Pancreatology 17 (2017) 651–657

Contents lists available at ScienceDirect

Pancreatology

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

The optimal timing of enteral nutrition and its effect on the prognosis of acute pancreatitis: A propensity score matched cohort study

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ARTICLE INFO

Article history:
Received 23 March 2017
Received in revised form
8 August 2017
Accepted 28 August 2017
Available online 1 September 2017

Keywords:
Early enteral nutrition
Acute pancreatitis
Infection
Propensity score matching

ABSTRACT

Background: Early enteral nutrition (EN) can improve the prognosis of acute pancreatitis (AP), but the optimal initiation time is unknown. In this study, the optimal time of early EN was analyzed to disclose the application of early EN in AP.
Methods: Data of 104 patients with AP were prospectively collected. With secondary infection (infected pancreatic necrosis and extrapancreatic infection) as the primary outcome variable, receiver operating characteristic (ROC) curve was used to calculate the optimal cut-off time of early EN. Propensity score matching was used to adjust for covariates. Secondary outcomes include acute gastrointestinal injury (AGI) grades, serum albumin level, and EN-related complications.
Results: The ROC curve analysis showed that the third day after hospital admission was the best cut-off time of early EN (with the area under the curve of 0.744). After PS matching, the proportion of secondary infection in the early EN group was significantly lower than the late EN group (8.6% vs. 36.5%, $P < 0.05$). Regression analysis showed that early EN was a protective factor against secondary infection (OR 0.161, 95%CI 0.036–0.718, $P < 0.05$). The AGI grades and serum albumin levels were better improved in the early EN group (AGI $F = 4.468$, $P < 0.05$; serum albumin $F = 3.794$, $P < 0.05$).The proportion of EN-related abdominal distension in the early EN group was significantly lower (8.8% vs. 38.5%, $P < 0.05$).
Conclusions: Early EN initiated within three days could reduce the risk of secondary infection and improve the nutritional status of patients with acute pancreatitis, with a better tolerance.

Introduction

Acute pancreatitis (AP) is one of the most common clinical acute abdomen diseases. It can be complicated with pancreatic necrosis and multiple organ failure. The mortality rate of severe patients is as high as 20–25% [1].

Enteral nutrition (EN), as an economical and effective treatment regimen, has been widely recognized in the management of AP. Compared to total parenteral nutrition (TPN), EN could significantly decrease the mortality and reduce the risk of organ failure of patients with AP [2]. Furthermore, an early initiation of EN was more effective than delayed EN in reducing the risk of pancreatic infection and mortality [3]. However, the current publications and consensus have inconsistent views for the timing of the early EN. The initiations of early EN were set at 24 h, 48 h, 48–72 h, 72 h and 96 h according to clinician's experience [4–11], which may cause bias.

The assumption of our study was that early initiation of EN improves the prognosis of acute pancreatitis and the state of nutrition. We performed this prospective cohort study to verify the efficiency of early EN in acute pancreatitis. Propensity score (PS) matching and receiver operating characteristic (ROC) curve analyze were used to explore the best initiation time of early EN.

Materials and methods

Study subjects

From October 2013 to June 2016, 104 patients with moderate

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http://dx.doi.org/10.1016/j.pan.2017.08.011
1424-3903/

severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) who were treated at Peking Union Medical College Hospital in China were prospectively consecutively enrolled. The diagnostic criteria of MSAP and SAP [12] were according to the revised Atlanta classification [12]. The exclusion criteria were (1) patients with gastrointestinal bleeding or gastrointestinal obstruction; (2) patients allergic to the components of EN fluid; (3) patients with malignant tumors; (4) patients with multiple onsets; (5) patients not able to describe the subjective uncomforting symptoms; and (6) pregnant patients.

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Study procedures

The prospective open-study was performed in this study. Patients who met the diagnostic criteria for MSAP or SAP received treatments of rehydration, correction of electrolyte disorders and organ function support after hospital admission, in accordance with the 2013 American College of Gastroenterology guideline [5]. Starting EN was determined from the admission to hospital, and when patient was fully resuscitated and/or stable [13]. The EN starting time was defined from hospital admission, and was determined by the clinician. The X ray-guided placement of a nasojejunal feeding tube was performed, and EN was initiated.

Peptide formulation was selected as the EN preparation. EN formulation was continuously input using an infusion pump following a strict volume regimen: 20 ml/h in the first 24 h, 40 ml/h between 24 and 48 h, 60–80 ml/h between 48 and 72 h, and reach a sufficient amount (25 kcal/kg/d, ideal weight) at 72 h and thereafter. Feeding intolerance was defined as the aggravation or new onset of vomiting, abdominal distention, abdominal discomfort, and diarrhea, which occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced. If the above feeding speed was not tolerated, it would be reduced to 50% and stepwise rebuilt gradually until tolerated. If after two of such attempts, full nutrition could not be attained, PN will be started to reach the required energy target. The EN-related side effects were observed and recorded, including (1) mechanical side effects, such as catheter obstruction; (2) aspiration pneumonia; (3) EN associated diarrhea: occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced; and (4) EN associated abdominal distension: occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced.

Data collection

Patients' gender, age, etiology, and BMI were recorded; the clinical manifestations and the laboratory and imaging data of the patients at hospital admission and on the 7th and 14th days after the hospital admission, as well as the length of hospital stay and cost, were collected. The acute gastrointestinal injury (AGI) was defined as the malfunctioning of the gastrointestinal tract in critically ill patients. According to the 2012 recommendations of the ESICM [14], AGI can be distinguished into four grades: Grade I = risk of developing gastrointestinal dysfunction or failure (a self-limiting condition); Grade II = gastrointestinal dysfunction (a condition that requires intervention); Grade III = gastrointestinal failure (gastrointestinal function cannot be restored with interventions); Grade IV = severe impact on distant organ function (a condition that in immediately life-threatening). The AGI ratings were performed for all of the patients at admission, and were reevaluated on a daily basis.

The primary outcome variables were secondary infection and death during hospitalization. Secondary infection included infected pancreatic necrosis and extrapancreatic infection (bacteremia, pneumonia and urinary tract infection) occurred during hospitalization [12,15]. The diagnosis of infected pancreatic necrosis was presumed when there was extraluminal gas in the pancreatic and/or peripancreatic tissues on computed tomography or when fine-needle aspiration was positive for pathogen culture [12]. The diagnosis of extrapancreatic infection was defined as positive pathogen culture obtained from blood, sputum or urine samples [15]. The secondary outcomes were defined as the need for percutaneous, endoscopy or surgical intervention, local complications (acute necrotic collection, walled-off necrosis) [12], admission to the ICU, the length of hospital stay, and cost.

Statistical analysis

The statistical analysis of the data was performed using SPSS 23.0 software. The counting data were represented as the percentage, with the χ^2 test; the measurement data were represented as the mean ± standard deviation, with a *t*-test for the normally distributed variables and a non-parametric test for the non-normally distributed variables.

The PS is the probability that a patient would receive the treatment of interest, based on characteristics of the patient, treating clinician, and clinical environment, estimated by multivariable statistical methods. The PS matching involves assembling 2 groups of study participants, while matching individuals with similar or identical PSs. The analysis of a PS-matched sample can approximate that of a randomized trial by directly comparing outcomes between different groups. In this study, the PS matching was performed as 1:2 match of the early and late EN groups through nearest-neighborhood method, with a caliper width of 0.25 times the SD of the logit of propensity scores. Age, sex, etiology, disease severity, abdominal pain, visual analogue scale of abdominal pain, abdominal distension, AGI grade and serum albumin level at admission were included for PS matching. After PS matching, all cases were equally matched for relevant confounders.

An ROC curve was used to determine the optimal EN starting time. A logistic regression was used to analyze the effect of early EN on secondary infection. The data of repeated measurements were analyzed using an analysis of variance (ANOVA) for repeated measures. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of study population

During the study period, a total of 135 patients admitted meeting the inclusion criteria. Thirty-one were excluded, including gastrointestinal bleeding (n = 1), multiple onsets (n = 11), pregnant (n = 7). During assessment, 12 patients were excluded for missing data. (Fig. 1)

As a result, 104 patients were eligible for final analysis. Among them, 68 were male (65.4%) and 36 were female (34.6%), with a mean age of 43.12 ± 15.13 years. There were 56 cases of MSAP (53.8%) and 48 cases of SAP (46.2%). All patients with SAP presented with local complications. The frequency distribution of EN initiation time was showed in Fig. 2. The average starting time of enteral nutrition was 5.7 ± 4.2 days, with a range of 1–20 days after admission.

Optimal EN starting time

With secondary infection as the outcome variable, the ROC

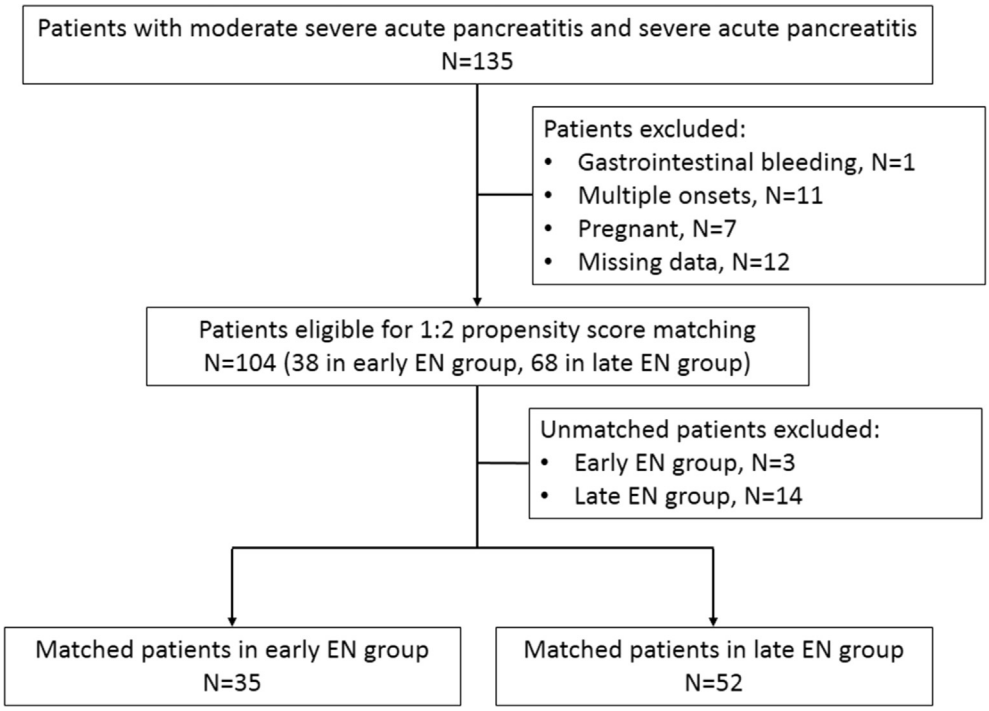

Fig. 1. The patient flowchart with respect to inclusion and exclusion.

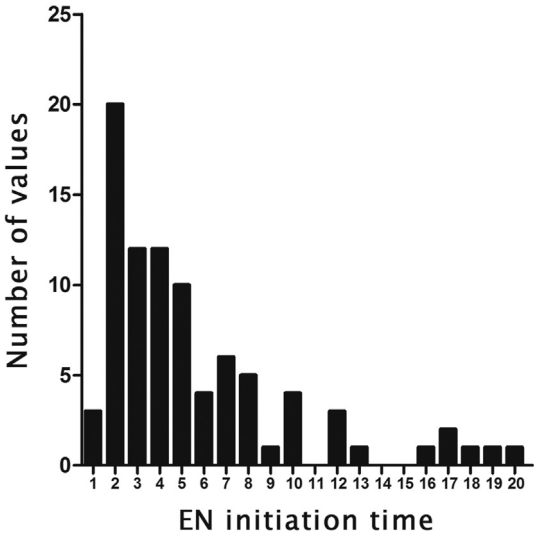

Fig. 2. The frequency distribution of EN initiation time.

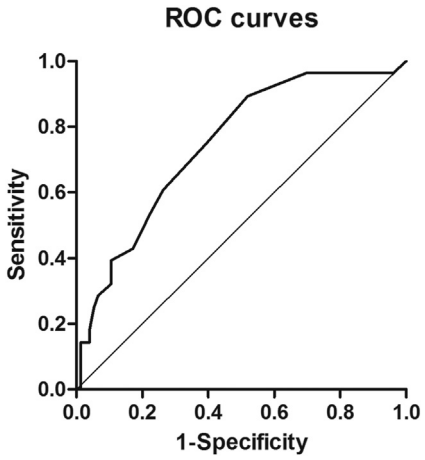

Fig. 3. ROC curve for EN starting time.

curve was used to analyze the optimal EN starting time, and the results are shown in Fig. 3. The optimal starting time was the third day after hospital admission, with the sensitivity of 0.893, specificity of 0.381, and Youden index of 0.373.The area under the curve (AUC) was 0.744. Since only one patient died in our cohort, it is impossible to perform further analysis.

The average EN initiation time in patients with percutaneous intervention was 8.3 ± 6.0 days, which was significantly longer than the others (5.3 ± 4.0 days, $P = 0.048$). The ROC curve showed that the third day for EN initiation would be the appropriate cut-off value to differentiate the outcome of percutaneous intervention, with a sensitivity of 0.889, specificity of 0.436, and Youden index of 0.325. The AUC was 0.671.

For other secondary outcomes, including surgery intervention, endoscopy intervention, necrotic collection and walled-off pancreatic necrosis, the average EN initiation time was 6.0 ± 6.7 days, 4.5 ± 2.1 days, 5.7 ± 4.6 days and 6.7 ± 5.3 days respectively. No significant difference was found on the EN initiation time between patients with and without these endpoints ($P > 0.05$).

Clinical data for the patients in the early EN group and the late EN group

The cases starting EN within three days of hospital admission (including the third day) were assigned to the early EN group (38 cases, 36.5%), and cases initiating EN after three days were assigned to the late EN group (66 cases, 63.5%). After 1:2 fixed ratio PS matching, a weighted analysis of 35 early EN versus 52 late EN was performed to examine outcomes of AP (Fig. 1). PS matched cases

were equally matched for relevant confounders (Table 1).

Impact of the EN starting time on the prognosis

For the primary outcome variables, one patient died in our cohort due to MODS. The profiles of 22 patients with secondary infection were provided in Table S1. For the infection site, infected pancreatic necrosis occurred in 7 patients (8.0%) and was diagnosed with a median of 60 days (interquartile range, 42–75 days) after admission. Extrapancreatic infection occurred in 17 patients (19.5%) and was diagnosed with a median of 11 days (interquartile range, 5–28 days) after admission. Multi-site secondary infections occurred in 6 patients (5.8%).

After PS matching, the proportion of patients with secondary infection, multi-site infection, and secondary infections at extrapancreatic sites in the early EN group were significantly lower than that in the late EN group ($P < 0.05$) (Table 2). The logistic regression analysis showed that early EN is a protective factor against secondary infection (OR 0.139, 95%CI 0.033–0.594, $P < 0.05$). For the secondary outcome variables, the proportion of patients who received percutaneous interventional therapy in the late EN group was significantly higher compared to the early EN group ($P < 0.05$) (Table 2).

For subgroup analysis, patients in the early EN group were divided into three groups (0–24 h, 24–48 h, 48–72 h). No differences were found on primary or secondary outcomes among the three groups ($P > 0.05$). (Table 2).

Impact of the EN starting time on AGI grade and serum albumin level

67 patients (64.4%) were classified as AGI grade IV at admission. On the 3rd day after admission, only one patient remains at AGI grade IV. On the 14th day after admission, 67 patients (64.4%) were classified as AGI grade I, 29 patients (33.3%) were classified as AGI grade II, the rest (2.3%) were classified as AGI grade III.

There was no significant differences in AGI grade or serum albumin level at hospital admission between the two groups after PS matching ($P > 0.05$) (Table 1). The ANOVA for the repeated measures showed significantly different of the AGI score and serum albumin level between the two groups after EN initiated (AGI $F = 4.468$, $P < 0.05$; serum albumin $F = 3.794$, $P < 0.05$).The AGI score of the patients in the early EN group was lower than that of the patients in the late EN group, and the serum albumin level was higher than that of the late EN group (Fig. 4).

Relationship of the EN starting time and EN-related complications

The incidences of EN-related complications in the 104 patients were as follows: 7 cases of mechanical complications (6.7%, all cases were catheter prolapse), 22 cases of diarrhea (21.2%), 29 cases of abdominal distension (27.9%), 4 cases of nausea and vomiting (3.8%), 60 cases of abnormal glucose metabolism (57.7%), and zero case of aspiration pneumonia. After PS matching, the proportion of abdominal distension was significantly lower in the early EN group ($P < 0.05$) (Table 3).

Discussion

The results of this propensity score matched cohort study showed that EN started within three days after hospital admission could significantly reduce the risk of secondary infection, including infected pancreatic necrosis and extrapancreatic infection. Patients who received early EN displayed a better improvement in AGI rating and serum albumin level than those who received late EN, and the proportion of EN-related abdominal distension complications was also significantly decreased.

Nutritional support is an important aspect of the early medical treatment of AP. Compared to TPN, EN can significantly reduce mortality in patients with AP and can reduce the risk of multiple

Table 1
Comparison of baseline characteristics for the early EN group and the late EN group before and after propensity score matching.

	Before PS matching			After PS matching		
	Early EN (N = 38)	Late EN (N = 66)	*P* Value	Early EN (N = 35)	Late EN (N = 52)	*P* Value
Male, n (%)	23 (60.5)	45 (68.2)	0.429	22 (62.9)	37 (71.2)	0.417
Age, years	43.7 ± 15.6	45.7 ± 14.4	0.504	43.9 ± 15.9	45.2 ± 13.5	0.684
BMI, kg/m^2	26.3 ± 3.7	26.2 ± 3.5	0.973			
Days from onset of symptom to admission	3.0 ± 2.0	2.7 ± 2.3	0.467			
Etiology, n (%)			0.180			0.540
Gallstone	13 (34.2)	23 (34.8)		12 (34.3)	16 (30.8)	
Hypertriglyceridemia	12 (31.6)	20 (30.3)		10 (28.6)	14 (26.9)	
Alcoholic	6 (15.8)	10 (15.2)		6 (17.1)	10 (19.2)	
SAP, n (%)	16 (42.1)	32 (48.5)		15 (42.9)	22 (42.3)	0.959
SIRS	0.7 ± 0.4	0.8 ± 0.6	0.715	0.8 ± 0.4	0.8 ± 0.4	0.808
BISAP	2.6 ± 0.4	2.8 ± 0.7	0.724	2.8 ± 0.5	2.8 ± 0.6	0.879
APACHE II	10.8 ± 5.6	11.4 ± 7.2	0.676	11.0 ± 2.2	11.1 ± 7.1	0.968
CTSI	5.6 ± 2.1	5.6 ± 2.2	0.898	5.7 ± 2.2	5.8 ± 2.2	0.848
BUN, mmol/L	8.5 ± 6.5	7.5 ± 6.5	0.460	8.7 ± 7.0	7.8 ± 7.0	0.562
Abdominal pain, n (%)	37 (97.4)	66(100.0)	0.365	35 (100.0)	52 (100.0)	1.000
VAS score	5.5 ± 1.6	6.4 ± 1.5	**<0.05**	5.6 ± 1.4	6.0 ± 1.4	0.207
Abdominal distension n (%)	35 (92.1)	63 (95.5)	0.666	33 (94.3)	50 (96.2)	1.000
AGI grades, n (%)			0.333			0.754
I	2 (5.3)	0 (0)		1 (2.9)	0	
II	8 (21.1)	10 (15.2)		8 (22.9)	10 (19.2)	
III	5 (13.2)	12 (18.2)		4 (11.4)	9 (17.3)	
IV	23 (60.5)	44 (66.7)		22 (62.9)	33 (63.5)	
Albumin, g/l	36.0 ± 6.2	35.9 ± 6.4	0.920	35.7 ± 6.1	35.9 ± 1.4	0.861

PS, propensity score; EN, enteral nutrition; BMI, body mass index; SAP, severe acute pancreatitis; SIRS, systemic Inflammatory Response Syndrome; BISAP, bedside index for severity in acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; CTSI, computed tomography severity index; BUN, blood urea nitrogen; AGI, acute gastrointestinal injury.

Table 2
Comparison of the outcome variables after propensity score matching.

	Whole cohort After PS matching			Early EN group			
	Early EN (N = 35)	Late EN (N = 52)	*P* Value	0-24 h (N = 3)	24-48 h (N = 20)	48-72 h (N = 12)	*P* Value
Primary outcome variable							
Secondary infection, n (%)	3 (8.6)	19 (36.5)	**<0.05**	1 (33.3)	0	2 (16.7)	0.073
Secondary infection of local complications	1 (2.9)	6 (11.5)	0.234	0	0	1 (8.3)	0.373
Secondary infection of other sites	2 (5.7)	15 (28.8)	**<0.05**	1 (33.3)	0	1 (8.3)	0.060
Multi-site secondary infection	0	6 (11.5)	**<0.05**	0	0	0	NA
Death, n (%)	0	1 (1.9)	1.000	0	0	0	NA
Secondary outcome variable							
Percutaneous intervention, n (%)	1 (2.9)	8 (15.4)	**<0.05**	1 (33.3)	0	0	0.072
Surgery intervention, n (%)	1 (2.9)	3 (5.8)	0.646	0	0	1 (8.3)	0.373
Endoscopy intervention, n(%)	1 (2.9)	1 (1.9)	1.000	0	0	1 (8.3)	0.373
Local complications, n (%)							
Necrotic collection	21 (60.0)	29 (55.8)	0.695	2 (66.7)	10 (50.0)	9 (75.0)	0.365
Walled-off pancreatic necrosis	10 (28.6)	21 (40.4)	0.259	0	5 (25.0)	5 (41.7)	0.311
ICU, n (%)	19 (54.3)	25 (48.1)	0.570	2 (66.7)	9 (45.0)	8 (66.7)	0.445
Days of hospitalization, day	21.3 ± 18.5	28.3 ± 22.4	0.128	31.3 ± 30.6	17.0 ± 10.5	25.9 ± 24.8	0.267
Cost of hospitalization, RMB	54795.5 ± 53686.9	68120.7 ± 64663.7	0.317	68593.1 ± 58377.0	43837.9 ± 39150.5	69608.6 ± 71639.1	0.390

EN, enteral nutrition; PS, propensity score; ICU, intensive care unit.
P value <0.05 was considered statistically significant and presented in bold type.

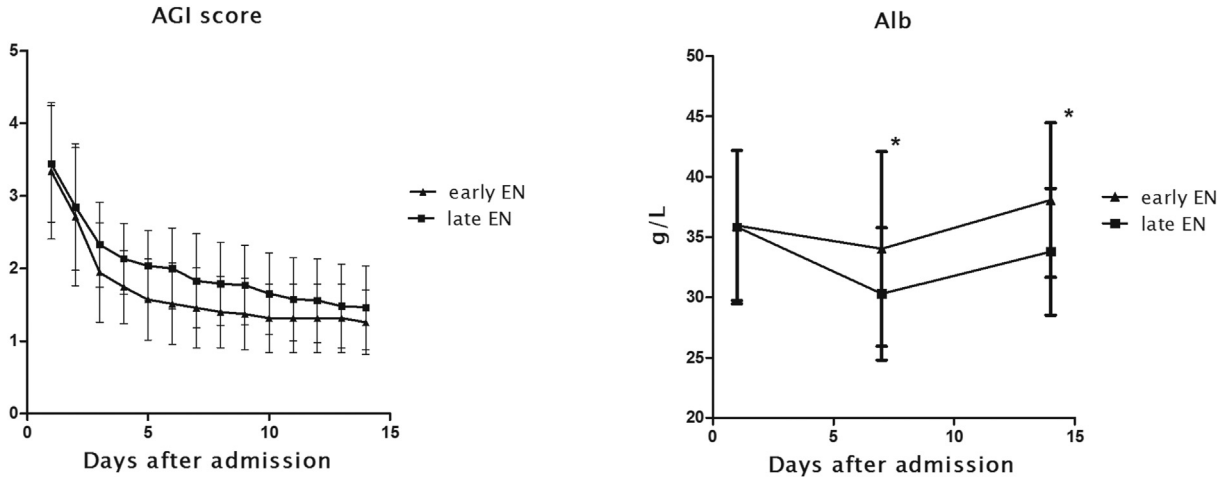

Fig. 4. Comparison of the AGI score (A) and serum albumin level (B) during the hospital stay for the early EN group and the late EN group. *$P < 0.05$.

Table 3
Comparison of EN-related complications for the early EN group and the late EN group.

	Early EN (N = 35)	Late EN (N = 52)	*P* Value
Mechanical complications, n (%)	2 (5.9)	4 (7.7)	1.000
Diarrhea, n (%)	6 (17.6)	13 (25.0)	0.422
Abdominal distension, n (%)	3 (8.8)	20 (38.5)	**<0.05**
Nausea and vomiting, n (%)	0	3 (5.8)	0.274
Abnormal glucose metabolism, n (%)	22 (62.9)	31 (59.6)	0.761

EN, enteral nutrition.
P value <0.05 was considered statistically significant and presented in bold type.

organ failure, systemic infection, and the need for surgical intervention [2]. Recently, EN researches have been focused on the timing of EN initiation in patients with predicted severe course. Available evidence suggests that start of EN has a trophic effect on gut wall integrity and may reduce the inflammatory response [16]. This hypothesis was confirmed by multiple studies [17,18] including several conventional meta-analyses [11,19] and a recent individual patient data meta-analysis [20]. However, none of the available studies primarily focused on the definition of timing of early EN. The reported timings of early EN varies from different studies, and were mostly predetermined by the researchers rather than derived from statistical analysis such as ROC curve. A total of 11 randomized controlled studies for EN were reported between 1997 and 2008, in which "early EN" was defined as within 6 h of hospital admission in one study, within 24 h in three studies, within 48 h in three studies, and within 48–72 h, 72 h, and 96 h in one study of each [11]. Between 2012 and 2016, 7 practice guidelines were published but with no consistent definition of early EN: three guidelines failed to clearly clarify the optimal timing [4–6], one defined as within 24–48 h [7], and three defined as within 48 h [8–10]. The inconsistent definitions among studies caused the issues in clinical practice. Recently, the first multicenter randomized trial specifically investigating timing of EN in patients with predicted severe acute pancreatitis (PYTHON trial) was published [15]. As a 19-center RCT of 208 patients with predicted SAP, the investigators found that early EN (begun within 24 h of randomization) was not superior to on demand oral feeding (begun 72 h after presentation) or EN if oral diet was not tolerated. However the majority of the patients (2/3) did not have actual severe AP, who would not be expected to benefit from EN treatment. In addition, 40% of feeding

tubes were dislodged, which further reduced the potential benefit of early EN treatment. Therefore, the optimal timing of EN initiation in predicted severe AP is unknown.

In this study, based on the ROC curve analysis, the third day after hospital admission was the optimal time to start EN in clinical practice. Furthermore, no significant difference was found between patients with EN initiated within 0–24 h, 24–48 h or 48–72 h of hospital admission. Thus, early EN should be defined as starting within three days of hospital admission.

The logistic regression showed that starting EN within three days was a protective factor of secondary infection, with an *OR* value of 0.161(95% CI 0.036–0.718), which is consistent with the previous findings [11]. However, previous studies mainly focused on the relationship between EN and infected pancreatic necrosis [17,20,21], while targeted analysis for infections in extrapancreatic organs is lacking. Studies showed that the extrapancreatic infection was common in acute pancreatitis with an overall incidence of 32% (95%CI 23–41%) [22], and was associated with higher mortality [23]. The most common extrapancreatic infections were respiratory infection, bacteremia and urinary tract infection [22]. The subgroup analysis in this study showed that early EN could significantly reduce the risk of secondary infections in the extrapancreatic organs, which may be related to the mechanism of EN in maintaining the intestinal mucosal barrier and reducing the chance for intestinal bacteria translocation [24].

In addition, AP has a major effect on gastrointestinal functions. In 2012, the European Society of Intensive Care Medicine (ESICM) recommended using the AGI grading system to assess gastrointestinal function in intensive care patients [14]. The results of this study showed that 64.4% of the patients with moderate and severe AP were classified as grade IV. The ANOVA for repeated measures showed that the improvement of gastrointestinal functions in the patients with early EN was better than that in patients with late EN, suggesting that early EN can promote the recovery of gastrointestinal functions.

Previous study has shown that EN can improve serum albumin levels after hospital admission [25], but it is not yet confirmed if early EN is better than late EN [26]. The results of this study showed that the serum albumin levels of the patients with acute pancreatitis rebounded on day 14 of hospital admission, with values approaching or even exceeding the baseline at hospital admission. The ANOVA for repeated measures showed that the albumin level of the patients with early EN was higher than that of the patients with late EN. Thus, the early initiation of EN may help improve the nutritional status.

As an observational study, it has some limitations. The starting time of EN, the adjustment of EN speed, and patient tolerance for EN were judged by the clinicians, which may cause bias. For example, clinicians might tend to delay EN initiation when patients presented with more severe disease, and vary in the EN speed acceleration. In fact, the VAS score of abdominal pain at admission was higher in the late EN group than in the early EN group. To overcome these limitations, we performed strict EN protocol for clinical implementation, and a propensity score matching to reduce the confounders in the statistical comparison of outcomes between two groups. After PS matching, all cases were matched for relevant confounders, including the VAS score of abdominal pain at admission. In addition, this study was a single-center clinical research study with a small sample size, which may cause bias. The results must be further confirmed with large-scale multi-center randomized control trials.

In summary, the optimal time to begin EN is within three days after hospital admission. Early EN can reduce the risk of secondary infection and improve the nutritional status of patients with AP, with a better tolerance.

Statement of authorship

HY and JQ conceptualized and designed the study. MJ designed the study and drafted the manuscript. MJ, HZ, BL, YL and DW collected and analyzed data. All authors critically revised the manuscript and agreed to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

We thank the emergency department, medical intensive care unit, general intensive care unit and gastrointestinal department of the Peking Union Medical College Hospital for their support on this study. We also would like to express our sincere gratitude to the patients participated in this study. This work was supported by the Health Research & Special Projects Grant of China (No.201002020) and Science Foundation for the Excellent Youth Scholars of Ministry of Education of China (No.20101106120059).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pan.2017.08.011.

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