https://doi.org/10.15360/1813-9779-2022-3-11-20



# Prognostic Tests of Intolerance to Postpyloric Feeding in Early Acute Pancreatitis

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# Прогностические тесты непереносимости постпилорического энтерального питания в раннюю фазу острого панкреатита

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**For citation:** *Oleg G. Sivkov, Ilya N. Leyderman, Alexey O. Sivkov, Anatoly A. Kolchanov, Georgy D. Bashlykov.* Prognostic Tests of Intolerance to Postpyloric Feeding in Early Acute Pancreatitis. *Obshchaya Reanimatologiya = General Reanimatology.* 2022; 18 (3): 11–20. https://doi.org/10.15360/1813-9779-2022-3-11-20 [In Russ. and Engl.]

## Summary

**Aim.** To evaluate the effectiveness of postpyloric feeding in early predicted severe acute pancreatitis using acetaminophen absorption test and gastric emptying rate.

**Material and methods.** An open observational prospective cohort study in the intensive care unit of OAO «Neftyanik» hospital in the city of Tyumen, Russia, from November 2012 to October 2018 was performed. All included patients were diagnosed with predicted severe acute pancreatitis (inclusion criterion). The rate of gastric emptying was assessed using an original ultrasound technique which involved measuring the fluid volume 30 min and 60 min after administering of 200 mL aliquote of water into the stomach. Acetaminophen absorption test was performed according to the following procedure: 0.5 g of acetaminophen was administered through the nasojunal tube placed 30–40 cm distal to the Treitz ligament using endoscope, the blood level of the drug was measured 5–20 min later.

**Results.** Gastric fluid volume at 60 min (OR=1.049, 95% CI: 1.028–1.07, $P$<0.001 with AUC=0.921, 95% CI: 0.808–0.944 and cutoff value of 73.5) was a significant predictor of residual gastric volume ⩾500 mL/d and intolerance to enteral feeding through the nasojejunal tube (OR=1.023, 95% CI: 1.009–1.036, $P$=0.001 with AUC 0.752, 95% CI: 0.629–0.875, with cutoff value of 79.5). The acetaminophen small intestine absorption test was reliable in predicting the residual gastric volume ⩾500 mL/d for the early period of disease. The acetaminophen absorption test was a significant predictor of intolerance to enteral feeding through the nasojejunal tube only in patients with severe acute pancreatitis (OR=0.834, 95% CI: 0.733–0.949, $P$<0.001 with AUC=0.894, 95% CI: 0.770–0.1 with cutoff value of 14.6).

**Conclusion.** Throughout the early period of acute pancreatitis, gastric fluid volume measured 60 min after the administration of 200 mL of water, accurately predicts the residual gastric volume ⩾500 mL/day. Acetaminophen absorption test in the small intestine can reliably predict intolerance to postpyloric feeding only for patients with severe acute pancreatitis.

***Keywords: pancreatitis; enteral feeding; feeding intolerance; gastric ultrasound; acetaminophen***

**Conflict of interest.** The authors declare no conflict of interest.

The full text version of the paper is available at www.reanimatology.com.

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## Introduction

Early phase of acute pancreatitis (AP) is always associated with acute injury to the gastrointestinal tract, which can result in feeding intolerance (FI) syndrome, where adequate enteral feeding is impossible due to a clinical reason (vomiting, high residual gastric volume (RGV), diarrhea, meteorism, gastrointestinal bleeding, intestinal fistula, etc.) [1]. There are no clearly defined constellation of signs and symptoms or quantitative characteristics to support and classify the FI. Enteral delivery of nutrients can be carried out through nasogastric (NG) or nasojejunal (NJ) tube. Most studies on early enteral nutrition (EN) in AP were performed before a new form of AP, moderately severe (MSAP), was identified in 2012 [2]. The form of disease is known to significantly affect the tolerance of early EP in the early AP [3], and existing predictors of severe disease are not always capable of correct prediction of the form of disease [4], which complicates the choice of nutrient delivery way. The FI is considered to be present if the EP is less than 20 kcal/kg body weight per day for the first 72 h or it has to be discontinued due to some reason [1]. At present there are enough methods capable to estimate the gastric emptying in seriously ill patients [5]. However, only one of them, paracetamol absorption test, allows to assess not only the gastric emptying, but also the intestinal absorption of nutrients [6, 7], which is important because even with minimal functional changes of the intestine its ability to absorb nutrients, drugs (in particular, acetaminophen) is reduced [8]. If the necessary equipment is available, it is not difficult to place a nasojejunal tube 30–50 cm distal to the Treitz ligament and deliver the nutrients into the small intestine, but no method can determine the extent of absorption. Finding a simple and reproducible routine test capable of determining the tolerability of post-pyloric feeding in the early phase of predicted severe acute pancreatitis would help to improve the outcome in these patients.

The aim of the study was to evaluate the tolerability of post-pyloric feeding in the early phase of predicted severe acute pancreatitis using acetaminophen absorption test and gastric emptying rate assessment.

## Material and Methods

An open observational prospective cohort study was conducted in the intensive care unit of OAO «Neftyanik» hospital in Tyumen from November 2012 to October 2018.

Inclusion criteria were diagnosed AP and at least one predictor of severe disease. Exclusion criteria were age over 80 years, terminal chronic diseases, pancreatogenic shock, lactate > 4 mmol/L, need for adrenomimetics to maintain mean arterial pressure > 70 mm Hg, hepatic failure, acetaminophen (paracetamol) intolerance. The diagnosis of AP was made based on typical clinical presentation, laboratory and instrumental findings [2]. Predictors associated with severe AP included C-reactive protein (CRP) level > 150 mg/L, APACHE (Acute Physiology and Chronic Health Evaluation) II score >8 points and SOFA (Sequential Organ Failure Assessment) score >2 points [9]. The rate of gastric emptying was assessed using an original ultrasound technique from 08:00 to 12:00 a.m. by two intensive care physicians, who had completed a 6-hour gastrointestinal ultrasound training course. Nasogastric tube was inserted while the patient was in the supine position with the head elevated at 30°, the stomach was emptied and then 200 ml of water was introduced. Immediately after introduction and 30 and 60 minutes later, a Mindray M7 portable ultrasound scanner (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China), with the C5-2s convex transducer performed ultrasound scan of stomach in B-mode in two mutually perpendicular planes, transverse and longitudinal, with subsequent calculation of volume (ml) using the formula A×B×C×0.523. After the last volume determination, gastric contents were evacuated through the NG tube and an acetaminophen absorption test (AAT) was performed. Through a 7 CH nasojejunal tube installed using a gastroscope, acetaminophen 0.5 g («Perfalgan», Bristol-Myers Squibb, France) was introduced 30–50 cm distal to the Treitz ligament, then 5 ml of venous blood was drawn within 5 to 20 minutes after the drug administration [10]. Acetaminophen concentration in blood serum was determined using an AxSYM (Abbott Laboratories, USA) immunoassay analyzer, using the fluorescent polarization immunoassay. Subsequently, the daily balance of administered (water + food) and excreted through the NG tube volume was recorded. Standard isocaloric enteric nutrition formula enriched with dietary fiber (Nutricom Standard Fiber, Bbraun, Germany) was administered into the tube. Additionally, the patient was able to drink water if necessary. The following criteria for feeding intolerance were used: loss of ⩾500 ml through NG tube either momentarily or during a day, increased pain, abdominal bloating, diarrhea (loose stool more than 3 times per day), nausea, and vomiting. If intolerance occurred, the rate of infusion of the formula was reduced by 50% or the infusion was discontinued. Later, after the symptoms of intolerance had subsided, the rate was gradually increased to the proper level. All operated patients underwent abdominal drainage through a laparoscopic access, under total intravenous anesthesia with muscular relaxation and lung ventilation. The study was performed if >6 hours elapsed after surgery. We included 39 patients, some of whom had undergone one to three exami-

**Table 1. Clinical and laboratory data in the studied groups.**

| Parameter | Values in the groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 (*n*=62) | 2 (*n*=17) | 3 (*n*=23) | 4 (*n*=22) | *P* (for groups 2–4) | 5 (*n*=34) | 6 (*n*=28) | *P* (for groups 5, 6) |
| Sex. m/f | 43/19 | 11/6 | 16/7 | 16/6 | | 20/14 | 23/5 | |
| Age, years | 50 [37; 58] | 46.4±12.4 | 52 [37; 58] | 52 [37; 58] | 0.919[e] | 56 [44; 58] | 44.4±13.5 | 0.103[g] |
| *P* value (Shapiro–Wilk test) | <0.001 | 0.351 | 0.043 | 0.041 | | <0.001 | 0.103 | |
| BMI[a], kg/m$^2$ | 29.3 [24.1; 31.1] | 27.6±4.8 | 28.3±4.4 | 28.1±4.6 | 0.954[f] | 29.6 [26.1; 30.9] | 29.0 [24.1; 32.8] | 0.635[g] |
| *P* value (Shapiro–Wilk test) | 0.003 | 0.6 | 0.236 | 0.131 | | 0.001 | 0.01 | |
| APACHE-II[b], points | 10 [7; 13] | 8.9±4.3 | 11.1±4.8 | 9 [6; 13] | 0.447[e] | 12[10;15] | 7.3±3.3 | <0.001[g] |
| *P* value (Shapiro–Wilk test) | <0.001 | 0.716 | 0.159 | <0.001 | | 0.001 | 0.091 | |
| SOFA[c], points | 2 [1; 3] | 2 [1; 2] | 2.5 [2; 4] | 2 [0; 4] | 0.142[e] | 3 [2; 4] | 1 [0; 2] | <0.001[g] |
| *P* value (Shapiro–Wilk test) | <0.001 | 0.001 | <0.001 | <0.001 | | <0.001 | <0.001 | |
| CRP[d], mg/l | 154.3±58.8 | 94.7±52.0 | 179±40.3 | 175.5±46.9 | 0.001[f] | 168.3±57.1 | 137.9±57.5 | 0.038[h] |
| *P* value (Shapiro–Wilk test) | 0.175 | 0.626 | 0.116 | 0.31 | | 0.404 | 0.441 | |
| Lung ventilation, *n* (%) | 8/(12.9) | 1(5.9) | 3(13) | 4(18.2) | 0.324[j] | 9 (26.5) | 0 (0) | 0.003[i] |
| Moderate severe disease, *n* (%) | 34/28 (54/46) | 9/8 (53/47) | 13/10 (56/44) | 12/10 (55/45) | 0.974[j] | 34/0 (100/0) | 0/28 (0/100) | — |
| Surgery 6–12 h prior to the examination | 27 (43.5) | 7 (41.2) | 9 (39.1) | 2 (9.1) | 0.037[j] | 9 (26.5) | 9 (32.1) | 0.78[i] |

**Note.** [a] — body mass index; [b] — Acute Physiology And Chronic Health Evaluation II; [c] — Sequential Organ Failure Assessment; [d] — C-reactive protein; [e] — Kruskal–Wallis test; [f] — ANOVA; [g] — Mann–Whitney U-test; [h] — Student's test; [i] — Fisher's exact test; [j] – Pearson's $\chi^2$ test.

**Table 2. Frequency of etiological factors and comorbidities in the studied groups.**

| Parameter | Values in the groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 (*n*=62) | 2 (*n*=17) | 3 (*n*=23) | 4 (*n*=22) | *P* (for groups 2–4) | 5 (*n*=34) | 6 (*n*=28) | *P* (for groups 5, 6) |
| Cholelithiasis, *n* (%) | 5 (8.1) | 1 (5.9) | 2 (8.7) | 2 (9.1) | 0.926[b] | 5 (14.7) | 0 (0) | 0.058[a] |
| Alimentary etiology, *n* (%) | 19 (30.6) | 9 (52.9) | 13 (56.5) | 13 (59.1) | 0.929[b] | 19 (55.8) | 16 (57.1) | 1.0[b] |
| Alcohol, *n* (%) | 35 (56.5) | 6 (35.3) | 7 (30.4) | 6 (27.3) | 0.865[b] | 10 (29.4) | 9 (32.1) | 1.0[a] |
| Other, *n* (%) | 3 (4.8) | 1 (5.9) | 1 (4.3) | 1 (4.5) | 0.972[b] | 0 | 3 (10.7) | 0.87[a] |
| Hypertension, *n* (%) | 29 (46.8) | 7 (41.1) | 11 (47.8) | 11 (50.0) | 0.854[b] | 20 (58.8) | 9 (32.1) | 0.044[a] |
| Coronary heart disease, *n* (%) | 13 (20.9) | 3 (17.6) | 5 (21.7) | 5 (22.7) | 0.922[b] | 10 (29.4) | 3 (10.7) | 0.116[a] |
| Chronic heart failure, *n* (%) | 11 (17.7) | 3 (17.6) | 3 (13.0) | 3 (13.6) | 0.91[b] | 6 (17.6) | 3 (10.7) | 0.317[a] |
| Type 2 diabetes mellitus, *n* (%) | 3 (4.8) | 1 (5.9) | 2 (8.7) | 2 (9.1) | 0.924[b] | 5 (14.7) | 0 (0) | 0.243[a] |
| Other, *n* (%) | 3 (4.8) | 1 (5.9) | 1 (4.3) | 1 (4.5) | 0.972[b] | 0 | 3 (10.7) | 0.087[a] |

**Note.** [a] — Fisher's exact test; [b] — Pearson's $\chi^2$ test.

nations. Six groups of parameters were identified. Group 1 included parameters for all days of the study (*n*=62), group 2 included investigations done during day 1 of ICU stay (*n*=17), group 3 comprised tests performed on days 2 and 3 (*n*=23), group 4 included tests carried out on days 4 and 5 (*n*=22), group 5 included patients who later progressed into severe AP (*n*=34), and group 6 included patients with moderate AP (*n*=28). The time after the last paracetamol administration was more than 24 h.

Statistical analysis was done using the SPSS 26.0 software package. The data distribution was assessed using the Shapiro–Wilk criterion, the data were presented as mean (*M*) with mean square deviation $M\pm\sigma$ or median (*Me*) with quartiles [Q25; Q75]. Parametric and nonparametric criteria were used for intergroup comparison. We used logistic regression to identify variables with prognostic significance. Total explained variance was assessed using the Nagelkerke $R^2$ method, and the constant of the regression equation was indicated. The discriminant ability of parameters was determined by ROC-analysis based on maximum combined sensitivity and specificity of the model. Model quality was assessed using an expert scale of Area Under Curve (AUC) values: 0.9–1.0 was considered excellent; 0.8–0.9, very good; 0.7–0.8, good; 0.6–0.7, average, and 0.5–0.6, poor. The null hypothesis was rejected at $P<0.05$.

## Results

As shown in Table 1, male patients outnumbered female ones; lung ventilation was used only in 8 patients, and the number of patients who progressed into severe disease later did not differ from the patients with moderate severe acute pancreatitis. The groups were comparable by age, sex, and body mass index. Groups 2, 3 and 4 were comparable in severity scores (APACHE II, SOFA). Patients in the group with subsequent severe disease were more

**Table 3. Symptoms, signs and test of enteral feeding tolerance and balance.**

| Parameter | Values in the groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 (*n*=62) | 2 (*n*=17) | 3 (*n*=23) | 4 (*n*=22) | *P* (for groups 2–4) | 5 (*n*=34) | 6 (*n*=28) | *P* (for groups 5, 6) |
| Pain, *n* (%) | 20 (32.3) | 9 (47.1) | 2 (8.7) | 2 (9.1) | 0.003[f] | 8 (23.5) | 4 (14.3) | 0.521[e] |
| Nausea/vomiting, *n* (%) | 39 (62.9) | 11 (64.7) | 6 (26.1) | 6 (27.3) | 0.022[f] | 16 (47.1) | 7 (25) | 0.113[e] |
| Abdominal bloating, *n* (%) | 37 (59.7) | 3 (17.6) | 8 (34.8) | 8 (36.4) | 0.392[f] | 18 (52.9) | 1 (3.6) | <0.001[e] |
| Diarrhea, *n* (%) | 1 (1.61) | 1 (5.9) | 0 | 0 | 0.26[f] | 0 (0) | 1 (3.6) | 0.456[e] |
| Loss >500 ml/day, *n* (%) | 25 (40.3) | 9 (52.9) | 9 (39.1) | 7 (31.8) | 0.224[f] | 20 (58.8) | 6 (21.4) | 0.004[e] |
| At least 1 clinical sign of feeding intolerance, *n* (%) | 36 (58) | 16 (94.1) | 11 (47.8) | 9 (40.9) | 0.002[f] | 25 (73.5) | 11 (39.3) | 0.007[e] |
| Gastric fluid volume after administration of 200 ml of water | 196 [186; 210] | 194 [186; 219] | 198 [194; 205] | 192 [184; 210] | 0.466[a] | 197 [189; 210] | 198.1±16.8 | 0.432[c] |
| *P* value (Shapiro–Wilk test) | 0.003 | 0.031 | 0.31 | 0.039 | — | 0.014 | 0.056 | — |
| V30, ml | 119. 8±26.8 | 124.5±30.8 | 123.7±24.3 | 112±25.5 | 0.262[b] | 130.2±24.2 | 107.5±24.8 | 0.001[d] |
| *P* value (Shapiro–Wilk test) | 0.708 | 0.928 | 0.694 | 0.802 | — | 0.592 | 0.781 | — |
| V60, ml | 25 [0; 101] | 84 [0; 104] | 25 [0; 101] | 0 [0; 84] | 0.256[a] | 84 [0; 104] | 0 [0; 12] | 0.001[c] |
| *P* value (Shapiro–Wilk test) | <0.001 | 0.006 | <0.001 | <0.001 | — | 0.001 | <0.001 | — |
| AAT, μg/ml | 17.2±9.1 | 18.8±9.9 | 16.7±7.1 | 16.6±10.4 | 0.734[b] | 10.4 [7.1; 18.3] | 22.2±6.7 | <0.001[c] |
| *P* value (Shapiro–Wilk test) | 0.211 | 0.694 | 0.474 | 0.389 | — | 0.02 | 0.108 | — |
| Fluid ingested, ml/day | 300 [250; 500] | 250 [250; 500] | 300 [250; 350] | 325 [250; 500] | 0.717[a] | 450 [250; 500] | 275 [250; 300] | 0.007[c] |
| *P* value (Shapiro–Wilk test) | <0.001 | <0.001 | 0.002 | 0.003 | — | <0.001 | <0.001 | — |
| Administered through the NJ tube, ml/day | 500 [500; 700] | 500 [350; 500] | 500 [500; 500] | 750 [700; 750] | <0.001[a] | 500 [500; 700] | 500 [500; 750] | 0.282[c] |
| *P* value (Shapiro–Wilk test) | 0.001 | 0.015 | <0.001 | <0.001 | — | 0.008 | 0.043 | — |
| Loss through the NG tubey, ml/day | 350 [150; 1000] | 650 [50; 1000] | 300 [75; 950] | 275 [180; 1100] | 0.73[a] | 722±482 | 175 [50; 400] | 0.001[c] |
| *P* value (Shapiro–Wilk test) | <0.001 | 0.02 | 0.005 | 0.001 | — | 0.092 | <0.001 | — |
| Balance between the enterally administered and lost through the NG tube, ml/day | 500 [–50; 800] | 173.5±469 | 525 [–50; 800] | 750 [–50; 950] | 0.065[a] | 0 [–100; 500] | 800 [575; 837] | 0.014[c] |
| *P* value (Shapiro–Wilk test) | 0.001 | 0.063 | 0.031 | 0.038 | — | 0.012 | <0.001 | — |

**Note.** [a] — Kruskal–Wallis test; [b] — ANOVA; [c] — Mann–Whitney *U*-test; [d] — Student's *t*-test; [e] — Fisher's exact test; [f] — Pearson's $\chi^2$ test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; AAT — acetaminophen absorption test.

severely ill than those with moderate severe disease. The proportion of patients who were examined within 6 and 12 h after surgery was 43.5%.

The most frequent etiology of AP was alimentary cause (30.6%). Hypertension was the most common comorbidity (46.8%) (Table 2).

The volume of nutrition administered through the NJ tube in group 4 was significantly greater than in groups 2 and 3, but there were no significant intergroup differences in the volume of orally ingested fluid, the daily loss through the NG tube, and the daily balance of enterally administered and excreted through NG tube (Table 3). Gastric fluid volume during gastric evacuation test at 30 and 60 minutes, as well as AAT results did not differ significantly between groups 2,3, and 4. Significant differences were found in APACHE II, SOFA scale scores, CRP level, proportion of patients with hypertension, frequency of lung ventilation, abdominal bloating, NG tube loss >500 ml/day, volume administered into the stomach, NG tube balance per day, residual gastric volume during the gastric evacuation test at 30 and 60 minutes, and AAT results between the group 5 (severe AP only) patients and those with MSAP (Tables 1–3).

Based on the obtained results, a binary model was formulated where the loss through the NG tube >500 ml/day was selected as the dependent variable.

In all groups except group 4, the percentage of exact responses was higher in the models where V30 and V60 min were the independent variables. The model with AAT as the independent variable was significant only in group 1 (Table 4). ROC analysis was performed to assess the quality of the models and determine the discriminatory values, the results are presented in Table 5.

ROC analysis corroborated the results obtained by logistic regression. The small intestinal AAT failed to predict nasogastric tube loss ⩾500 ml/day. We created another model where «at least one clinical sign of feeding intolerance» (nausea and vomiting, abdominal bloating, diarrhea, pain) was selected as the dependent binary variable (Table 6).

In almost all groups, the percentage of exact responses was higher with AAT. The second group's model for AAT was not significant because the pain

**Table 4. Prognostic significance of acetaminophen absorption test and gastric evacuation capacity for the loss through nasogastric tube ⩾500 ml/day in the early phase of acute pancreatitis.**

| Independent variables | *P* value | Constant | B | Nagelkerke $R^2$ | OR | 95% confidence interval for the OR | | Se | Sp | % exact responses |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit | | | |
| **Group 1 (all days)** | | | | | | | | | | |
| AAT, μg/ml | 0.01 | 6.63 | –0.087 | 16.0 | 0.917 | 0.858 | 0.979 | 0.5 | 0.8 | 67.2 |
| V30, мл | <0.001 | –8.299 | 0.066 | 42.5 | 1.068 | 1.03 | 1.107 | 0.654 | 0.861 | 77.4 |
| V60, мл | <0.001 | –2.658 | 0.048 | 69.6 | 1.049 | 1.028 | 1.07 | 0.808 | 0.917 | 87.1 |
| **Group 2 (day 1)** | | | | | | | | | | |
| AAT, μg/ml | 0.373 | 1.279 | –0.48 | 6.5 | 0.953 | 0.857 | 1.06 | 0.8 | 0.286 | 58.8 |
| V30, ml | 0.071 | –7.74 | 0.67 | 45.0 | 1.069 | 0.994 | 1.15 | 0.8 | 0.714 | 76.5 |
| V60, ml | 0.013 | –2.27 | 0.045 | 67.0 | 1.046 | 1.01 | 1.084 | 85.7 | 0.9 | 88.2 |
| **Group 3 (days 2–3)** | | | | | | | | | | |
| AAT, μg/ml | 0.264 | 0.889 | –0.77 | 8.1 | 0.926 | 0.89 | 1.06 | 0.444 | 0.769 | 63.6 |
| V30, ml | 0.037 | –14.679 | 0.114 | 56.0 | 1.12 | 1.077 | 1.246 | 0.556 | 0.929 | 78.3 |
| V60, ml | 0.008 | –3.053 | 0.057 | 72.7 | 1.059 | 1.015 | 1.104 | 0.889 | 0.929 | 91.3 |
| **Group 4 (days 4–5)** | | | | | | | | | | |
| AAT, μg/ml | 0.05 | 4.139 | –0.428 | 75.5 | 0.652 | 0.425 | 1.0 | 1.0 | 0.867 | 90.9 |
| V30, ml | 0.052 | –6.313 | 0.048 | 28.9 | 1.049 | 1.0 | 1.1 | 0.571 | 0.93 | 81.8 |
| V60, ml | 0.006 | –2.637 | 0.041 | 64.0 | 1.042 | 1.012 | 1.73 | 0.857 | 0.933 | 90.9 |
| **Group 5 (severe AP)** | | | | | | | | | | |
| AAT, μg/ml | 0.23 | 1.11 | –0.051 | 6.0 | 0.951 | 0.875 | 1.033 | 0.8 | 0.154 | 54.5 |
| V30, ml | 0.043 | –4.669 | 0.039 | 19.4 | 1.04 | 1.001 | 1.081 | 0.8 | 0.571 | 70.6 |
| V60, ml | 0.001 | –2.036 | 0.039 | 56.5 | 1.04 | 1.016 | 1.064 | 0.9 | 0.786 | 85.3 |
| **Group 6 (MSAP)** | | | | | | | | | | |
| AAT, μg/ml | 0.161 | 1.438 | –0.132 | 13.4 | 0.876 | 0.728 | 1.054 | 0 | 0.955 | 75.0 |
| V30, ml | 0.031 | –16.756 | 0.131 | 62.3 | 1.14 | 1.012 | 1.283 | 0.5 | 0.955 | 85.7 |
| V60, ml | 0.01 | –3.356 | 0.064 | 75.3 | 1.067 | 1.016 | 1.12 | 0.833 | 1.0 | 96.4 |

**Note.** AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; B — regression equation coefficients; OR — odds ratio; Se — sensitivity; Sp — specificity.

**Table 5. ROC analysis of acetaminophen absorption test and gastric evacuation capacity as a predictor of nasogastric tube loss ⩾500 mL/day.**

| Parameter | *P*-value | AUC | 95% confidence interval for AUC | | Cutoff value | | |
|---|---|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | Value | Se[a] | Sp[b] |
| **Group 1 (all days)** | | | | | | | |
| AAT, μg/ml | 0.004 | 0.715 | 0.582 | 0.848 | 14.6 | 0.8 | 0.538 |
| V30, ml | <0.001 | 0.830 | 0.723 | 0.936 | 111.5 | 0.885 | 0.611 |
| V60, ml | <0.001 | 0.921 | 0.843 | 0.999 | 73.5 | 0.808 | 0.944 |
| **Group 2 (day 1)** | | | | | | | |
| AAT, μg/ml | 0.145 | 0.6 | 0.316 | 0.884 | 8.3 | 1.0 | 0.3 |
| V30, ml | 0.019 | 0.843 | 0.613 | 1.0 | 111.0 | 0.9 | 0.714 |
| V60, ml | 0.003 | 0.936 | 0.83 | 1.0 | 78.0 | 0.9 | 1.0 |
| **Group 3 (days 2–3)** | | | | | | | |
| AAT, μg/ml | 0.483 | 0.59 | 0.334 | 0.846 | 15.25 | 0.769 | 0.556 |
| V30, ml | 0.006 | 0.849 | 0.688 | 1.0 | 120.5 | 0.889 | 0.643 |
| V60, ml | <0.001 | 0.948 | 0.852 | 1.0 | 52.5 | 0.889 | 0.929 |
| **Group 4 (days 4–5)** | | | | | | | |
| AAT, μg/ml | 0.113 | 0.665 | 0.477 | 0.854 | 8.0 | 0.923 | 0.5 |
| V30, ml | 0.062 | 0.752 | 0.489 | 1.0 | 126.5 | 0.714 | 0.933 |
| V60, ml | 0.005 | 0.881 | 0.7 | 1.0 | 54.5 | 0.857 | 0.933 |
| **Group 5 (severe AP)** | | | | | | | |
| AAT, μg/ml | 0.113 | 0.665 | 0.477 | 0.854 | 11.7 | 0.615 | 0.700 |
| V30, ml | 0.026 | 0.727 | 0.553 | 0.9 | 118.5 | 0.8 | 0.571 |
| V60, ml | 0.001 | 0.875 | 0.747 | 1.0 | 52.5 | 0.9 | 0.786 |
| **Group 6 (MSAP)** | | | | | | | |
| AAT, μg/ml | 0.263 | 0.652 | 0.454 | 0.849 | 15.8 | 0.909 | 1.0 |
| V30, ml | 0.001 | 0.936 | 0.846 | 1.0 | 112 | 1.0 | 0.818 |
| V60, ml | 0.002 | 0.99 | 0.722 | 1.0 | 62.5 | 0.833 | 1.0 |

**Note.** AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; AUC — area under the curve.

**Table 6. Prognostic significance of acetaminophen absorption test and gastric evacuation capacity for feeding intolerance in the early phase of acute pancreatitis.**

| Independent variables | *P* value | Constant | B | Nagelkerke $R^2$ | OR | 95% confidence interval for the OR | | Se | Sp | % exact responses |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit | | | |
| **Group 1 (all days)** | | | | | | | | | | |
| AAT, μg/ml | <0.001 | 3.367 | –0.171 | 40.7 | 0.843 | 0.77 | 0.923 | 0.8 | 0.577 | 70.5 |
| V30, ml | 0.021 | –2.842 | 0.027 | 13.0 | 1.027 | 1.004 | 1.051 | 0.833 | 0.423 | 66.1 |
| V60, ml | 0.001 | –0.554 | 0.022 | 28.4 | 1.023 | 1.009 | 1.036 | 0.694 | 0.769 | 72.6 |
| **Group 2 (day 1)** | | | | | | | | | | |
| AAT, μg/ml | 0.445 | 15.36 | –0.433 | 50.2 | 0.649 | 0.214 | 1.971 | 1.0 | 0 | 94.1 |
| V30, ml | 0.463 | –0.326 | 0.027 | 9.1 | 1.027 | 0.956 | 1.105 | 1.0 | 0 | 94.1 |
| V60, ml | 0.998 | 1.609 | 0.323 | 33.6 | 1.385 | 0 | 2.431 | 1.0 | 0 | 94.1 |
| **Group 3 (days 2–3)** | | | | | | | | | | |
| AAT, μg/ml | 0.011 | 6.4 | –0.296 | 71.5 | 0.744 | 0.592 | 0.936 | 0.889 | 1.0 | 95.5 |
| V30, ml | 0.22 | –3.123 | 0.025 | 9.4 | 1.025 | 0.985 | 1.066 | 0.455 | 0.833 | 65.2 |
| V60, ml | 0.176 | –0.612 | 0.013 | 10.9 | 1.013 | 0.994 | 1.032 | 0.636 | 0.667 | 65.2 |
| **Group 4 (days 4–5)** | | | | | | | | | | |
| AAT, μg/ml | 0.006 | 7.589 | –0.181 | 43.6 | 0.834 | 0.733 | 0.949 | 87.5 | 44.4 | 75.8 |
| V30, ml | 0.081 | –1.677 | 0.38 | 21.4 | 1.039 | 0.995 | 1.084 | 0.556 | 0.846 | 72.7 |
| V60, ml | 0.014 | –1.511 | 0.032 | 47.2 | 1.032 | 1.006 | 1.059 | 0.667 | 0.923 | 81.8 |
| **Group 5 (severe AP)** | | | | | | | | | | |
| AAT, μg/ml | 0.006 | 3.722 | –0.181 | 43.6 | 0.834 | 0.733 | 0.949 | 0.875 | 0.444 | 75.8 |
| V30, ml | 0.337 | –1.176 | 0.017 | 4.2 | 1.017 | 0.982 | 1.054 | 1.0 | 0 | 73.5 |
| V60, ml | 0.04 | –0.004 | 0.018 | 19.2 | 1.019 | 1.001 | 1.037 | 0.84 | 0.667 | 79.4 |
| **Group 6 (MSAP)** | | | | | | | | | | |
| AAT, μg/ml | 0.083 | 2.355 | –0.13 | 17.0 | 0.878 | 0.758 | 1.017 | 0.455 | 0.706 | 60.7 |
| V30, ml | 0.253 | –2.544 | 0.019 | 6.6 | 1.02 | 0.986 | 1.054 | 0.273 | 0.941 | 67.9 |
| V60, ml | 0.073 | –0.871 | 0.02 | 18.5 | 1.02 | 0.998 | 1.043 | 0.364 | 0.882 | 67.9 |

**Note.** AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; B — regression equation coefficients; OR — odds ratio.

**Table 7. ROC analysis of the prognostic significance of the acetaminophen absorption test and gastric evacuation capacity for feeding intolerance in the early phase of acute pancreatitis.**

| Parameter | *P*-value | AUC | 95% confidence interval for AUC | | Cutoff value | | |
|---|---|---|---|---|---|---|---|
| | | | Lower limit | Upper limit | Value | Se[a] | Sp[b] |
| **Group 1 (all days)** | | | | | | | |
| AAT, μg/ml | <0.001 | 0.83 | 0.726 | 0.934 | 14.6 | 1.0 | 0.629 |
| V30, ml | 0.009 | 0.696 | 0.564 | 0.827 | 103.5 | 0.861 | 0.423 |
| V60, ml | 0.001 | 0.752 | 0.629 | 0.875 | 79.5 | 0.528 | 0.885 |
| **Group 2 (day 1)** | | | | | | | |
| AAT, μg/ml | 0.221 | 0.875 | 0.713 | 1.0 | 30.5 | 1.0 | 0.875 |
| V30, ml | 0.221 | 0.875 | 0.713 | 1.0 | 95.0 | 0.875 | 1.0 |
| V60, ml | 0.262 | 0.844 | 0.597 | 1.0 | 25 | 0.688 | 1.0 |
| **Group 3 (days 2–3)** | | | | | | | |
| AAT, μg/ml | 0.001 | 0.942 | 0.838 | 1.0 | 15.2 | 1.0 | 0.8 |
| V30, ml | 0.196 | 0.659 | 0.43 | 0.888 | 111.5 | 0.909 | 0.417 |
| V60, ml | 0.176 | 0.667 | 0.440 | 0.893 | 52.5 | 0.545 | 0.650 |
| **Group 4 (days 4–5)** | | | | | | | |
| AAT, μg/ml | <0.001 | 0.983 | 0.941 | 1.0 | 12.25 | 1.0 | 0.9 |
| V30, ml | 0.077 | 0.726 | 0.501 | 0.952 | 100.0 | 0.889 | 0.385 |
| V60, ml | 0.01 | 0.829 | 0.636 | 1.0 | 12.5 | 0.778 | 0.846 |
| **Group 5 (severe AP)** | | | | | | | |
| AAT, μg/ml | 0.001 | 0.894 | 0.777 | 1.0 | 14.6 | 1.0 | 0.875 |
| V30, ml | 0.226 | 0.638 | 0.418 | 0.858 | 118.5 | 0.720 | 0.556 |
| V60, ml | 0.114 | 0.704 | 0.481 | 0.928 | 12.5 | 0.84 | 0.667 |
| **Group 6 (MSAP)** | | | | | | | |
| AAT, μg/ml | 0.095 | 0.69 | 0.484 | 0.896 | 17.6 | 0.706 | 0.364 |
| V30, ml | 0.279 | 0.623 | 0.399 | 0.847 | 105.0 | 0.727 | 0.529 |
| V60, ml | 0.269 | 0.626 | 0.398 | 0.853 | 81.5 | 0.364 | 1.0 |

**Note.** AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; AUC — area under the curve.

syndrome in this group was most likely not related to food intake but was a clinical manifestation of the underlying disease and/or recent surgery (Table 1). To assess the quality of the models, ROC analysis was performed, which is shown in Table 7.

From the day 2 onward, the prognostic significance of the AAT increased in comparison with the residual gastric volume test. In patients with MSAP, the AAT test was not informative.

## Discussion

Acute pancreatitis and its progression are associated with GI injury. As a result, serious systemic complications are triggered, since the impairment of intestinal barrier is associated with translocation of bacteria and inflammatory and toxic products produced in the intestinal wall, which can result in infection of necrotic pancreatic tissues, systemic inflammatory response, and sepsis [11, 12].

Non-inflammatory apoptosis of intestinal epithelial cells is known to occur every 4–5 days [13]. R. Tian et al. suggested that inflammatory factors such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and ischemia-reperfusion of the intestinal mucosa in AP caused severe oxidative stress accompanied by a significant increase in the apoptosis of intestinal mucosal cells [14].

Impairment of intestinal chemical barrier, which consists of mucins, antimicrobial peptides and other digestive enzymes, occurs. Mucins are the main component of the intestinal chemical barrier, covering enterocytes and forming the intestinal mucus layer. This is the first line of the intestinal mucosal barrier [15]. The intestine contains inner and outer mucosal layers, which accelerate nutrient absorption, provide adhesion sites for symbiotic bacteria, and limit pathogen binding to enterocytes [16]. Fishman et al. have shown that the loss of the mucosal layer, followed by disruption of the intestinal barrier, is an indirect effect of AP [17].

The biological intestinal barrier formed by the close adhesion of symbiotic bacteria (such as Bifidobacterium and Lactobacillus) to the mucosal surface of the intestinal epithelium, which counteracts pathogenic bacteria, is also compromised [18]. Symbiotic bacteria play a crucial role in regulating the function of the intestinal barrier and host health. Their functions include formation of the intestinal mucous layer and secretion of immunoglobulin A, building bacterial membrane barrier against foreign pathogens [19], regulation of intestinal paracellular permeability by enhancing intercellular connections with occlusion of intercellular spaces [20], expression of anti-inflammatory genes accompanied by a decrease in inflammation of the intestinal epithelium [20]. Kelly et al. found that bacteria-derived butyric acid can stabilize the expression of a hypoxia-inducible factor and its target genes, strengthening the intestinal barrier [21]. Multiple studies have shown that the gut microbiota is significantly altered in AP. A retrospective clinical study of 108 patients with AP showed a correlation between an increase in Enterococcus and a decrease in Bifidobacterium with the severity of inflammation, multiple organ failure, and the frequency of infectious complications [22]. Zhu et al. found that the number of beneficial bacteria, such as Blautia, decreases with increasing severity of AP and the degree of gut microflora impairment correlates with the severity of AP [23]. The impact of bacterial translocation on severe AP is very strong, because upon entering the bloodstream, bacteria and endotoxins can trigger a series of reactions, stimulating the production of various cytokines, such as TNF-$\alpha$, IL-6 and IL-12, which promotes systemic inflammatory response and multiple organ failure [24]. Many studies have shown that bacteremia in severe AP is associated with an increased risk of infected pancreatic necrosis, multiple organ failure, and mortality [25–27].

The immune intestinal barrier, which consists of lymphoid tissue associated with the intestine and scattered immune cells, is also compromised. The intestinal lymph vessels link the gut and lungs, bypassing the portal circulation and directly transporting toxic components such as toxins, trypsin, activated cytokines and immune cells directly from the gut to the pulmonary circulation [28]. This connection is sometimes referred to as the «gut-mesentery-lung axis» and plays a key role in the development of acute lung injury in AP. Aydin et al. demonstrated 100% bacterial translocation to the mesenteric lymph node in AP [29]. Most infections in AP occur within the first week after the onset, which was an independent predictor of death [25]. Fritz et al. [30] in an experimental murine model after ileostomy and selective digestive system (either small or large intestines) decontamination with gentamicin and polymyxin B solution, induced experimental AP and showed that bacterial translocation occurred much more frequently from the small than from the large intestine. These findings highlight the importance of EF in the early stages of AP for maintaining the integrity of the small intestinal barrier. This is supported by reduced mortality, frequency of sepsis, number of surgical procedures and length of hospital stay in patients with AP and EF compared with complete parenteral nutrition [31–33]. Thus, EF is a key element of AP therapy [34] which supports normal activity of physiological intestinal barriers [35]. Enteral feeding reduces overall disease severity as measured by CRP level, severity of hyperglycemia, and promotes faster improvement (judged by the duration of systemic inflammatory response and length of hospital stay) [36]. Additional advantages of EF include decreased intra-abdominal pressure

and improved postoperative closure of pancreatic fistula [37]. The diagnosis of EF intolerance is controversial, as its development is impacted by the rate of formula administration, mode of administration (continuous or bolus), access (gastric or post-pyloric), ingredients, individual patient characteristics, intestinal motility, intra-abdominal pressure, and the skills of medical staff [38]. Several prospective randomized small-sample studies have shown that NG feeding is not inferior to the NJ one by assessing the incidence of infectious complications and analgesic use, as well as the changes in the levels of inflammatory markers [39, 40]. To date, there is no convincing evidence of superiority of any of these methods [41], so both are acceptable. Transition to post-pyloric feeding is recommended only in gastric feeding intolerance despite prokinetic drug administration or in patients with a high risk of aspiration. Routine use of feeding through the NJ tube is not supported [43, 44], as in rare cases it can cause severe dilatation of the small intestine and its perforation [1]. The survival of a critically ill patient is known to be related to the dietary energy content. This relationship can be represented as a U-shaped curve. Post-pyloric feeding improves survival in patients with high nutritional risk and gastric feeding intolerance [45]. Thus, objective assessment of feeding adequacy is a crucial aspect of initiating the NJ tube feeding. The identified patterns can be used as a guidance in daily practice of intensive care unit physicians to determine feeding tolerance through the NJ tube, helping verify patients with small intestinal feeding intolerance and timely introduce the parenteral feeding to maintain optimal energy and protein intake.

## Conclusion

In the early phase of acute pancreatitis, plasma acetaminophen level, measured between minutes 5 and 20 after the administration of the drug into the small intestine at a dose of 0.5 g, and residual gastric volume values as measured 30 and 60 minutes after gastric administration of 200 ml of water, independently predict the feasibility of a complete post-pyloric feeding. In patients with severe acute pancreatitis, the acetaminophen absorption test is the best predictor of post-pyloric feeding intolerance diagnosed based on clinical signs and symptoms (nausea, vomiting, pain, abdominal bloating, diarrhea). Moreover, regardless of the disease form, on days 4-5 of the patient's stay in the intensive care unit this test helps effectively predict high daily residual gastric volumes (⩾500 ml/day). The gastric fluid volume determined 60 min after the administration of 200 ml of water posseses very good to excellent prognostic value for residual gastric volume ⩾500 ml/day during the entire early period of the disease, regardless of its future progression.

## Authors' contribution to the work

Oleg G. Sivkov was responsible for developing the concept and design of the study, collecting data, analyzing and interpreting the data, as well as completing the manuscript and verification of essential intellectual content.

Ilya N. Leiderman was responsible for concept and design development, data interpretation, and verification of essential intellectual content.

Alexey O. Sivkov performed collection of material, statistical analysis of the data and participated in writing the draft version of the manuscript.

Anatoly A. Kolchanov collected material and performed statistical analysis of raw data.

Georgy D. Bashlykov was responsible for collection of material and statistical analysis of raw data.

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**Received 2022.01.12**
**Accepted 2022.03.24**