2010 ²⁹	Exp	69	45.4	42	19	30	2	18	27.1	—	—	—	—
	Con	74	46.7	51	24	34	0	16	32.4	—	—	—	—

TABLE 2. (continued)

Study, year	group	n	Age, mean	Male, n	Etiology						Hours from onset to admission	Serum amylase	Serum lipase	Leukocytes	CRP
					Biliary	Alcoholic	Hyperlipidemia	Miscellaneous							
Wu, 2009 ³¹	Exp	34	47	14	14	6	0	14	29.5 (6.2)	752 (253)	—	8.2 (2.2)	90 (32)		
	Con	35	50	16	17	3	0	15	32.8 (5.7)	789 (247)	—	7.5 (3.4)	88 (27)		
Eckerwall, 2007 ⁴	Exp	30	57	13	18	3	0	9	32 (5.9)	897 (323.5)	—	—	—		
	Con	30	51	14	14	2	0	11	27 (3.4)	762 (264.7)	—	—	—		
Powell, 2000 ²⁷	Exp	13	—	—	7	4	1	1	—	—	—	—	—		
	Con	14	—	—	3	7	2	2	—	—	—	—	—		
Total (%)		2169	55.5	54.5	55	—	—	—	—	—	—	—	—		

Con indicates controlled group; CRP, C-reactive protein; Exp, experimental group (early feeding group).

A990). In the subgroup of the severity of acute pancreatitis, 8 trials are MAP and 12 trials are moderate, severe, or predicted severe acute pancreatitis. There was no significant statistical difference between this subgroup ($P_{int} = 0.27$, Supplemental Fig. S5, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>). In the subgroup of Computed Tomography Severity Index, patients in both groups could benefit from early feeding, and there was no significant statistical difference between this subgroup ($P < 0.001$, $P = 0.03$, $P_{int} = 0.11$; Supplemental Fig. S6, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>). In the subgroup of feeding material, low-fat seems to be more beneficial than clear liquid or nutrition drinks ($P < 0.001$, $P = 0.02$, $P = 0.08$, respectively), but the difference between groups did not reach statistical significance ($P_{int} = 0.09$, Supplemental Fig. S7, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>). The feeding timing was divided into immediate, within 24 hours, and without 24 hours. There was no difference among the 3 groups ($P_{int} = 0.73$, Supplemental Fig. S8, Supplemental Digital Content 1, <http://links.lww.com/JCG/A990>).

Stratification Analysis

To obtain more accurate data to guide clinical work, the included studies were stratified analysis according to disease severity. In MAP patients, oral feeding was significantly better than tube feeding ($P_{int} = 0.006$). A similar advantage was observed in severe pancreatitis patients ($P = 0.009$ in the oral feeding group and $P = 0.40$ in the tube feeding group), but it was not statistically significant ($P_{int} = 0.35$). In the severity acute pancreatitis (SAP) group, the low-fat diet was significantly better than the other 2 diets ($P_{int} = 0.005$). A similar advantage was observed in mildly ill patients ($P = 0.16$ in the clear liquid group, $P < 0.0001$ in the low-fat group, and $P < 0.0001$ in the nutrition drinks group), but it was not statistically significant ($P_{int} = 0.78$). In terms of feeding time, feeding within 24 hours in mild patients ($P = 0.009$ in the immediate group, $P < 0.0001$ in the within 24 hours group, and $P = 0.07$ in the without 24 hours group) and after 24 hours in severe patients ($P = 0.95$ in within 24 hours group and $P = 0.0005$ in without 24 hours group) appeared to be more advantageous. However, there was no statistical significance between the two groups ($P = 0.21$ in the MAP group and $P = 0.11$ in the SAP group). All of the results were shown in Figure 4.

DISCUSSION

Results of this meta-analysis suggest that early feeding reduces LOHS without increasing feeding intolerance or mortality in patients with acute pancreatitis. Meantime, the cost was significantly reduced in the early feeding group. Subgroup and stratified analysis suggested that oral feeding seems to be more beneficial than tube feeding. Starting with a low-fat diet seemed to be a better plan. It may be more beneficial to start feeding within 24 hours in mild cases and 24 hours later in severe cases.

Due to increased catabolism and reduced intake, patients with acute pancreatitis were considered at moderate to high nutritional risk, especially severely ill patients. Previous studies have shown that gut-barrier dysfunction can occur in about 60% of acute pancreatitis patients, leading to bacterial translocation and infection of necrosis.⁹ Enteral nutrition may help protect the intestinal mucosal barrier and

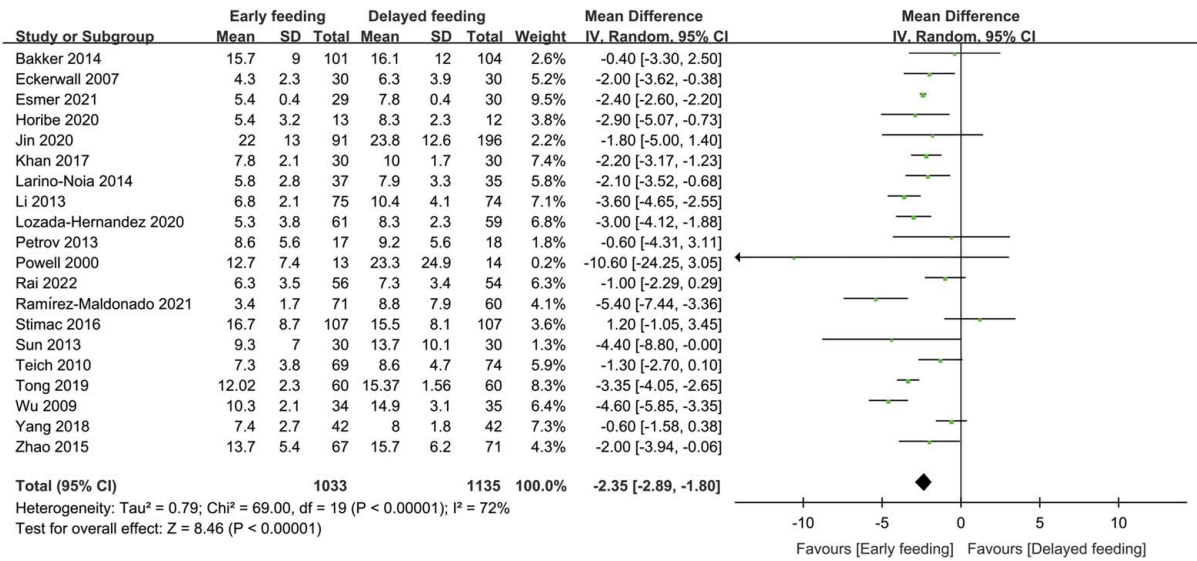


FIGURE 2. The forest plot of the length of hospital stays.

reduce bacterial translocation, which will reduce the risk of pancreatic infection and necrosis around the pancreas.⁹ Makola et al³³ also demonstrated the effectiveness of enteral nutrition through clinical studies. Thus, nutritional support for acute pancreatitis aims not only to prevent and treat malnutrition but also to modulate and reduce altered inflammatory responses. “European Society of Parenteral and Enteral Nutrition” guideline on clinical nutrition in acute and chronic pancreatitis suggested that patients predicted to MAP should be given a low-fat, soft oral diet as soon as clinically tolerated.¹⁰ Meanwhile, the American Gastroenterological Association recommends that patients with acute pancreatic should have oral feeding within 24 hours, with moderate quality evidence.¹¹ Although the

guidelines recommend early feeding, the feeding timing, and the material were not uniform. And the refeeding recommendations on severe acute pancreatitis lack high-quality evidence. At present, there are some randomized controlled studies on the refeeding of patients with severe pancreatitis, but there are various feeding patterns and materials, and the results were mixed.^{14,16} Most previous meta-analyses were focused on mild or moderate acute pancreatitis, and some of them included case-control studies, which may reduce the quality of evidence.³⁴ Therefore, it is necessary to review and analyze the available evidence to produce more refined recommendations to guide clinical practice.

We included the trials comprehensively, comparing early with delayed feeding in patients with mild, moderate,

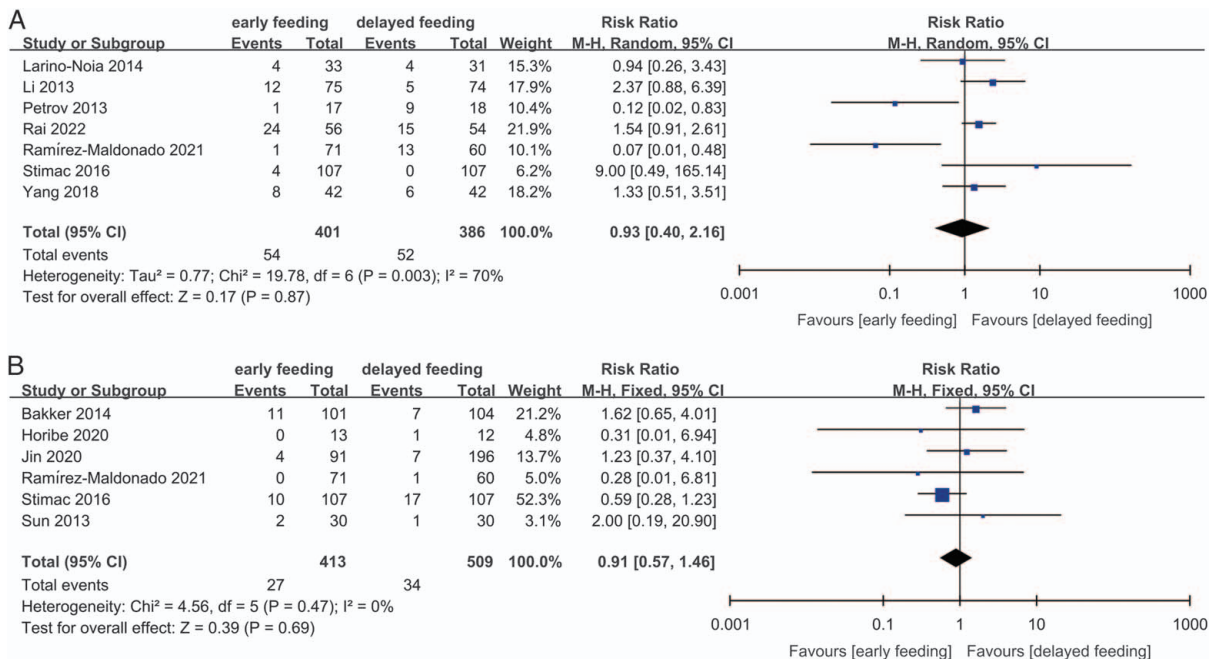


FIGURE 3. Forest plot of feeding intolerance (A) and mortality (B).

TABLE 3. Hospitalization Cost of Included Trials

Study, year	Early feeding group (\$)	Delayed feeding group (\$)	Cost saving (\$)	Saving rate (%)
Horibe, 2020 ²¹	830	1340	510	61.9
Lozada-Hernandez, 2020 ²⁵	2080	3310	1221	63.1
Ramirez-Maldonado, 2021 ¹²	1230.1	2556.8	1325.7	48.1
Average	1380	2402.3	1018.9	57.7

and severe pancreatitis. Among the primary outcome, early feeding was more significant efficacy than delayed feeding, which was consistent with guidelines recommendations. Although the result was highly heterogeneous ($P = 72\%$), sensitivity analysis did not find a single study that influenced the results. In addition, Begg’s test found no significant publication bias. The source of heterogeneity was considered due to the differences between the etiology, severity, and feeding patterns. To comprehensively analyze the optimal feeding strategies for acute pancreatitis, the inclusion criteria were broad in this analysis, which increased the heterogeneity meanwhile decrease the accuracy of the results. In addition, the impact of invasive procedures on outcomes has not been explained in this article. According to Shrode et al,³⁵ a bridging stent could get a good prognosis for pancreatic duct disruptions. The data displayed that the LOHS is significantly affected by those accepted invasive procedures. But it could not be analyzed in this paper, the effect of invasive procedures on prognosis and outcomes needs to be discussed in specific trials.

No significant differences were observed in feeding intolerance of the secondary outcome. Although most studies suggested that early feeding would increase the rate of vomiting, nausea, and abdominal pain.^{14,24} But the phenomenon was not observed in this meta-analysis. The recently published PADI study noted that compared with conventional oral refeeding, immediate oral feeding was with lower rates of recurrent abdominal pain, feeding

intolerance, complications, and intensive care unit admission.¹² Current results support that enteral nutrition reduces intestinal dysfunction, but there is no clear clinical or pathophysiological explanation. Further pathophysiological research and more clinical data are expected.

In terms of cost-effectiveness, early feeding significantly reduced hospitalization costs, but the result was only drawn from 3 trials of MAP. For severe patients, because of the higher incidence of systemic inflammatory reactions, sepsis, and multiple organ failure, the cost composition was more complicated. More data are needed to determine whether early enteral nutrition can reduce hospitalization costs in severe patients by improving intestinal permeability and reducing bacterial ectopic and infection rates.

Subgroup analysis showed that both severe and mild patients could benefit from early feeding, and the low-fat diet seemed to be the preferred strategy. This was consistent with the recommended guidelines. As shown in the “acute experimental pancreatitis” study, basal and stimulated pancreatic enzyme secretion may be significantly reduced early after the onset of acute pancreatitis.³⁶ Previous studies have supported these results.^{37,38} Start refeeding with clear liquid may unnecessarily prolong hospital stays and incur unnecessary costs. Jacobson et al³⁷ study has shown that starting a low-fat solid diet does not increase dietary intolerance in patients, which is consistent with our conclusion. We further concluded that starting with a low-fat solid diet can reduce the LOHS and

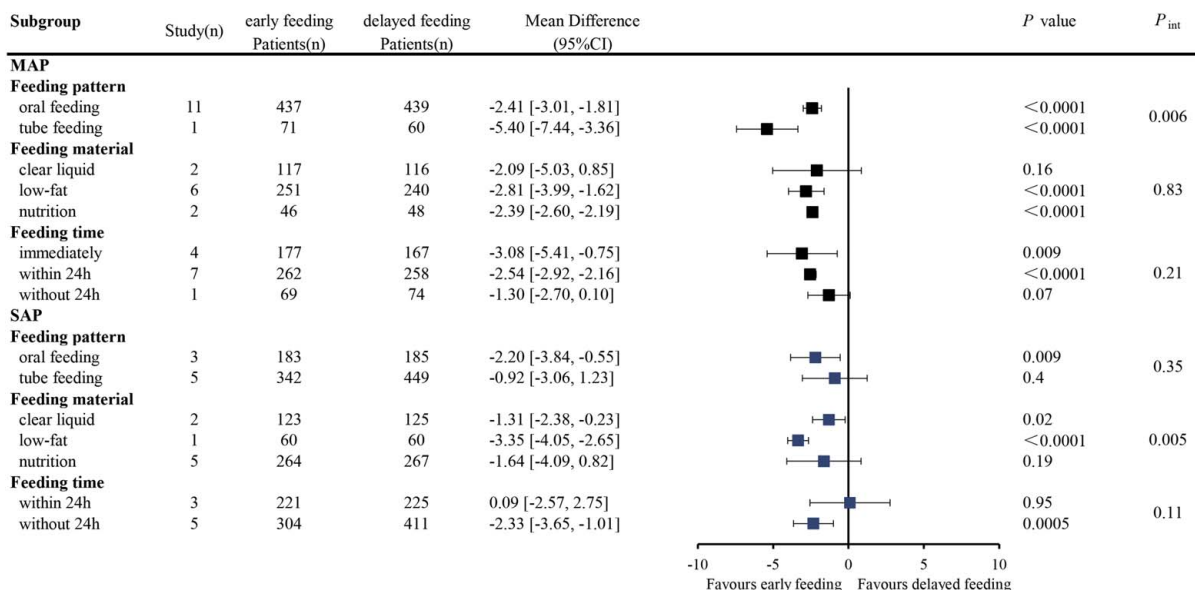


FIGURE 4. Stratification analysis according to the severity of disease. MAP indicates mild acute pancreatitis, SAP, severity acute pancreatitis.

save costs. In further feeding patterns, the European Society of Parenteral Enteral Nutrition guideline recommended nasogastric should be admitted in enteral nutrition, and nasojejunal tube only could be performed in case of digestive intolerance.¹⁰ The studies included in this meta-analysis were insufficient to explain the difference between nasogastric and nasojejunal feeding. This issue needs to be analyzed by targeted studies.

In terms of feeding time, it is recommended to start within 24 hours for mild cases and without 24 hours for severe cases. In patients with severe pancreatitis, the more pronounced clinical symptoms, metabolic disturbances, and gastrointestinal motility disorders caused by abdominal hypertension are usually only more pronounced within the first 24 hours, so it is usually not possible to start eating earlier. Khaliq et al³⁹ reported that eating within 48 hours of symptom control reduced mortality in patients with SAP. This has a certain guiding significance for the feeding strategy of severe patients, which is also consistent with most current intensive care unit guidelines.^{40,41} However, the methodological quality of the underlying trials from these suggested sources has been questioned, and as a result, there is still a lack of large, high-quality, randomized, controlled trials of early feeding in patients with severe acute pancreatitis.⁴²

Limitation

Although the trials included in this meta-analysis were comprehensive and the results were significant statistical differences, the conclusion still should be interpreted cautiously. Heterogeneity is a problem that cannot be ignored. Although this problem can be explained in stratified analysis, it is a very important problem that the number of people included in most studies is small and statistical effect cannot be achieved. Secondly, due to the limitation of the study design, most studies adopted open-label or single-blind, which resulted in significant performance and detection bias. Despite the inclusion of 20 studies, except for the main outcome, other outcomes have not been fully reported by all studies, which is one of the limitations of this study. Therefore, we look forward to the results from larger RCTs of acute pancreatitis, especially severe pancreatitis.

CONCLUSIONS

Early oral feeding is recommended for patients with acute pancreatitis, meta-analysis results are consistent with current guidelines, which could reduce LOHS and hospitalization costs without increasing feeding intolerance or mortality. In patients with severe pancreatitis, early feeding after 24 hours may be beneficial. This study contributes further evidence to existing recommendations that health care teams more closely adhere to clinical guidelines and focus on early enteral nutrition.

REFERENCES

1. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. *Gastroenterology*. 2019;156:254–272.e211.
2. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019;16:175–184.
3. Marta K, Farkas N, Szabo I, et al. Meta-analysis of early nutrition: the benefits of enteral feeding compared to a nil per os diet not only in severe, but also in mild and moderate acute pancreatitis. *Int J Mol Sci*. 2016;17:1691.
4. Eckerwall GE, Tingstedt BB, Bergenzaun PE, et al. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. *Clin Nutr*. 2007;26:758–763.
5. Qi D, Yu B, Huang J, et al. Meta-analysis of early enteral nutrition provided within 24 hours of admission on clinical outcomes in acute pancreatitis. *JPEN J Parenter Enteral Nutr*. 2018;42:1139–1147.
6. Al-Omran M, Albalawi ZH, Tashkandi MF, et al. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Sys Rev*. 2010;2010:CD002837.
7. Jabłońska B, Mrowiec S. Nutritional support in patients with severe acute pancreatitis—current standards. *Nutrients*. 2021;13:1498.
8. Petrov MS, Windsor JA. Nutritional management of acute pancreatitis: the concept of ‘gut rousing’. *Curr Opin Clin Nutr Metab Care*. 2013;16:557–563.
9. Wu LM, Sankaran SJ, Plank LD, et al. Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis. *Br J Surg*. 2014;101:1644–1656.
10. Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. *Clin Nutr*. 2020;39:612–631.
11. Crockett SD, Wani S, Gardner TB, et al. American gastroenterological association institute guideline on initial management of acute pancreatitis. *Gastroenterology*. 2018;154:1096–1101.
12. Ramirez-Maldonado E, Gordo S, Pueyo EM, et al. Immediate oral refeeding in patients with mild and moderate acute pancreatitis: a multicenter, randomized controlled trial (PADI trial). *Ann Surg*. 2021;274:255–263.
13. Stimac D, Poropat G, Hauser G, et al. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: a randomized clinical trial. *Pancreatol*. 2016;16:523–528.
14. Rai A, Anandhi A, Sureshkumar S, et al. Hunger-based versus conventional oral feeding in moderate and severe acute pancreatitis: a randomized controlled trial. *Dig Dis Sci*. 2022;67:2535–2542.
15. Lariño-Noia J, Lindkvist B, Iglesias-García J, et al. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. *Pancreatol*. 2014;14:167–173.
16. Zhao XL, Zhu SF, Xue GJ, et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. *Nutrition*. 2015;31:171–175.
17. Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Eng J Med*. 2014;371:1983–1993.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
19. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
20. Esmer D, Rivera-Villalobos O, Hernandez-Sierra JF, et al. Immediate feeding tolerance in patients with mild acute biliary pancreatitis. *Cir Cir*. 2021;89:243–247.
21. Horibe M, Iwasaki E, Nakagawa A, et al. Efficacy and safety of immediate oral intake in patients with mild acute pancreatitis: a randomized controlled trial. *Nutrition*. 2020;74:110724.
22. Jin Z, Wang Z, Wang J. Early enteral nutrition prevent acute pancreatitis from deteriorating in obese patients. *J Clin Gastroenterol*. 2020;54:184–191.
23. Khan S, Ranjha WA, Tariq H, et al. Efficacy of early oral refeeding in patients of mild acute pancreatitis. *Pak J Med Sci*. 2017;33:899–902.
24. Li J, Xue GJ, Liu YL, et al. Early oral refeeding wisdom in patients with mild acute pancreatitis. *Pancreas*. 2013;42:88–91.
25. Lozada-Hernández EE, Barrón-González O, Vázquez-Romero S, et al. Non-inferiority comparative clinical trial between early oral REFEEDING and usual oral REFEEDING in predicted mild acute biliary pancreatitis. *BMC Gastroenterol*. 2020;20:228.

26. Petrov MS, McIlroy K, Grayson L, et al. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. *Clin Nutr*. 2013;32:697–703.
27. Powell JJ, Murchison JT, Fearon KC, et al. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. *Br J Surg*. 2000;87:1375–1381.
28. Sun JK, Mu XW, Li WQ, et al. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol*. 2013;19:917–922.
29. Teich N, Aghdassi A, Fischer J, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. *Pancreas*. 2010;39:1088–1092.
30. JiaZhao T, ShuTang W, YiNuo H, et al. Correlation of hunger and oral refeeding in the treatment of acute pancreatitis. *China J Modern Med*. 2019;29:81–84.
31. WeiHong W, Ling W, QiaoYu W, et al. Clinical research of early oral feeding in mild acute pancreatitis patients. *Parenteral Enteral Nutrition*. 2009;16:212–214.
32. Jun Y, Qin Q, Tian W, et al. Effect of very early feeding on clinical outcomes in patients with mild acute pancreatitis. *Parenteral Enteral Nutrition*. 2018;25:301–303+307.
33. Makola D, Krenitsky J, Parrish C, et al. Efficacy of enteral nutrition for the treatment of pancreatitis using standard enteral formula. *Am J Gastroenterol*. 2006;101:2347–2355.
34. Vaughn VM, Shuster D, Rogers MAM, et al. Early Versus delayed feeding in patients with acute pancreatitis a systematic review. *Ann Intern Med*. 2017;166:883–88.
35. Shrode CW, Macdonough P, Gaidhane M, et al. Multimodality endoscopic treatment of pancreatic duct disruption with stenting and pseudocyst drainage: how efficacious is it? *Dig Liver Dis*. 2013;45:129–133.
36. Niederau C, Niederau M, Lüthen R, et al. Pancreatic exocrine secretion in acute experimental pancreatitis. *Gastroenterology*. 1990;99:1120–1127.
37. Jacobson BC, Vander Vliet MB, Hughes MD, et al. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. *Clin Gastroenterol Hepatol*. 2007;5:946–951; quiz 886.
38. Moraes JM, Felga GE, Chebli LA, et al. A full solid diet as the initial meal in mild acute pancreatitis is safe and result in a shorter length of hospitalization: results from a prospective, randomized, controlled, double-blind clinical trial. *J Clin Gastroenterol*. 2010;44:517–522.
39. Khaliq A, Dutta U, Kochhar R, et al. Management of acute pancreatitis: “PANCREAS” contains eight easy steps to remember the treatment. *J Pancreas*. 2010;11:492–493.
40. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27:355–373.
41. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr*. 2006;25:210–223.
42. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Eng J Med*. 2014;370:1227–1236.