





ORIGINAL ARTICLE

Incidence and risk factors of oral feeding intolerance in acute pancreatitis: Results from an international, multicenter, prospective cohort study

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Abstract

Background: Inability to advance to an oral diet, or oral feeding intolerance, is a common complication in patients with acute pancreatitis associated with worse clinical outcomes. The factors related to oral feeding intolerance are not well studied.

Objective: We aimed to determine the incidence and risk factors of oral feeding intolerance in acute pancreatitis.

Methods: Patients were prospectively enrolled in the Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience, an international acute pancreatitis registry, between 2015 and 2018. Oral feeding intolerance was defined as worsening abdominal pain and/or vomiting after resumption of oral diet. The timing of the initial feeding attempt was stratified based on the day of hospitalization. Multivariable logistic regression was performed to assess for independent risk factors/predictors of oral feeding intolerance.

Results: Of 1233 acute pancreatitis patients included in the study, 160 (13%) experienced oral feeding intolerance. The incidence of oral feeding intolerance was similar irrespective of the timing of the initial feeding attempt relative to hospital admission day ($p = 0.41$). Patients with oral feeding intolerance were more likely to be younger (45 vs. 50 years of age), men (61% vs. 49%), and active alcohol users (44% vs. 36%). They also had higher blood urea nitrogen (20 vs. 15 mg/dl; $p < 0.001$) and hematocrit levels (41.7% vs. 40.5%; $p = 0.017$) on admission; were more likely to have a nonbiliary acute pancreatitis etiology (69% vs. 51%), systemic inflammatory response syndrome of 2 or greater on admission (49% vs. 35%) and at 48 h (50% vs. 26%), develop pancreatic necrosis (29% vs. 13%), moderate to severe acute pancreatitis (41% vs. 24%), and have a longer hospital stay (10 vs. 6 days; all $p < 0.04$). The adjusted analysis showed that systemic inflammatory response syndrome of 2 or greater at 48 h (odds ratio 3.10; 95% confidence interval 1.83–5.25) and a nonbiliary acute pancreatitis etiology (odds ratio 1.65; 95% confidence interval 1.01–2.69) were independent risk factors for oral feeding intolerance.

Conclusion: Oral feeding intolerance occurs in 13% of acute pancreatitis patients and is independently associated with systemic inflammatory response syndrome at 48 h and a nonbiliary etiology.

KEYWORDS

acute pancreatitis, APPRENTICE, diet, enteral feeding, intolerance, oral feeding, predictors, prognosis, severity

Key Summary

Current knowledge on this subject

- Oral feeding intolerance is a relatively common complication of acute pancreatitis.
- Oral feeding intolerance results in longer hospitalization and frequent readmissions.

What is new in this study

- The incidence of oral feeding intolerance is similar irrespective of the timing of the initial feeding attempt.
- Oral feeding intolerance is independently associated with systemic inflammatory response syndrome at 48 h and nonbiliary etiology.

INTRODUCTION

Oral feeding intolerance (OFI) is a well-known complication of acute pancreatitis (AP).¹ This condition is characterized by recurrent gastrointestinal symptoms on resuming an oral diet, such as abdominal pain, nausea, and vomiting, often seen in association with biochemical abnormalities and increased opioid requirements during hospitalization.¹ It is estimated that approximately one in five patients with AP are diagnosed with OFI.¹⁻³ AP patients with OFI achieved lower scores in five out of six quality of life domains,⁴ and have a higher risk of readmission following hospital discharge.⁵

There is no standardized approach to oral refeeding in AP and it varies based on the treating physician's preference on timing, route, and type of nutrition.⁶ In mild AP, evidence-based and societal guidelines support early oral refeeding.⁷ In contrast, patients with predicted moderately severe or severe AP may require the initiation of early enteral nutritional support rather than oral diet.^{6,8}

A few studies in AP have assessed the potential predictors of OFI, but none of these has been adopted into clinical practice.^{1-3,5,8-14} As such, a "one size fits all" approach as it relates to oral refeeding in AP is likely to result in suboptimal clinical outcomes. A novel approach to address this problem could evaluate and incorporate unique patient and disease-related risk factors for OFI to guide the nutrition management plan in AP. Patients determined to be at high risk of OFI may require early enteral nutrition as the initial approach. On the other hand, patients at low risk of OFI could start oral feeds early in the hospital course, aiming for early discharge and reducing the length of hospitalization.

The aim of our study was to determine clinically meaningful risk factors and predictors of OFI utilizing an international, prospective cohort of AP patients.

METHODS

Study design

The Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE) is an international, multicenter collaboration including 22 centers around the world.^{15,16} This consortium includes eight centers in the United States, five in Latin America, six in Europe, and three in India. Patients were prospectively enrolled between November 2015 and January 2018. The study protocol was approved by the institutional review board or ethics committee at each participating study site (PRO15040389/

approval date: 07/14/2015). Each participating site submitted a data-use agreement form to the coordinating center. The study protocol conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The inclusion/exclusion criteria were universally implemented throughout all sites. Subjects were at least 18 years old, willing to participate, and enrolled within 7 days from onset of pain. Patients with chronic pancreatitis or pancreatic cancer were excluded. Written, informed consent was obtained from all subjects. Standardized questionnaires were used to obtain information on demographics, etiology of AP, coexisting comorbidities, laboratory values, and clinical outcomes of enrolled subjects. For transferred patients, early data were collected from the referral hospital. All data were entered by the enrolling site in a centralized research electronic data capture database. The data were deidentified and monitored by the University of Pittsburgh, which functioned as the coordinating center.

Study variables/definitions

The AP cohort was categorized in groups based on the nutrition route. The oral group included all patients who were initially fed orally. Patients in the oral group were further characterized as either tolerant or intolerant. OFI was defined as worsening abdominal pain and/or vomiting after resumption of any type of oral diet. Patients who consumed their initial meal with minimal abdominal pain and/or nausea that was not enough to discourage them from eating were classified as tolerant. Subjects who did not tolerate the oral feeding attempt were unable to consume a significant portion of their meal due to the recurrence of symptoms, required increased doses of analgesic, and antiemetic medications, or developed emesis were termed intolerant. Patients who were initially fed through the enteral route or parenteral route were classified in the nonoral group.

Active alcohol use was defined as the consumption of alcohol over the past 6 months and smoking as active tobacco use in the past 6 months. Patients who fulfilled at least two out of the four systemic inflammatory response syndrome (SIRS) criteria were characterized as SIRS positive. The revised Atlanta classification (RAC) was used to define severity, dividing patients into three groups: mild, moderately severe, and severe.¹⁷ The lipase ratio was defined as the recorded lipase level divided by the upper limit of normal for a given institution. Length of stay was defined as the total hospital stay, including days of hospitalization in both the initial and the referral hospital for

transferred patients. The timing of the initial feeding attempt was determined relative to the initial admission date.

Statistical analysis

Categorical variables were described using percentages, and continuous variables were described using the median and interquartile range (IQR). Pearson's χ^2 and Wilcoxon's rank-sum tests were used to compare categorical and continuous variables across groups, respectively. Univariate analysis was performed to examine the association between clinical variables and OFI. Covariates included age, gender, comorbidities, active alcohol and tobacco use, transfer status, previous history of AP, etiology of AP, admission blood urea nitrogen (BUN) and hematocrit levels, positive SIRS status on admission, and at 48 h of hospitalization and the development of pancreatic necrosis.

A multivariable logistic regression model was subsequently constructed to determine whether any of the variables found to be significant in univariate analyses (p value < 0.05) were independently associated with OFI. We set out to develop a model to predict OFI including the following variables: age, gender, alcohol and smoking use, transfer status, recurrent attacks, nonbiliary etiology, admission BUN, hematocrit, and admission and 48-h SIRS. Cross validation was performed by splitting the dataset into 10 equally sized training sets. Logistic regression analysis was performed in nine of them to estimate the probability of having OFI as a function of predictors. Subsequently, the predicted probability of OFI was calculated in the omitted training set. This was repeated until all 10 training sets had predicted probabilities calculated. The above process was then iterated 200 times by randomly splitting the patient cohort. A receiver operating characteristic curve was developed including the predictive probabilities of all the 200 models.

Finally, patients with an initial oral feeding attempt and patients who were directly introduced to enteral or total parenteral nutrition (TPN) were compared with respect to demographics, laboratory values, and clinical outcomes. All statistical analysis was conducted using STATA 15.1. A p value of less than 0.05 was considered statistically significant.

RESULTS

Overall, 1544 patients were enrolled, of which 105 were excluded from the study due to incomplete data related to OFI (Figure 1). Out of the included 1439 patients, 1233 (85.6%) were categorized in the oral group and 206 patients (14.3%) had a nonoral initial feeding attempt. More specifically, in the nonoral group the feeding route initially attempted was enteral for 119 patients (nasogastric or percutaneous endoscopic gastrostomy for 25 patients, nasojejunal or percutaneous endoscopic jejunostomy for 94) and TPN for 87 patients.

Out of the 1233 patients in the oral group, 1073 (87%) were tolerant and 160 (13%) met the criteria for OFI.

Patients who developed OFI were younger (45 vs. 50 years; $p = 0.018$), predominantly men (61% vs. 49%; $p = 0.004$), active drinkers (44% vs. 36%; $p = 0.034$), and smokers (29% vs. 21%; $p = 0.022$; Table 1). Patients intolerant of oral feeding were more likely to be transferred from an outside hospital (38% vs. 29%; $p = 0.02$), and had a lower lipase ratio on admission (9.4 vs. 14.7; $p = 0.019$). A nonbiliary etiology was found to be more common in the intolerant group (69% vs. 51%; $p < 0.001$). The intolerant patients also had higher BUN (20 vs. 15 mg/dl; $p < 0.001$) and hematocrit levels on admission (41.7% vs. 40.5%; $p = 0.017$). They were more likely to be SIRS positive on admission (49% vs. 35%; $p < 0.001$) and at 48 h (50% vs. 26%; $p < 0.001$), develop pancreatic necrosis (29% vs. 13%; $p < 0.001$), and moderate to severe AP (41% vs. 24%; $p < 0.01$). They also had more frequent intensive care unit (ICU) admission (20% vs. 6%; $p < 0.001$), longer hospital stay (10 vs. 6 days; $p < 0.001$), and higher mortality (3% vs. 0.2%; $p < 0.001$).

With respect to the timing of the initial feeding attempt, 291 (23.6%) patients started an oral diet on the day of admission (Day 1) or Day 2, 342 (27.7%) patients on Day 3, 232 (18.8%) patients on Day 4, 158 (12.8%) patients on Day 5, and 206 (16.7%) patients on Day 6 or later. Data were missing for the exact timing of the initial feeding attempt for four (0.03%) patients (Table 2). The rate of OFI was similar regardless of the day of the initial feeding attempt ($p = 0.41$). The timing of feeding was different between continents, being earliest in North America (2 days, IQR 1–3), followed by Europe (2 days, IQR 2–4), Central/Latin America (3 days, IQR 2–4), and India (3 days, IQR 2–4; $p < 0.001$).

Based on multivariable logistic regression, OFI was found to be independently associated with nonbiliary etiologies (odds ratio [OR] 1.65, 95% confidence interval [CI] 1.01–2.7; $p = 0.046$) and SIRS at 48 h (OR 3.1, 95% CI 1.8–5.2; $p < 0.01$; Table 3).

The predictive model including probabilities of all 200 randomly split training set runs revealed an area under the curve (AUC) of 0.663 (95% CI 0.61–0.71; Figure 2).

Finally, we performed a comparative analysis with respect to the initial feeding route (Table 4). The group having an initial nonoral (enteral or parenteral) route was younger (47 vs. 49 years; $p = 0.045$) predominantly men (67% vs. 50%; $p < 0.001$), with more frequent alcohol (47% vs. 37%; $p = 0.006$) and smoking use (30% vs. 22%; $p = 0.008$) compared to patients who were fed orally at the beginning. The nonoral group was more likely to be transferred from an outside hospital (62% vs. 30%; $p < 0.001$), had increased BUN (24 vs. 15.1 mg/dl; $p < 0.001$) and hematocrit levels (42.6% vs. 40.6%; $p < 0.001$) on admission. Patients fed initially through either the enteral or parenteral routes were more likely to have moderate/severe AP (81% vs. 26%; $p < 0.001$), more frequently had SIRS-positive status on admission (69% vs. 36%; $p < 0.001$) and at 48 h (79% vs. 29%; $p < 0.001$). They required ICU care more often (70% vs. 8%; $p < 0.001$), had a longer hospital stay (16 vs. 7 days; $p < 0.001$) and an increased mortality rate (12% vs. 0.6%; $p < 0.001$).

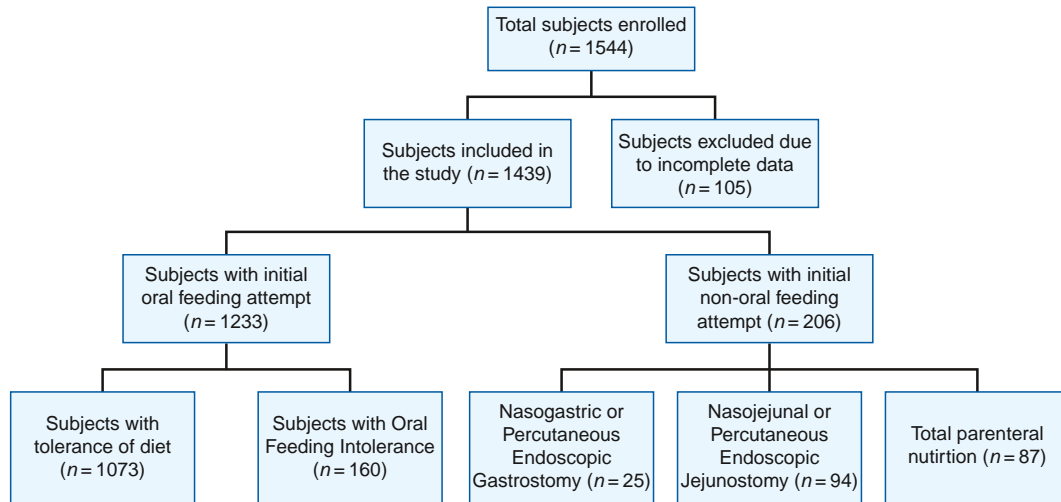


FIGURE 1 Flow chart of the subjects through the study

TABLE 1 Demographic characteristics and clinical outcomes of patients according to tolerance of oral diet

Variables	Patients with OFI (n = 160)	Patients without OFI (n = 1073)	p
Age, median (IQR)	45 (33.5, 58.5)	50 (35, 65)	0.018
Gender, male (%)	97 (61%)	521 (49%)	0.004
BMI \geq 30, N (%)	45 (28%)	303 (29%)	0.904
Active alcohol use, N (%)	71 (44%)	379 (36%)	0.034
Active smoking, N (%)	46 (29%)	220 (21%)	0.022
Transfers, N (%)	61 (38%)	312 (29%)	0.020
Lipase ratio on admission, median (IQR)	9.4 (3.9, 33.3)	14.7 (5.2, 53.3)	0.019
Recurrent AP, N (%)	52 (33%)	271 (25%)s	0.052
Etiology, N (%)			<0.001
Biliary	49 (31%)	524 (49%)	
Nonbiliary	111 (69%)	549 (51%)	
RAC severity, N (%)			<0.001
Mild	95 (59%)	814 (76%)	
Moderate	45 (28%)	217 (20%)	
Severe	20 (13%)	42 (4%)	
BUN on admission, median (IQR)	20 (13, 31)	15 (10,23)	<0.001
Hematocrit on admission, median (IQR)	41.7 (37.0, 47.9)	40.5 (36.8, 44.6)	0.017
SIRS on admission, N (%)	78 (49%)	370 (35%)	<0.001
SIRS at 48 h, N (%)	80 (50%)	264 (26%)	<0.001
Pancreatic necrosis, N (%)	46 (29%)	140 (13%)	<0.001
ICU admission, N (%)	32 (20%)	68 (6%)	<0.001
Length of stay, median (IQR)	10 (7, 14)	6 (4,11)	<0.001
Mortality, N (%)	5 (3%)	2 (0.2%)	<0.001

Abbreviations: AP, acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; IQR, interquartile range; lipase ratio, lipase level/upper limit of normal; OFI, oral feeding intolerance; RAC, revised Atlanta classification; SIRS, systemic inflammatory response syndrome.

TABLE 2 Timing of first feeding in the oral feeding group

	N (%) of tolerance	p ^a
All (N = 1229)	1069 (87%)	0.41
Day 1–2 (N = 291)	246 (85%)	
Day 3 (N = 342)	302 (88%)	
Day 4 (N = 232)	208 (90%)	
Day 5 (N = 158)	137 (87%)	
Day 6 or later (N = 206)	176 (85%)	

^aCalculated with Pearson's χ^2 test.

TABLE 3 Multivariable logistic regression analysis to determine factors independently associated with oral feeding intolerance

Variables	Odds ratio (95% CI)	p
Age	0.99 (0.98, 1.01)	0.410
Gender	0.93 (0.59, 1.46)	0.753
Transfers	0.74 (0.45, 1.21)	0.231
Recurrent AP	1.27 (0.79, 2.04)	0.334
Lipase ratio	1.00 (0.99, 1.00)	0.610
Nonbiliary etiology	1.65 (1.01, 2.69)	0.046
Admission BUN	1.01 (0.99, 1.02)	0.391
Admission hematocrit	1.02 (0.99, 1.05)	0.146
SIRS on admission	0.97 (0.59, 1.60)	0.899
SIRS at 48 h	3.10 (1.83, 5.25)	<0.001
Pancreatic necrosis	1.77 (0.79, 3.96)	0.168
Moderately severe/severe AP	0.79 (0.37, 1.65)	0.526

Abbreviations: AP, acute pancreatitis; BUN, blood urea nitrogen; CI, confidence interval; lipase ratio, lipase level/upper limit of normal; SIRS, systemic inflammatory response syndrome.

DISCUSSION

To the best of our knowledge, this is the largest, international, prospective, cohort study to assess the incidence, clinical predictors and outcomes of OFI in patients with AP. We found that OFI developed in 13% of our cohort. Younger, male patients, and those with active smoking and alcohol use were more likely to develop OFI. Hemoglobin concentration and elevated BUN at admission are potential predictors of OFI. Nonbiliary etiology and SIRS at 48 h after admission were independent risk factors for OFI. The timing of the initiation of an oral diet does not appear to be associated with the development of OFI. OFI was associated with worse clinical outcomes including longer hospital length of stay.

The incidence of OFI was 13% in our study, with the previously reported rates varying between 8% and 25%.^{1–3,11} Bevan et al.¹⁸ reported an overall incidence of OFI at 16% in a meta-analysis including centers from multiple continents. Our data are, therefore, comparable to contemporary literature on this subject. Overall, it

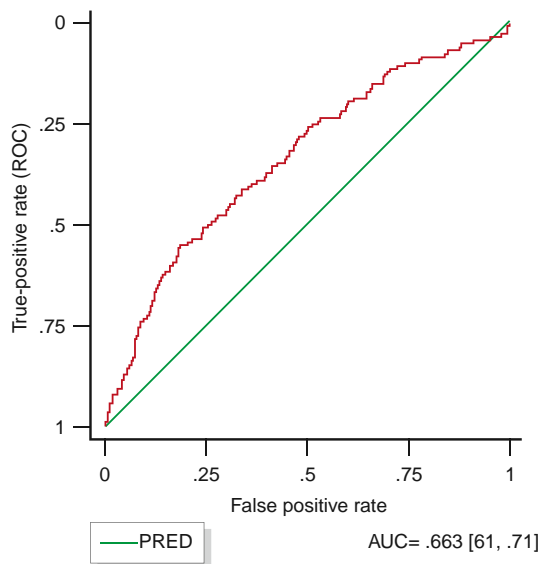


FIGURE 2 Receiver operating characteristic curve for model predicting oral feeding intolerance in patients with acute pancreatitis

appears that the rates of OFI in AP have not improved over the years. This could be due to poor recognition of high-risk patients for OFI and a lack of personalized refeeding protocols in patients with AP.

The optimal timing to start refeeding remains a challenge in the management of AP patients. In our analysis no significant difference was noted with respect to the incidence of OFI based on the day of the initial oral refeeding attempt. The day of initiation of an oral diet was based on the treating physician's judgment, according to the subject's symptomatology, and clinical course. The continental difference in the timing of oral feeding initiation in our cohort can be partially explained by variations in the severity of AP among different geographical areas, as it was reported from a previous study of our consortium.¹⁶ Typically, AP patients are initially kept NPO (nil per os), and diet is resumed with clinical improvement. It has been suggested that feeding stimulates the release of cholecystokinin, which causes the secretion of proteolytic enzymes that lead to autodigestion and as a result further damage of the pancreas.¹⁹ Several randomized controlled trials have sought to determine the optimal timing of initiating an oral diet with mixed results.^{8–10,12–14} Recent data suggest that early oral refeeding in mild AP has no difference in terms of OFI clinical outcomes or incidence compared to delayed feeding.^{10,12,14} Based on these data, it appears that OFI depends on unique patient and disease-related factors and is not entirely a function of the timing of refeeding. Early oral refeeding in patients at low risk of OFI may enable early discharge and reduce the economic impact of AP.

Patients with certain baseline clinical characteristics, including younger age and male gender, were more likely to develop OFI. Other factors associated with OFI include active alcohol use and smoking, probably due to their association with the severity of AP. Multiple studies have reported an association of alcohol consumption with a more severe clinical course of AP.^{20,21} Alcohol use has also

	Nonoral (n = 206)	Oral (n = 1233)	p
Age, median (IQR)	47 (33, 60)	49 (34, 64)	0.045
Gender, male, N (%)	137 (67%)	618 (50%)	<0.001
BMI ≥30, N (%)	52 (25%)	348 (29%)	0.352
Active alcohol use, N (%)	95 (47%)	450 (37%)	0.006
Active smoking, N (%)	61 (30%)	266 (22%)	0.008
Transferred status, N (%)	127 (62%)	373 (30%)	< 0.001
Recurrent AP, N (%)	45 (22%)	323 (26%)	0.210
Etiology, N (%)			0.003
Biliary	72 (35%)	573 (46%)	
Nonbiliary	134 (65%)	660 (54%)	
RAC severity, N (%)			< 0.001
Mild	39 (19%)	909 (74%)	
Moderate	70 (34%)	262 (21%)	
Severe	97 (47%)	62 (5%)	
BUN on admission, median (IQR)	24 (17, 42)	15.1 (11, 24)	< 0.001
Hematocrit on admission, median (IQR)	42.6 (37.8, 48.6)	40.6 (36.8, 45.0)	< 0.001
SIRS on admission, N (%)	142 (69%)	448 (36%)	< 0.001
SIRS at 48 h, N (%)	161 (79%)	344 (29%)	< 0.001
ICU admission, N (%)	145 (70%)	100 (8%)	< 0.001
Length of stay, median (IQR)	16 (10, 25)	7 (5,11)	< 0.001
Mortality, N (%)	25 (12%)	7 (0.6%)	< 0.001

TABLE 4 Comparison between subjects with initial oral versus non-oral feeding attempt

Abbreviations: AP, acute pancreatitis; BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; IQR, interquartile range; OFI, oral feeding intolerance; RAC, revised Atlanta classification; SIRS, systemic inflammatory response syndrome.

been associated with a higher need for ICU care, infectious complications and mortality.^{22,23} Even though smoking is a well-known risk factor for chronic pancreatitis,²⁴ it has been difficult to examine its association with OFI in AP, because tobacco use is closely related to alcohol consumption,²⁴ and it has been challenging to control for confounding secondary to alcohol use.²⁵

Biliary etiology was found to be associated with a reduced rate of OFI in our study. Nonbiliary causes included alcohol, hypertriglyceridemia, and idiopathic causes. Both alcoholic and hypertriglyceridemia-induced causes are associated with a more complicated course of AP compared to other etiologies.^{26,27} Our findings suggest adopting a cautious approach with oral refeeding in patients with alcoholic, hypertriglyceridemia and idiopathic etiology.

Laboratory parameters such as BUN and hematocrit on admission were elevated in the OFI group. These markers are also associated with disease severity.²⁸⁻³² Elevated BUN is associated with increased mortality,^{31,32} while hemoconcentration can predict pancreatic necrosis and organ failure.^{28,29} These conventional laboratory markers provide information about the intravascular volume

status of patients, and changes in their values can reflect patient's response to fluid resuscitation.

Pancreatic necrosis was also noted to be associated with OFI in the univariate analysis. Patients with elevated BUN and hematocrit on admission,^{29,30} as well as significant alcohol use^{20,21} are at risk of pancreatic necrosis. After controlling for these confounding factors in multivariable analysis, a trend was noted showing an independent correlation of pancreatic necrosis with OFI, which did not reach statistical significance ($p = 0.06$).

In terms of clinical outcomes, we found that patients with OFI had a more severe clinical course, with longer hospital stay and requirement for ICU management. These patients frequently have SIRS on admission and at 48 h. The latter was identified as an independent risk factor for OFI in the multivariable regression analysis. Singh et al.³³ showed that positive SIRS on admission is associated with a severe clinical course. Other studies proposed that SIRS at 48 h is associated with organ dysfunction and increased mortality.^{34,35} Our findings suggest that SIRS has the potential to be used in clinical practice to risk stratify patients for OFI.

We found an association of OFI with longer length of stay, which was consistent with previous reports.^{1,3,4,18} Early recognition, prevention, and appropriate management of OFI will likely improve patients' symptomatology during hospitalization and reduce the economic burden associated with AP.⁴ It has been reported that AP patients who are discharged with gastrointestinal symptoms, or without having tolerated solid diet during their stay, are at high risk of early readmission.⁵ The tolerance of a solid oral diet could be used to guide physicians in the discharge planning of AP patients.

In order to examine the predictability of OFI, we constructed a statistical model composed of key clinical variables. The results of our model suggest that a clinician has a 66% probability of correctly predicting OFI using the above variables. However, an AUC of 0.663 is only of low to modest predictive accuracy and is unlikely to be adapted in clinical practice.

Finally, patients who received enteral/parenteral nutrition had a similar risk profile as patients who developed OFI. Factors associated with nonoral nutrition included young age, men, active smoking and alcohol, nonbiliary etiology, moderate/severe AP based on RAC, elevated BUN/hemoconcentration at admission, SIRS at admission, and 48 h. A more proactive approach at the initiation of enteral nutrition is likely to be warranted after stabilization of hemodynamics and fluid resuscitation in patients with a predicted moderate or severe course of AP.

This study had several limitations. Given that this is an observational study, no causal association can be established with regard to potential risk factors of OFI. Also, most of the participating centers of the study are academic tertiary centers. Therefore, the results might not be generalizable. The strengths of this study derive from the fact that this is the first international study to examine clinical predictors of OFI. A diverse population of AP patients was prospectively enrolled and carefully phenotyped from multiple leading pancreatic centers around the globe. The questionnaires were standardized, and data were monitored and analyzed centrally at the coordinating site.

In conclusion, our study confirmed that OFI is relatively common and is associated with worse clinical outcomes in AP. Young age, male gender, alcohol use, smoking, elevated BUN, and hemoconcentration are potential predictors of OFI. The nonbiliary etiology of AP and SIRS at 48 h may serve as important prognostic factors in stratifying patients at risk of OFI. Detecting patients with these clinical features should rationalize a more cautious approach by the treating physicians with their refeeding strategy. Additional research in the form of randomized clinical trials is needed to determine the optimal timing and consistency of suggested diets in patients with AP stratified by clinical risks and laboratory predictors of OFI.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS APPROVAL

The study protocol was approved by the Institutional Review Board (IRB) or Ethics Committee at each participating study site (PRO15040389/approval date: 07/14/2015).

INFORMED CONSENT

Written, informed consent was obtained from all subjects.

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REFERENCES

- Chebli JM, et al. Oral refeeding in patients with mild acute pancreatitis: prevalence and risk factors of relapsing abdominal pain. *J Gastroenterol Hepatol.* 2005;20:1385–9.
- Francisco M, et al. Factors associated with intolerance after refeeding in mild acute pancreatitis. *Pancreas.* 2012;41:1325–30.
- Levy P, et al. Frequency and risk factors of recurrent pain during refeeding in patients with acute pancreatitis: a multivariate multicentre prospective study of 116 patients. *Gut.* 1997;40:262–6.
- Pendharkar SA, et al. Association between oral feeding intolerance and quality of life in acute pancreatitis: a prospective cohort study. *Nutrition.* 2015;31:1379–84.
- Whitlock TL, et al. Early readmission in acute pancreatitis: incidence and risk factors. *Am J Gastroenterol.* 2010;105:2492–7.
- Bevan MG, Asrani V, Petrov MS. The oral refeeding trilemma of acute pancreatitis: what, when and who?. *Expert Rev Gastroenterol Hepatol.* 2015;9:1305–12.
- Vege SS, et al. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute technical review. *Gastroenterology.* 2018;154:1103–39.
- Zhao XL, et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. *Nutrition.* 2015;31:171–5.
- Bakker OJ, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med.* 2014;371:1983–93.
- Eckerwall GE, et al. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery—a randomized clinical study. *Clin Nutr.* 2007;26:758–63.
- Jacobson BC, 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;5:946–51.
- Larino-Noia J, et al. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. *Pancreatol.* 2014;14:167–73.
- Petrov MS, 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.
- Teich N, et al. Optimal timing of oral refeeding in mild acute pancreatitis: results of an open randomized multicenter trial. *Pancreas.* 2010;39:1088–92.
- Papachristou GI, et al. Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE): an international, multicenter consortium for the study of acute pancreatitis. *Ann Gastroenterol.* 2017;30:106–13.

16. Matta B, et al. Worldwide variations in demographics, management, and outcomes of acute pancreatitis. *Clin Gastroenterol Hepatol.* 2020;18:1567-75.
17. Banks PA, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut.* 2013;62:102-11.
18. Bevan MG, et al. Incidence and predictors of oral feeding intolerance in acute pancreatitis: a systematic review, meta-analysis, and meta-regression. *Clin Nutr.* 2017;36:722-9.
19. Leach SD, et al. Intracellular activation of digestive zymogens in rat pancreatic acini. Stimulation by high doses of cholecystokinin. *J Clin Invest.* 1991;87:362-6.
20. Easler JJ, et al. Patients with sentinel acute pancreatitis of alcoholic etiology are at risk for organ failure and pancreatic necrosis: a dual-center experience. *Pancreas.* 2016;45:997-1002.
21. Papachristou GI, et al. Chronic alcohol consumption is a major risk factor for pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol.* 2006;101:2605-10.
22. Gacouin A, et al. At-risk drinkers are at higher risk to acquire a bacterial infection during an intensive care unit stay than abstinent or moderate drinkers. *Crit Care Med.* 2008;36:1735-41.
23. Gacouin A, et al. At-risk drinking is independently associated with ICU and one-year mortality in critically ill nontrauma patients*. *Crit Care Med.* 2014;42:860-7.
24. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. *Nat Rev Gastroenterol Hepatol.* 2010;7:131-45.
25. Morton C, Klatsky AL, Udaltsova N. Smoking, coffee, and pancreatitis. *Am J Gastroenterol.* 2004;99:731-8.
26. Deng LH, et al. Effect of admission hypertriglyceridemia on the episodes of severe acute pancreatitis. *World J Gastroenterol.* 2008;14:4558-61.
27. Pothoulakis I, et al. Clinical features of hypertriglyceridemia-induced acute pancreatitis in an international, multicenter, prospective cohort (APPRENTICE consortium). *Pancreatology.* 2020;20:325-30.
28. Baillargeon JD, et al. Hemoconcentration as an early risk factor for necrotizing pancreatitis. *Am J Gastroenterol.* 1998;93:2130-4.
29. Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas.* 2000;20:367-72.
30. Koutroumpakis E, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. *Am J Gastroenterol.* 2015;110:1707-16.
31. Wu BU, et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. *Arch Intern Med.* 2011;171:669-76.
32. Wu BU, et al. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterology.* 2009;137:129-35.
33. Singh VK, et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin Gastroenterol Hepatol.* 2009;7:1247-51.
34. Buter A, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg.* 2002;89:298-302.
35. Mofidi R, et al. Prognostic factors in patients undergoing surgery for severe necrotizing pancreatitis. *World J Surg.* 2007;31:2002-7.

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