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Effects of immediate or early oral feeding on acute pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Background: The timing of oral refeeding can affect length of stay (LOS) and recovery of acute pancreatitis (AP). However, the optimal timing for oral refeeding is still controversial for AP. This meta-analysis investigated the effects of immediate or early versus delayed oral feeding on mild and moderate AP, regardless of improvement in clinical signs or laboratory indicators.

Methods: This systematic review and meta-analysis of randomized controlled trials (RCTs) based on data from Embase, Cochrane Library, PubMed, Web of science, and CBM before August 2021. Two researchers independently used Stata16 to extract and analyse study data. Random effect model was performed for meta-analysis to calculate the risk ratio (RR) and standardized mean difference (SMD).

Results: 8 RCTs were selected, including 748 patients with mild to moderate AP. Patients in IOR (Immediate or early Oral Refeeding) group had less costs [SMD -0.83, 95%CI (−1.17, −0.5), P < 0.001] and shorter LOS [SMD -1.01, 95%CI (−1.17, −0.85), P < 0.001] than the DOR (Delayed Oral Refeeding) group patients. However, there was no difference in mortality [RR 0.54, 95%CI (0.11, 2.62), P = 0.44], pain relapse rate [RR 0.58, 95%CI (0.25, 1.35), P = 0.27], feeding intolerance rate [RR 0.61, 95%CI (0.28, 1.3), P = 0.2], AP progression rate [RR 0.21, 95%CI (0.04, 1.07), P = 0.06] and overall complications rate [RR 0.41, 95%CI (0.17, 1.01), P = 0.05] between the IOR and DOR groups.

Conclusions: Limited data suggest that IOR could reduce LOS and costs without increasing adverse events in mild to moderate AP.

1. Introduction

Acute pancreatitis (AP) is seriously affecting the health and safety of people, and its morbidity is increasing [1,2]. Nutritional support is a critical component in the early management of AP, preventing malnutrition and reducing serious complications and mortality [3]. It is clear that enteral nutrition (EN) is superior to parenteral nutrition (PN) for AP patients. And guidelines have recommended EN rather than PN should be preferred for AP patients who cannot feed orally [4,5]. At one time, "pancreatic rest " (fasting) was prevalent in the initial treatment of AP to prevent disease relapse and pain. However, studies found that the mitochondrial damage and ATP (energy) depletion play a key role in the early phase of AP, there is a strong energy breakdown in the early phase of AP [6–8]. Therefore, early energy intake either by tube feeding or oral feeding can be beneficial for AP [2,9,10].

Oral feeding is one approach of EN in AP. It is more acceptable than tube feeding, relieving the intubation discomfort and reducing the intubation complications [11,12]. Timing of oral refeeding affects the recovery and length of stay (LOS) for AP patients [13]. However, the timing of oral refeeding is still controversial in mild and moderate acute pancreatitis (MAP). Moreover, the outdated treatment regimen of fasting and gradually increasing intake over 5–7 days remains the current clinical treatment options for AP [14]. To address this issue, we conducted this meta-analysis of RCTs to assess whether immediate or early oral feeding affects the LOS, costs and adverse events for MAP, regardless of clinical signs or laboratory indicators.

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2. Materials and methods

2.1. Objectives

According to PICOs of the Preferred Report Items for Systematic Reviews and Meta-Analysis (PRISMA), the component of this systematic review (population, intervention, comparison, outcome) as follows:

2.1.1. Population

Patients diagnosed with MAP.

2.1.2. Intervention

IOR, defined as oral feeding was resumed immediately once admission or subjective feeling of hunger, rather than waiting for clinical symptoms and laboratory indices to improve.

2.1.3. Comparison

DOR, defined as oral feeding was resumed after clinical symptoms and laboratory indices improved.

2.1.4. Outcome

Primary outcomes: LOS and costs. Secondary outcomes: adverse events (mortality, feeding intolerance, pain relapse, progress of AP and overall complications).

2.2. Data and searches

We performed a systematic literature search for the RCTs of IOR in AP before August 2021 in Cochrane Library, PubMed, CBM, Embase, Web of science and Wanfang Database. The search terms were “Pancreatitis”, “oral refeed”, “eating”, “Nutritional Intake” and “randomized controlled trial” (Supplementary material shows the complete search strategy). We also searched Clinical Trials.gov for completed trials before August 2021.

2.3. Eligibility criteria

Inclusion criteria: (1) original RCT of IOR versus DOR, regardless of language, race or publication status; (2) patients diagnosed with MAP. Exclusion criteria: (1) duplicate publications; (2) patients <18 years of age; (3) lack of relevant clinical outcomes (4) not the original article (editorial, case report, report review).

2.4. Study selection and data extraction

The determination of articles is divided into two stages: (1) Two authors (QY, SYP) independently screened the possible studies through the eligibility criteria. And references of the included articles were screened to find the studies which were not determined in the initial search. (2) the extraction of data is completed by the first author (QY) and independently verified by two co-authors (XX,

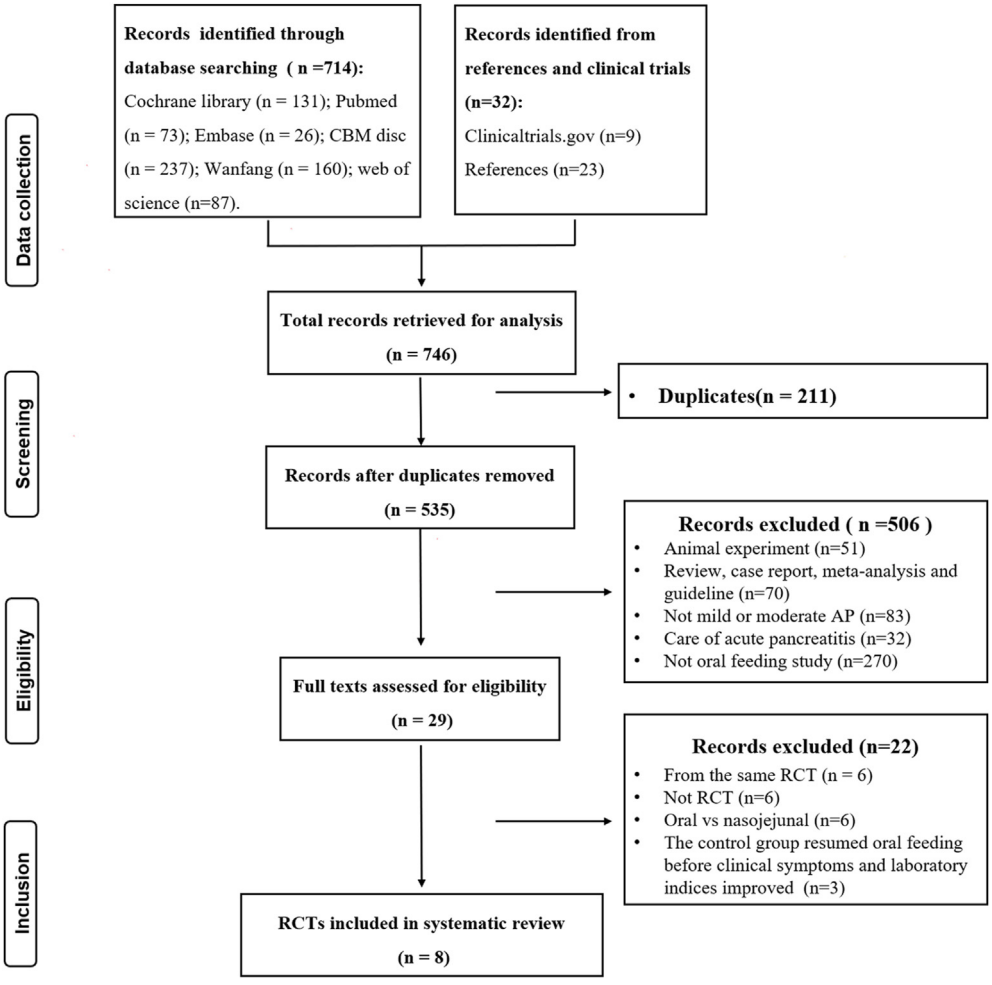

Fig. 1. Study flow diagram. RCT = randomized controlled trial.

SYP). The differences in the interpretation of the extracted data were resolved through mutual consensus.

2.5. Risk of bias assessment

Three authors (QY, YPW and XX) independently completed quality assessments of the selected studies according to the Cochrane guidelines [15]. Differences were resolved by discussion.

2.6. Statistical analysis

We extracted information from the included study: first author, year, study period, country, classification of AP severity, sample size, diet type, oral refeeding time, basic characteristics of participants and outcomes. A meta-analysis would be performed when data from at least two studies was available. DerSimonian-Laird method based on an inverse variance weighted random effects model was used to calculate risk ratios (RR) and 95% confidence intervals (CI) of dichotomous data and standardized mean differences (SMD) and 95% CI of continuous data [16]. Subgroup analyses were performed on pain relapse and feeding intolerance. I [2] was used to evaluate Heterogeneity. There are three levels of heterogeneity: low (I2< 25%), moderate (I2 = 25–50%) and high (I2>50%) [17]. Publication bias was evaluated by Begg's and Egger's tests [18]. Stata16 (StataCorp, College Station, TX) was used for analysis. Results $P < 0.05$, the difference was statistically significant.

3. Results

3.1. Study selection

As shown in Fig. 1, 746 records identified through database searching, references and clinical trials. 29 of these records qualified for inclusion in this review. After carefully reviewed, 6 of the included articles were duplicate publications, 6 of were not RCT, 6 of were not just oral refeeding, and the control group resumed oral feeding before clinical symptoms and laboratory indicators improved in 3 studies. Finally, 8 trials examining the timing of oral refeeding on MAP were qualified for inclusion [2,13,19–24].

3.2. Characteristics of studies

Table 1 shows the characteristics of the included trials [2,13,19–24]. The 8 studies contained 748 MAP patients, conducted between 2003 and 2019, involved China, Spain, Turkey, Sweden, Japan and Mexico. In 5 of the included trials, oral refeeding of the IOR group patients was resumed immediately once admission regardless of clinical signs and laboratory indicators [2,13,19,22,23]. In 3 trials, patients in the IOR group immediately resumed oral refeeding when they felt subjectively hungry [20,21,24].

3.3. Patient characteristics

As shown in Table 2, a total of 748 MAP patients were selected, 375 (50.1%) of whom were male. Among them, the cause was gallstones in 450 (60.2%), alcohol in 127 (16.9%), and others in 171 (22.9%). APACHE II was used more frequently than Ranson score.

3.4. Risk of bias within studies

Table 3 summarizes the risk of bias in the included studies

Table 1
The characteristics analysis of included trials.

Studies	Study period	Country	severity of AP	Group (n)		Oral feeding condition		Type of diet		Oral refeeding time after admission		
				IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	*P*
Eckerwall, 2007 [19]	2003–2005	Sweden	Mild AP	29	30	Immediately	Clinical symptoms and laboratory indices had improved	Eating freely if tolerated	Increased the intake during 3-7d	0 ± 0.7	3 ± 0.7	<0.001*
Li, 2013 [20]	2009	China	Mild AP	75	74	Subjective feeling of hunger	Clinical symptoms and laboratory indices had improved	Progressed from CLD to LFSD	Progressed from CLD to LFSD	4.6 ± 1.5	6.8 ± 2.3	<0.001*
Larin -o-Noia 2014 [21]	2years	Spain	Mild AP	37	38	Subjective feeling of hunger	Clinical symptoms and laboratory indices had improved	Stepwise increase kcal during 3d	Stepwise increase kcal during 3d	2 ± 0.9	3 ± 2.2	<0.001*
Karabulut, 2019 [13]	2011–2013	Turkey	Mild AP	49	49	Immediately	Clinical symptoms and laboratory indices had improved	Liquid, soft, solid diet	Liquid, soft, solid diet	N	N	N
Lozada-Her nández2020 [22]	2018–2019	Mexico	Mild AP	61	59	Immediately	Clinical symptoms and laboratory indices had improved	The soft diet	The soft diet	0.8 ± 0.3 d	3 ± 2.0	0.001*
Cao2020 [24]	2018	China	Mild AP	45	46	Subjective feeling of hunger	Clinical symptoms and laboratory indices had improved	progressed from CLD to LFSD	progressed from CLD to LFSD	3.6 ± 1.1	5.4 ± 1.5	0.037*
Horibe, 2020 [23]	2015–2017	Japan	Mild AP	13	12	Immediately	Clinical symptoms and laboratory indices had improved	LFSD	progressed from CLD to LFSD	0.8 ± 0.6	N	N
Rami'rez-Mal donado2021 [2]	2017–2019	Spain	MAP	71	60	Immediately	Clinical symptoms and laboratory indices had improved	LFSD	progressed from CLD to LFSD	0 d	2.8 ± 1.7	<0.001*
Total	2003–2019		MAP	380	368	/	/	/	/	/	/	/

IOR = immediate oral refeeding, DOR = delayed oral refeeding, AP = acute pancreatitis, MAP = mild and moderate severe acute pancreatitis, CLD = clear liquid diet, LFSD = low-fat-solid diet, N = Non, * = the difference was statistically significant.

Table 2
The baseline characteristics of patients in this meta-analysis.

	Eckerwall 2007 [19]		Li 2013 [20]		Larin ~o-Noia 2014 [21]		Karabulut 2019 [13]		Lozada-Hernán dez 2020 [22]		Cao 2020 [24]		Horibe 2020 [23]		Ramı rez -Maldonado 2021 [2]	
	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR
Male sex (n)	14	13	53	47	18	15	25	22	15	18	24	26	10	8	37	30
Age(y) Mean ± SD	52± 16.3	56± 17.8	48± 13.5	49± 12.8	67.8 ± 14.3	63.3 ± 14	53± 15.8	56± 14.8	45.3 ± 17	50 ± 14.2	45± 7.9	51± 11.3	50.1 ± 5.3	60.8 ± 5.3	70.2± 16.4	64.9 ± 17.9
BMI Kg/m2	N	N	N	N	N	N	27 ± 4.4	26 ± 3.8	28 ± 3.9	27.6 ± 4.7	N	N	N	N	28.5 ± 4.7	27.5 ± 5.2
APACHEII	5 ± 2.2	6 ± 1.48	N	N	N	N	3.9 ± 3.2	3.2 ± 2.9	N	N	N	N	N	N	N	N
Ranson score	N	N	0.8 ± 0.8	1.0 ± 0.9	N	N	1.1 ± 0.9	1 ± 0.7	N	N	N	N	N	N	N	N
Etiology(n)																
Biliary	18	14	41	37	20	20	37	35	61	59	6	4	0	2	54	42
Alcohol	3	5	19	19	9	7	10	14	0	0	6	8	7	4	6	10
Others	10	11	15	18	8	8	2	0	0	0	33	34	6	7	11	8

IOR = immediate or early oral refeeding, DOR = delayed oral refeeding, BMI = body mass index, APACHE II = Acute physiology and chronic health evaluation II, N = Non.

Table 3
Risk of bias in the included studies comparing IOR versus DOR in MAP patients, using the cochrane risk of bias tool of RCTs.

Bias	Eckerwall 2007 [19]	Li 2013 [20]	Lariño-Noia 2014 [21]	Karabulut 2019 [13]	Lozada- Hernández 2020 [22]	Cao 2020 [24]	Horibe 2020 [23]	Ramı rez - Maldonado 2021 [2]
Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low
Allocation concealment	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Low
Blinding of participants and personnel	Low	Unclear	High	Unclear	High	Unclear	Low	Low
Blinding of outcome assessment	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low
Reporting bias	Low	Low	Low	Low	Low	Low	Low	Low
Other bias	Low	Unclear	Low	High	High	High	Low	Low
Summary bias	Unclear	Unclear	High	High	High	High	Low	Low

MAP = mild and moderate severe acute pancreatitis, IOR = immediate oral refeeding, DOR = delayed oral refeeding, RCTs = randomized controlled trials.

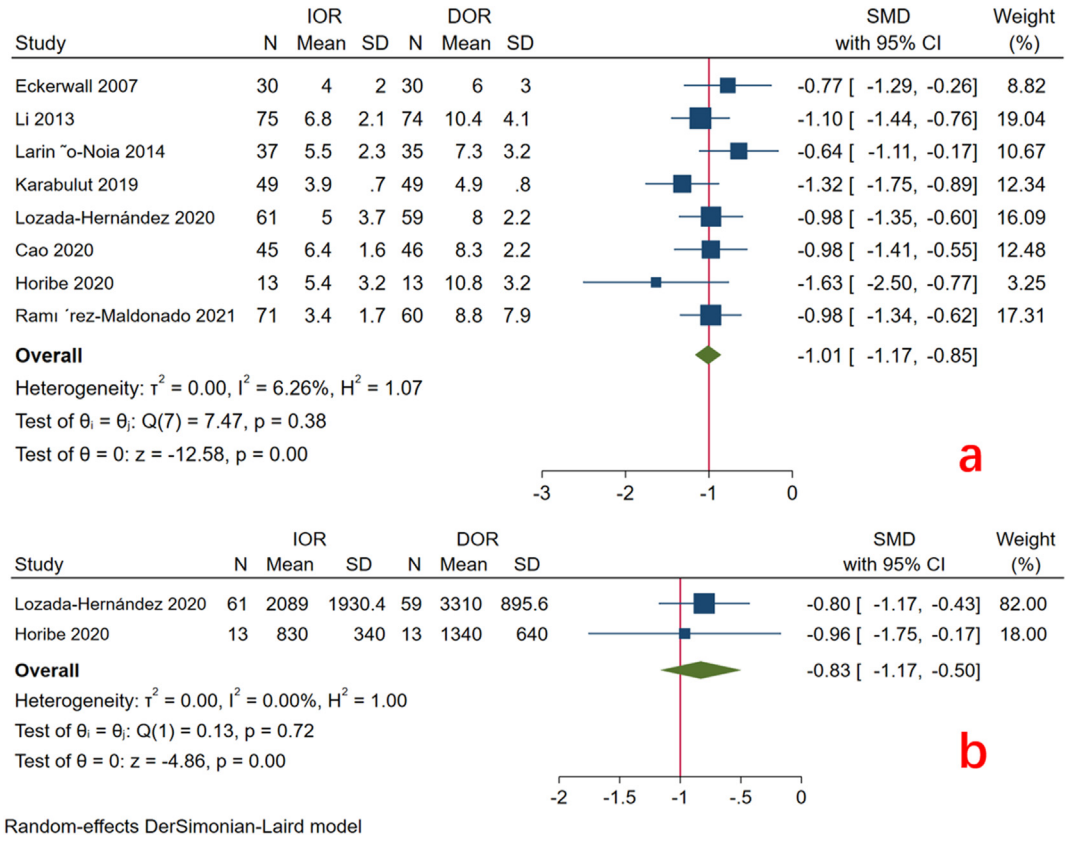

Fig. 2. Forest plot of comparison of IOR vs. DOR on MAP. The solid squares represent the SMD, the horizontal lines denote the 95% confidence intervals (CI), and the diamond represents the pooled effect size. a) LOS. b) costs. IOR = immediate or early oral refeeding. DOR = delay oral refeeding. MAP = mild and moderate acute pancreatitis. SMD = standardized mean differences.

using the Cochrane risk of bias tool of randomized controlled trial. Randomization was mentioned in all included studies, with 6 studies [13,16–20] using randomized number table and 2 studies [2,19] using random sample. 4 studies mentioned specific methods of allocation concealment [2,20,21,23]. It was not possible to be absolutely blind due to the characteristics of intervention. However, only 4 studies have shown the blinding of outcome assessment [2,19,22,23]. 3 of the included studies were judged as "high risk" due to they did not well-described protocol [13,22,24].

3.5. Primary outcome

3.5.1. LOS

All studies reported LOS (748 patients in total, 380 patients in IOR group) [2,13,19–24]. The pooled results showed the IOR group had shorter LOS [SMD -1.01, 95%CI (−1.17, −0.85), P < 0.001] than the DOR group, and the heterogeneity among these studies is low (I [2] = 6.3%, p = 0.38) (Fig. 2a or Table 4).

3.5.2. Costs

Data on costs came from three trials (276 patients, 145 IORs) [2,22,23]. Three trials consistently showed that IOR could significantly reduce costs compared with DOR. one trial was not included in the meta-analysis because it only provided average values without other data [2]. Meta-analysis showed that the IOR group had less costs [SMD -0.83, 95%CI (−1.17, −0.5), P < 0.001] than the DOR group. No heterogeneity (I [2] = 0%, p = 0.72) (Fig. 2b or Table 4).

3.6. Secondary outcomes

3.6.1. Mortality

Data on mortality were available for 4 of the included studies (463 patients, 238 IORs) [2,13,19,20,23]. Meta-analysis showed IOR did not affect the mortality in MAP patients [RR 0.54, 95%CI (0.11, 2.62), P = 0.44]. No heterogeneity among the included studies (I [2] = 0%, p = 0.97) (Fig. 3a or Table 4).

3.6.2. Progress of AP

Three studies reported on the incidence of AP progression (228 patients, 121 IORs) [2,21,23]. Meta-analysis showed the incidence of AP progression in the IOR and DOR groups was no significant difference [RR 0.21, 95%CI (0.04, 1.07), P = 0.06]. There was no heterogeneity (I [2] = 0%, p = 0.4) (Fig. 3b or Table 4).

3.6.3. Overall complications

Data of overall complications came from four of the included studies (281 patients, 145 IORs) [2,19,24]. Meta-analysis showed that IOR had no advantage over DOR for the overall complications in patients with AP [RR 0.41, 95%CI (0.17, 1.01), P = 0.05]. No heterogeneity among the four studies (I [2] = 0%, p = 0.4). (Fig. 3c or Table 4)

3.6.4. Relapse of pain

Five studies reported the data on pain relapse (563 patients, 389 IORs) [2,20–22,24], The pooled results showed there was no difference in pain relapse rate between the IOR and DOR groups [RR 0.53, 95%CI (0.17, 1.63), P = 0.27]. The heterogeneity among these studies were moderate levels. (I [2] = 44.5%, p = 0.13). (Fig. 4a or Table 4)

Subgroup Meta-analysis in 4 trials of mild AP showed that the incidence of pain relapse in the IOR and DOR groups was no significant difference [RR 0.78, 95%CI (0.33, 1.86), P = 0.58] [20–22,24]. The subgroup heterogeneity was low (I [2] = 8%,

Table 4
Summary of primary and secondary outcomes in the included trials evaluating IOR versus DOR in patients with MAP.

	Eckerwall2007 [19]		Li2013 [20]		Larin -o-Noia 2014 [21]		Karabulut2019 [13]		Lozada-Hernández2020 [22]		Cao2020 [24]		Horibe2020 [23]		Rami'rez-Maldonado2021 [2]		Pooled estimate (95% CI)	P	I
	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR	IOR	DOR			
Death (n)	0	0	0	0	N	N	0	0	N	N	N	N	0	1	0	1	0.54[0.11, 2.62]	0.44	0%
LOS(d) Mean ± SD	4 ± 2	6 ± 3	6.8 ± 2.1	10.4 ± 4.1	5.5 ± 2.3	7.3 ± 3.2	3.9 ± 0.7	4.9 ± 0.8	5 ± 3.7	8 ± 12.2	6.4± 1.6	8.3 ± 2.2	5.4 ± 3.2	10.8 ± 3.2	3.4 ± 1.7	8.8 ± 7.9	−1.01[-1.17, −0.85]	<0.001*	6.3%
Feeding intolerance (n)	22	30	N	N	4	4	3	1	1	3	N	N	0	1	1	13	0.61[0.28, 1.3]	0.2	39.1%
Complications (n)	3	4	N	N	N	N	N	N	N	N	0	0	N	N	3	11	0.41[0.17, 1.01]	0.05	0%
Relapse of pain (n)	N	N	3	6	1	1	N	N	2	4	2	4	N	N	0	10	0.58[0.25,1.35]	0.27	44.5%
Progress of AP	N	N	N	N	1	1	N	N	N	N	N	N	0	3	0	6	0.21[0.04, 1.07]	0.06	0%
Cost									2089 ± 1930	3310 ± 895.6			830 ± 340	1340 ± 640	1451.9 ± N	3016.6 ± N	−0.83[-1.17, −0.5]	<0.001*	0%

MAP = mild and moderate severe acute pancreatitis, IOR = immediate oral refeeding, DOR = delayed oral refeeding, LOS = length of stay, N = Non, * = the difference was statistically significant.

p = 0.35). (Fig. 4a).

3.6.5. Feeding intolerance

Data on feeding intolerance were available from 7 of the included trials (505 patients, 260 IORs) [2,13,19,21–23]. The pooled results showed IOR group did not affect the feeding intolerance rate compared with DOR [RR 0.61, 95%CI (0.28, 1.3), P = 0.2]. The heterogeneity was moderate levels (I [2] = 39.1%, p = 0.15). (Fig. 4b or Table 4)

Subgroup analysis of 6 trials with mild AP showed there was no difference in the overall complications between IOR group and DOR group [RR 0.77, 95%CI (0.62, 0.94), P = 0.01] [13,19,21–23], and there is no heterogeneity (I [2] = 0%, p = 0.65). (Fig. 4b)

3.7. Sensitivity analysis and publication bias

Fig. 5 shows the sensitivity analysis results. For the removal of any one study, the 95%CI of combined SMD for the remaining studies did not exceed the 95%CI of combined SMD for the all studies, suggesting that no single trial dominated the results. Begg's test (P = 0.9) and Egger's test (P = 0.52) suggested that there is no publication bias.

4. Discussion

AP is a common gastrointestinal cause, which has become a difficult problem to be solved clinically [25]. There is a strong energy breakdown and negative nitrogen balance in the early phase of AP [26]. 80% of AP patients have prolonged recovery time due to increased negative nitrogen balance [27]. In terms of the pathogenesis of AP, alcohol and other causes can lead to the accumulation of intracellular Ca^{2+}, resulting in the loss of mitochondrial membrane potential and subsequent intracellular ATP depletion in the early phase of AP, which in turn impairs the Ca^{2+} transport, leading

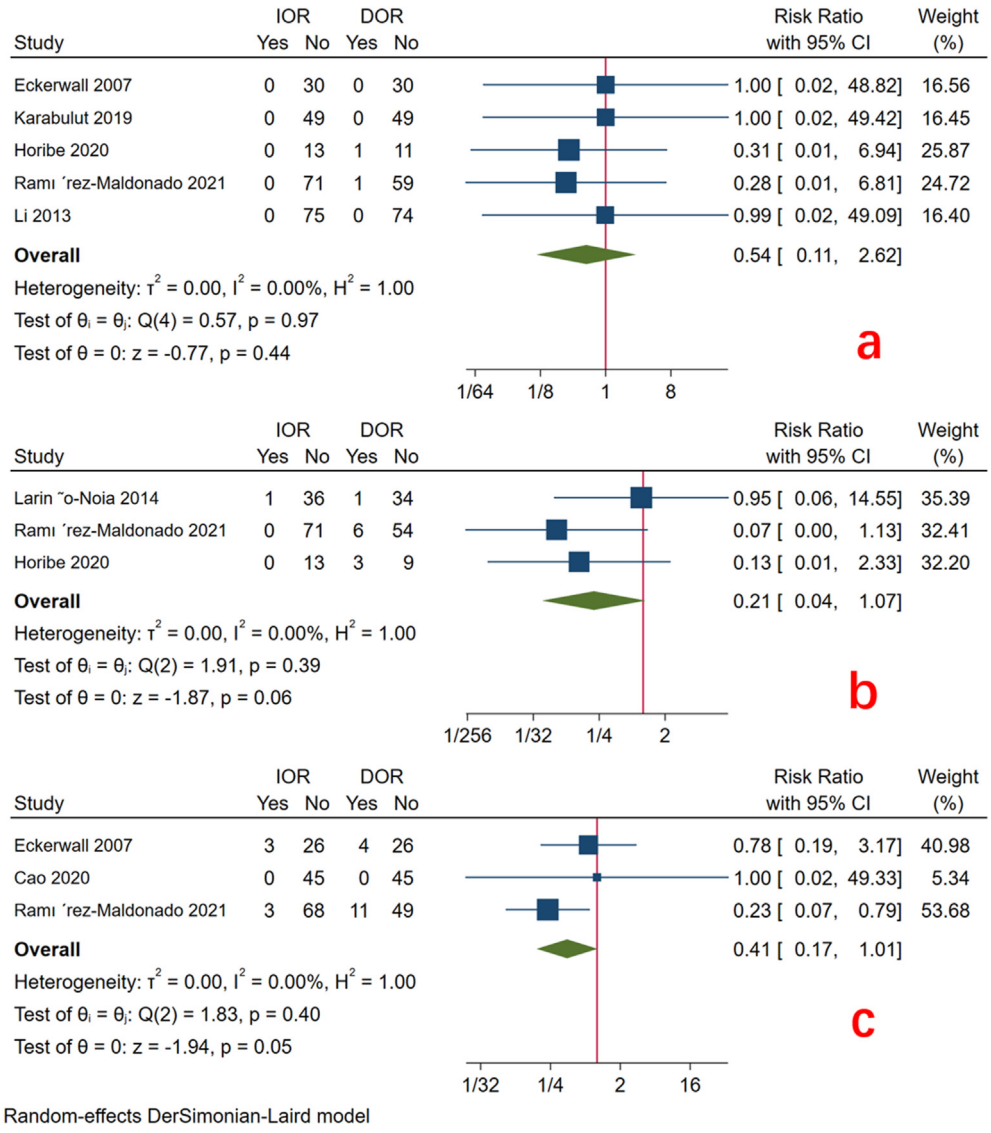

Fig. 3. Forest plot of comparison of IOR vs. DOR on MAP. The solid squares represent the RR, the horizontal lines denote the 95% confidence intervals (CI), and the diamond represents the pooled effect size. a) mortality. b) progress of AP. c) overall complications. IOR = immediate or early oral refeeding. DOR = delay oral refeeding. MAP = mild and moderate acute pancreatitis. RR = risk ratio.

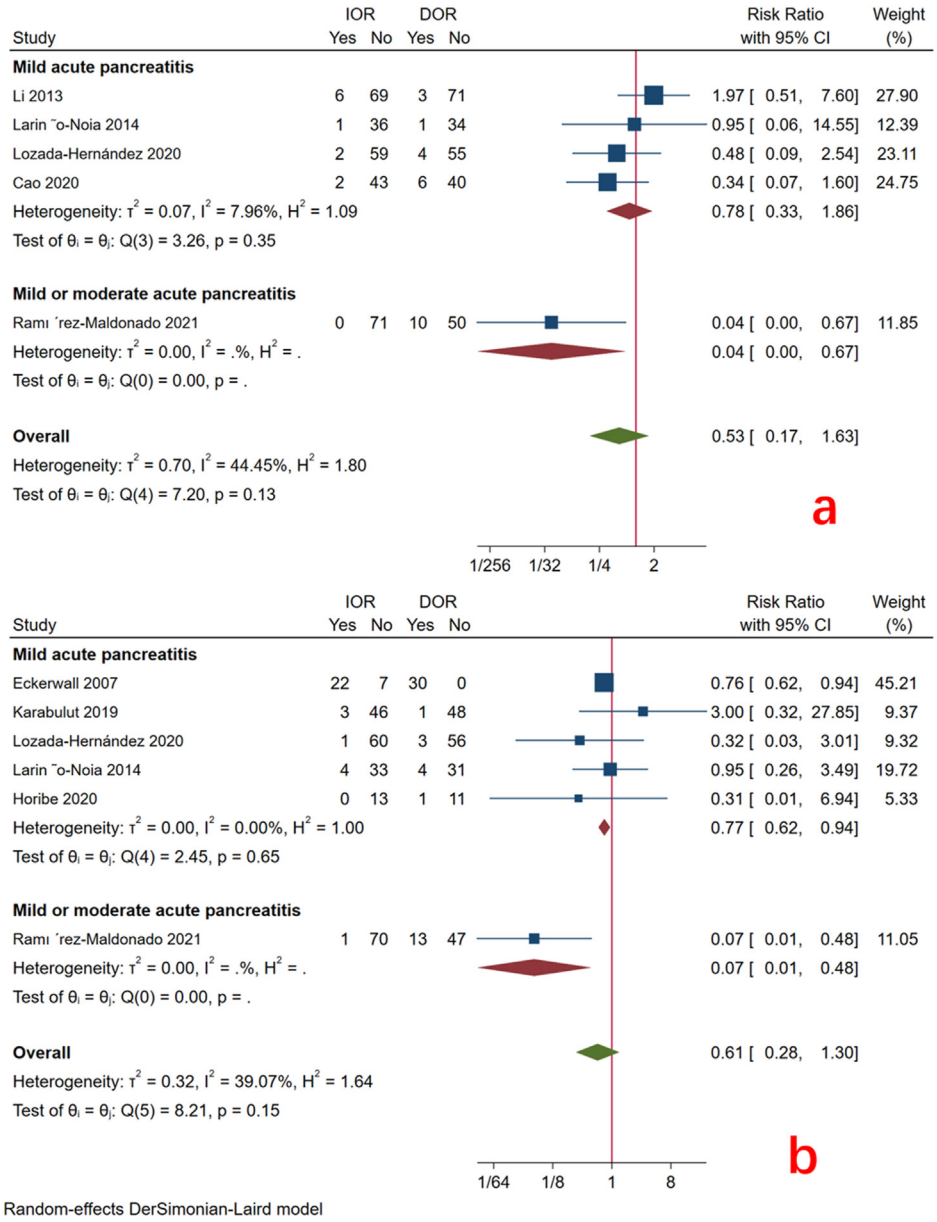

Fig. 4. Forest plot of the meta-analysis of EOR vs. DOR on pain relapse rate and feeding intolerance rate stratified by severity of AP. The solid squares represent the RR, the horizontal lines denote the 95% confidence intervals (CI), and the diamond represents the pooled effect size. a) pain relapse rate, b) feeding intolerance rate. IOR = immediate or early oral refeeding. DOR = delay oral refeeding. AP = acute pancreatitis. RR = risk ratio.

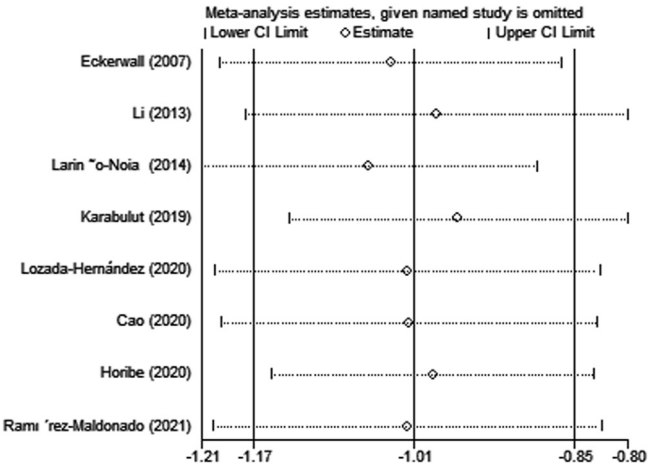

Fig. 5. Effect of each of included studies on the pooled SMD for the effect of early oral refeeding on LOS. The overall SMD is the horizontal axis number-1.01, 95% CI is −0.85 and −1.17. SMD = standardized mean differences.

to a vicious cycle that aggravates the disease [6,7,28]. Study found that the supplementation of ATP in pancreatic ductal cells could prevent the cellular dysfunction and cell damage [8]. Therefore, regardless of feeding type, early energy intake is beneficial for AP [2,9,10]. In other words, it's not the feeding type that matters, but the feeding itself (energy) [9].

Reduced intestinal vascular perfusion in AP patients leads to intestinal mucosa damage and bacterial translocation, followed by pancreatic infections, peripancreatic necrosis, and even organ failure and sepsis [29]. In patients with AP, EN is superior to PN [4,5]. Early EN can improve AP prognosis by supplementing energy loss, increasing visceral blood flow to maintain intestinal mucosal integrity, stimulating intestinal motility and reducing systemic inflammatory response syndrome [3,30]. Oral feeding is one way of EN. It is more acceptable than tube feeding, reducing the intubation discomfort and complications, promoting the recovery of gastrointestinal function [11,12]. Different guidelines differ on the oral feeding timing of MAP, with some recommending after clinical symptoms and laboratory indicators have improved, and others recommending once the diet is tolerable [31–33]. And a meta-analysis showed that early EN was not beneficial for MAP [34]. These differences views may help explain why the outdated theory of "pancreatic rest" is still prevalent in clinical treatment today. Greenberg et al. found that 80.6% of AP patients used outdated theory of nutritional support, resulting in unnecessary costs [14]. To provide more clinical evidence on the timing of oral refeeding in AP patients, we conducted this meta-analysis encompassing 748 MAP patients. Table 5 summarizes the results of the level of evidence for the outcomes, using the methodology of GRADE.

4.1. Main finding

Compared with DOR, IOR could reduce LOS and costs without increasing adverse events (death, relapse of pain, overall complications and progress of AP) in patients with MAP. The resumption of oral feeding in patients with MAP doesn't seem to require consideration of clinical symptoms and laboratory indicators.

4.2. Comparison with other studies

There was consistency among the included studies in terms of

Table 5
Summary of findings for IOR compared with DOR for MAP.

Outcomes	Participants (n)		Studies (n)	Relative effect (95% CI)	Certainty of evidence (GRADE)	Comments
	IOR	DOR				
LOS	380	368	8RCTs	SMD -1.03, 95%CI (−1.17, −0.88)	⊕⊕⊕◯ Moderate	IOR may results in a reduction in LOS
Costs	145	131	2RCTs	SMD -0.84, 95%CI (−1.18, −0.5)	⊕⊕◯◯ Low	IOR may reduce hospital costs
Mortality	218	206	5RCTS	RR 0.54, 95%CI (0.11, 2.62)	⊕⊕⊕◯ Moderate	IDR is probably to reduce death
Progress of AP	121	107	3RCTs	RR 0.23, 95%CI (0.04, 1.16)	⊕⊕⊕⊕ High	IOR did not increase the risk of AP progression
Feeding intolerance	260	245	6RCTs	RR 0.61, 95%CI (0.28, 1.30)	⊕◯◯◯ Very low	There is uncertainty about the difference in effect of IOR and DOR on feeding intolerance rate in AP.
Overall complications	145	136	3RCTs	RR 0.41, 95%CI (0.17, 1.01)	⊕⊕◯◯ Low	EOR may not increase the rate of overall complications
Relapse of pain	289	274	5RCTs	RR 0.53, 95%CI (0.17, 1.63)	⊕◯◯◯ Very low	There is uncertainty about the difference in effect of EOR and DOR on relapse of pain in AP.

MAP = mild and moderate severe acute pancreatitis, IOR = immediate oral refeeding, DOR = delayed oral refeeding, RCTs = randomized controlled trials, LOS = length of stay.

LOS. In previous studies, the experimental group could be oral feeding or with feeding tubes without stratification. While in this meta-analysis, the experimental group was given oral feeding only. However, we obtained the same results as previous studies that early resumption of diet could shorten the LOS of AP [35,36]. Study had shown that either oral refeeding or other EN type in mild AP can reduce LOS [30], so our results are also credible. AP has become a massive medical and social burden, the total annual cost of AP is more than US $2 billion in the United States [37]. Whereas, there few meta-analyses have been conducted to compare costs between early and delay diet in AP. In this systematic review, there was consistency among the included 3 studies in terms of costs, IOR could reduce costs in MAP [2,22,23]. So IOR may be an effective strategy for MAP in the present environment of increasing cost-conscious.

As in previous studies, early nutritional support did not increase the risk of death in AP [2,35]. This study showed there is no difference in mortality between the IOR and DOR groups. Mild AP is self-limited with a good prognosis and a mortality rate of less than 1% [38]. So, a great caution is need when considering this result because small sample size. In this meta-analysis, 3 of the 5 studies with mortality data reported no deaths [13,19,20], the overall mortality was 0.4% [2,13,19,20,23]. Thus, further study is needed to determine whether IOR affects mortality in mild and moderate AP.

In the past, some scholars believed empirically that the early solid diets could stimulate the pancreatic secretion, resulting in pain relapse [39], which in turn increases medical resources and LOS [40]. Therefore, a gradual increase in intake from a clear liquid diet to a solid diet became the clinical treatment options for AP. However, studies found that a soft or solid diet in mild AP can reduce LOS compared with clear liquid diet, and there were no differences in rates of feeding intolerance and pain relapse between two groups [2,41]. In addition, two studies encompassing 2018 AP patients also showed that no association between feeding intolerance and nutrition formulas [43,44]. Thus, although nutrition formulas varied among the studies included in this meta-analysis, its pooled results showed that there was no difference in the rates of feeding intolerance and pain relapse between the IOR and DOR groups, as in previous studies [35,41,42].

Early EN could reduce complications compared to delayed EN [45,46]. This meta-analyse shows the overall complications rate in IOR group were lower than in DOR group, but the difference is not statistically significant [2,19,24]. It is widely known that severe AP often has been accompanied by complications, while MAP is uncommon [47]. Unlike previous studies, this meta-analysis did not include severe AP patients. Therefore, differences in the severity of AP in enrolled patients may account for the different results on the overall complications rate between this and previous meta-analysis. Nutritional status of AP patient could predict the severity of AP [42]. However, it appears that the timing of oral refeeding does not affect the progression of AP. In this review, as previous studies, no statistically difference in AP progression between the IOR and DOR groups [2,21,23]. In summary, these data suggest that early oral refeeding may be beneficial for mild to moderate AP patients.

5. Limitations

Limitations of this systematic review are as follows: First, determining the generality of a study result requires a multicentre study, but 7 of the included studies were single-centre studies. Three studies that assessed the costs lacked an assessment of AP complications and intervention costs. Accurate time of oral refeeding was not available in the 2 studies. Second, some truncated RCTs were not included in the literature search. 6 of the included studies were of poor quality, 4 of may have overvalued the intervention effect due to inadequate allocation concealment. However, there was no methodological defect in the RCTs included in this systematic evaluation, and the Begg's and Egger's test showed no obvious evidence of publication bias. Third, effects of IOR on feeding intolerance and progression of AP appear to be moderate heterogeneity among the included trials. This heterogeneity may be come from the differences in the severity of AP. So, patients were stratified according to the severity of AP, with no heterogeneity between groups. Finally, rare outcomes could be difficult to detect due to only 8 RCTs met inclusion and exclusion criteria and some trials were small.

Despite these limitations, this meta-analysis still gives clinicians some important implications for the nutritional support of AP. Results of this meta-analysis show that IOR can reduce LOS and costs without increasing adverse events. IOR may be an effective strategy for MAP in current environment of increasing cost-conscious.

6. Conclusions

In conclusion, IOR could reduce LOS and costs without increasing adverse events in patients with MAP. However, in the context of its limitations, further deeper and wider study are necessary.

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Declaration of competing interest

There are no competing interests in authors of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.11.009.

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