Predictive Performance of Lactate as a Mortality Predictor in Patients with Acute Pancreatitis

Fatih Doganay[1], Rohat Ak[2] and Erdal Yilmaz[2]

[1]*Department of Emergency Medicine, Edremit State Hospital, Alıkesir, Turkey*
[2]*Department of Emergency Medicine, Kartal Dr. Lutfi Kırdar City Hospital, Istanbul, Turkey*

ABSTRACT

Objective: To investigate the relationship in the blood gas lactate levels and the prognosis of Emergency Department (ED) patients diagnosed with acute pancreatitis (AP).

Study Design: Analytical study.

Place and Duration of Study: Department of Emergency Medicine, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey between January 2018 and January 2020.

Methodology: Hospital database was scanned according to the International Classification of Diseases (ICD) codes, and the relationship between lactate levels at admission and the 30-day mortality status of patients diagnosed with AP was analysed. The performance of lactate in predicting mortality was determined by receiver operating characteristic (ROC) analysis. In addition, the measurements such as the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve (AUC), and Youden J Index (YJI) were calculated.

Results: There were 147 patients, with median age of 65 (50-76) years, where 91 were females (61.9%) and 56 were males (38.1%). The predictive values of lactate in terms of 30-day mortality were analysed by ROC analysis. Sensitivity (82.61%), specificity (79.84%), PPV (43.2%), NPV (96.1%), AUC (0.821), and YJI values (0.6245) were determined.

Conclusion: Early recognition of patients with AP and initiation of appropriate treatment without delay will reduce morbidity and mortality. According to the conclusions, the lactate elevation measured at the time of admission can be used as a useful, fast and simple method in estimating mortality of AP patients.

Key Words: *Acute pancreatitis, Lactate, Mortality.*

How to cite this article: Doganay F, Ak R, Yilmaz E. Predictive Performance of Lactate as a Mortality Predictor in Patients with Acute Pancreatitis. *J Coll Physicians Surg Pak* 2022; **32(04)**:440-444.

INTRODUCTION

Acute pancreatitis (AP), a sudden-onset inflammatory disease, occurs in the pancreas. The clinical course of the disease ranges from asymptomatic to sepsis, organ failure and mortality.[1-3] AP is at the forefront of gastrointestinal system-related ED admissions and hospitalisations worldwide. In the United States of America (USA) alone, there was 13.2% increase in the incidence of AP between 2009-2012 compared to 2002-2005.[4]

According to the guidelines of the American Gastroenterology Society, it is recommended that the hemodynamic status of the patients should be evaluated quickly at the beginning, the risk assessment should be made at the time of admission, the cases should be divided into low-high risk groups at this stage, and if necessary, they should be referred to the intensive care unit rapidly.[5]

Correspondence to: Dr. Rohat Ak, Department of Emergency Medicine, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey
E-mail: rohatakmd@gmail.com

Received: September 14, 2021; Revised: December 07, 2021; Accepted: January 05, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.04.440

For these purposes, various risk scores and laboratory parameters were investigated.[6-9]

The lactate is a production of the anaerobic metabolism of glucose and is commonly considered a marker of tissue hypoxia. Additionally, it was also determined that the appearance in the high lactate levels indicates serious tissue hypoperfusion in the previous studies, which is greatly associated with increased morbidity and mortality in severe illness.[10-12]

The aim of this study was to examine the accuracy of the blood gas lactate levels for predicting the 30-day prognosis of patients, who visited ED and were diagnosed with acute pancreatitis.

METHODOLOGY

This observational study was managed in the ED of Kartal City Hospital, where their Institutional Review Board confirmed the study, then declared a waiver of approval (The Ethics Committee Ruling No. 2021/514/204/5, Date: 22.06.2021). This study was managed in accordance with the Helsinki-Ethical Rules of the Declaration.

The Hospital's electronic patient database was searched between January 1, 2018 and January 1, 2020, and patients over the age of 18, who were diagnosed with AP according to

the International Classification of Diseases (ICD), 10th Review, codes and hospitalised from ED, were included in the study. The diagnosis of the AP was done on at least two of the following criteria: characteristic abdominal pain, elevation of serum amylase and/or lipase greater than three times the upper limit of normal, and characteristic imaging findings of AP with abdominal imaging methods.[13]

Pregnant women, patients transferred from another hospital, patients whose lactate levels were not checked at the admission time, and patients diagnosed with other than AP, were excluded from the study. The data including age, gender, comorbidities, and laboratory results were collected for each patient. The mortality status of the patients, 30 days after hospitalisation, was the primary outcome in this study.

Statistical analysis was applied by using the IBM SPSS Statistics version 26.0 and MedCalc Statistical Software version 19.0.6. The normality of measurable variables was checked by applying Shapiro-Wilk test. A Mann-Whitney U-test was applied for the analysis of non-normal distributed variables. An Independent t-test was applied for the analysis of the continuous variables having a normal distribution. The Chi-square test and the Fisher's Exact test were made for the analyses of the categorical data. The continuous data having normal distribution were expressed as mean ± SD. The non-normal distributed variables were shown as medians and the interquartile ranges (IQR). The categorical data was presented as frequency and percentage. A p-value less than 0.05 was accepted as statistically significant.

The ROC analysis was made to evaluate the performance of lactate for predicting 30-day mortality in acute pancreatitis patients, by using the DeLong method.[14] The sensitivity, specificity, PPV, NPV, AUC, and YJI were measured to determine the performance of the lactate in predicting 30-day mortality. In addition, YJI analysis was performed to determine the optimal threshold value at which the prognostic performance of lactate is highest.[15]

RESULTS

This study was carried out utilising data from the remaining 147 patients after the exclusion criteria were ordered. The presence of mortality in the groups was 124 for the survivors group and 23 for the non-survivors group. Of the patients in the study population, 91 were females (61.9%) and 56 were males (38.1%). In terms of genders, there was no significant difference between the groups (Table I).

The median age in the study population was 65 (50-76) years, with minimum age of 21 and maximum age of 94. The median ages of the groups were determined as 61 (49-73) for the survivors group and 72 (55-82) for the non-survivors group. There was statistically significant difference between the groups, according to the age (Table I).

When the effect of the etiology of pancreatitis on mortality was examined, there was no statistically significant difference was found between the groups in biliary and non-biliary pancreatitis (Table I).

When considering the conclusions of consequences in chronic diseases on pancreatitis prognosis, hyperlipidemia (HL), diabetes mellitus (DM), hypertension (HT), congestive heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), chronic kidney failure (CRF), chronic neurological diseases (CND), and history of malignancy, did not differ significantly between the groups (Table I).

When the vital parameters of the patients diagnosed with pancreatitis at the admission time in the ED were examined, there was no statistically significant difference revealed between the survivors and non-survivors groups (Table II).

When the effectiveness of laboratory parameters on predicting 30-day mortality in pancreatitis was analysed, a significant difference was found between the groups lactate ($p < 0.001$), LDH ($p < 0.001$), calcium ($p < 0.001$), HGB ($p = 0.003$), albumin ($p = 0.001$), urea ($p = 0.036$). There was no significant difference between the groups according to the white blood cells, neutrophil, lymphocyte, hematocrit, ALT, AST, CRP, glucose, sodium, potassium, chlorine, and creatinine (Table II).

The predictive values of lactate in terms of 30-day mortality were analysed by ROC analysis, then the sensitivity, specificity, PPV, NPV, AUC and YJI values were determined as 82.61%, 79.84%, 43.2%, 96.1%, 0.821, 0.6245, respectively ($p < 0.001$, Figure 1). The ideal value of the threshold for lactate to predict 30-day mortality in pancreatitis patients was calculated as lactate level >2.2 mmol/L, based on the 0.6245 YJI value.

DISCUSSION

In this study, it was investigated whether the use of lactate levels measured at the time of ED admission to predict mortality in AP patients would be beneficial in the early detection of critical illness, early intervention and treatment. The outcomes of the study showed that there is a significant association between lactate elevation and mortality, and it was found that lactate elevation at admission was successful in predicting mortality.

AP is a fatal condition, if appropriate treatment is not given. In a study examining the epidemiological data of 3,260 AP patients in China, it was reported that biliary causes were prominent in 58.7%.[16] In this study, 48.2% of the patients diagnosed with AP were biliary and 51.8% were non-biliary pancreatitis. The etiological differences between countries may be due to genetic differences that may predispose to cholelithiasis, dietary habits, and prevalence of alcohol use.

Table I: Demographic and comorbidity data of the study population.

Variables	Category	Survivor (n=124)		Non-survivor (n=23)		Total (n=147)	Sig.
		n	%	n	%	n	p
Gender	Female	79	86.8	12	13.2	91	0.295
	Male	45	80.4	11	19.6	56	
Etiology	Non-Biliary	65	85.5	11	14.5	76	0.686
	Biliary	59	83.1	12	16.9	71	
HL	No	120	83.9	23	16.1	143	>0.999*
	Yes	4	100	0	0	4	
COPD	No	119	85	21	15	140	0.301*
	Yes	5	71.4	2	28.6	7	
DM	No	102	83.6	20	16.4	122	0.766*
	Yes	22	88	3	12	25	
HT	No	89	84	17	16	106	0.834
	Yes	35	85.4	6	14.6	41	
CHF	No	121	84	23	16	144	>0.999*
	Yes	3	100	0	0	3	
CAD	No	110	83.3	22	16.7	132	0.467*
	Yes	14	93.3	1	6.7	15	
AF	No	122	84.1	23	15.9	145	>0.999*
	Yes	2	100	0	0	2	
CRF	No	118	83.7	23	16.3	141	0.590
	Yes	6	100	0	0	6	
CND	No	114	83.2	23	16.8	137	0.363*
	Yes	10	100	0	0	10	
Malignancy	No	120	84.5	22	15.5	142	0.578
	Yes	4	80	1	20	5	
		Survivor Median (IQR)		**Non-survivor Median (IQR)**		**Total Median (IQR)**	
Age		61 (49-73)		72 (55-82)		65 (50-76)	0.033

*HL: Hyperlipidemia, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, CHF: Congestive heart failure, CAD: Coronary artery disease, AF: Atrial fibrillation, CRF: Chronic kidney failure, CND: Chronic neurological diseases, Malignancy: History of malignancy, Sig: Significance. *Fisher's Exact Test.*

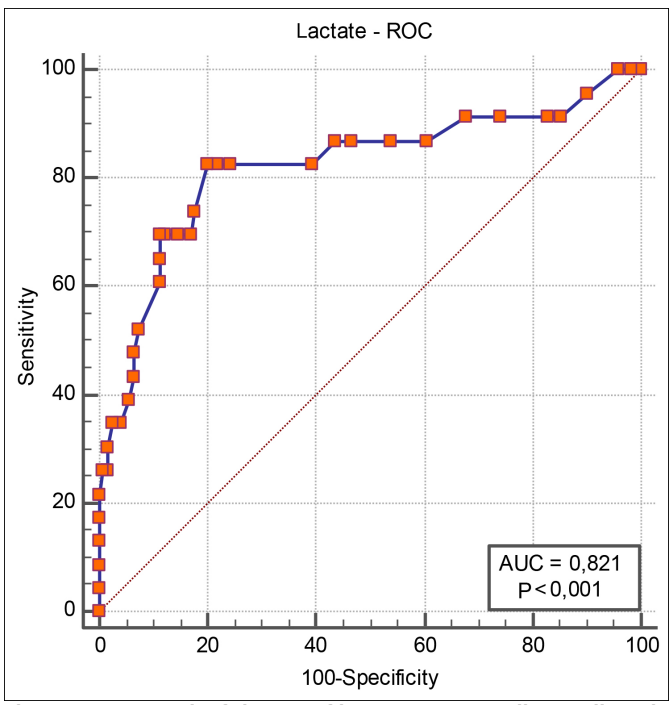

Figure 1: ROC graph of the use of lactate as a mortality predictor in patients with acute pancreatitis.

AP continues to be a great challenge for clinicians. In a study conducted by Peery *et al*., it was stated that AP is a major reason for mortality and a medical distress in gastrointestinal diseases.[17] Various risk scores are used to identify critically ill patients early. There are also studies showing that high levels of serum markers are nearly correlated with the severity of AP, which includes C-reactive protein (CRP), procalcitonin (PCT), blood urea nitrogen (BUN), white blood cells, and serum creatinine.[18-20] Additionally, a recently conducted study has stated that a high lactate level is severely correlated with the organ failure in AP.[20]

Lactate is produced by most of the tissues in the human body and this production is highest in muscle tissue. Lactate, which occurs under usual conditions, is rapidly removed, mostly by the liver, and to a small extent by the kidneys. The blood lactate concentration shows the equivalence between production and uptake of lactate in the tissues. In a retrospective study performed for patients in intensive care unit (ICU), it was reported that there was a predictive value of high blood lactate level on mortality. In the study conducted by Khosravani *et al*., an admission lactate level of ≥2 mmol/L in adult patients admitted to the ICU is an important free predictor of mortality.[21] In addition, the literature studies have revealed that there was no significant difference between arterial lactate level and venous lactate level measurements.[22]

Shu *et al.* reported that a lactate value upper than 2.1 mmol/L was successful in predicting mortality with an AUC of 0.83 in AP patients.[18] Valverde-Lopez *et al*. reported that serum lactate level had 0.87 and 0.77 AUC values for the prediction of mortality and intensive care unit admission, respectively; and that lactate could be a useful prognostic marker in AP.[20]

Table II: Statistical data of laboratory measurements and vital parameters of the study population.

	All patients (n=147) Median (IQR)	Survivor (n=124) Median (IQR)	Non-survivor (n=23) Median (IQR)	p
Non-normal distributed variables				
Vital parameters				
SBP (mmHg)	130 (125-142)	130 (125-142)	132 (128-140)	0.885
HR (bpm)	75 (70-82)	75.5 (70-82)	75 (68-86)	0.909
spO2 (%)	97 (95-98)	97 (95-98)	98 (96-99)	0.036
Temp (°C)	36.3 (36-36.9)	36.3 (36-36.9)	36.3 (36-36.9)	0.991
Laboratory parameters				
WBC ($(10^3$/uL)	8.7 (6.6-12.3)	8.30 (6.63-11.58)	11 (6.3-13.4)	0.202
Neu (10^3/uL)	6.2 (4.1-10.3)	6 (4-9.46)	8.5 (4.45-10.9)	0.101
Lym (10^3/mm^3)	1.4 (1-2)	1.4 (1.03-2)	1.1 (0.8-1.7)	0.073
HCT (%)	34.6 (30.7-39.3)	34.75 (30.88-39.2)	32.7 (26.7-39.5)	0.465
HGB (g/dL)	11.3 (10.4-12.6)	11.5 (10.7-12.7)	10.9 (9.1-11.34)	0.003
Albumin (g/L)	26 (3.1-32)	28 (3.2-32.9)	3 (2.5-27)	0.001
ALT (U/L)	49 (17-109)	50.5 (18-109)	30 (15-108)	0.681
AST (U/L)	32 (21-59)	30.5 (21-57.5)	43 (24-95)	0.080
CRP (mg/L)	105 (33.7-186)	98.9 (28.2-168.25)	121 (67.8-224.1)	0.078
Glucose (mg/dL)	96 (78-116)	93.5 (77.25-120.5)	102 (79-112)	0.382
Lactate (mmol/L)	1.9 (1.4-2.5)	1.7 (1.3-2)	3.1 (2.3-4.5)	<0.001
LDH (U/L)	264 (196-356)	249 (184.25-319.75)	476.00 (286-760)	<0.001
Sodium (mmol/L)	139 (136-140)	139 (136-140)	139 (135-140)	0.953
Calcium (mg/dL)	8.41 (8.04-8.85)	8.48 (8.13-8.91)	7.82 (7.48-8.48)	<0.001
Creatinin (mg/dL)	0.66 (0.53-0.89)	0.63 (0.52-0.88)	0.7 (0.56-1.21)	0.078
Urea (mg/dL)	27 (18-39)	26 (18.25-36)	38 (18-83)	0.036
Normally distributed variables				
Chloride (mmol/L)	101.67 ± 4.18	101.89 ± 3.78	100.52 ± 5.86	0.292
Potassium (mmol/L)	3.87 ± 0.59	3.88 ± 0.56	3.82 ± 0.71	0.683

SBP: Systolic blood pressure, HR: Heart rate, SPO_2: Blood oxygen saturation, Temp: Body temperature, WBC: White blood cell, Neu: Neutrophil, Lym: Lymphocyte, HCT: Hematocrit, HGB: Hemoglobin, ALT: Alanine amino transferase, AST: Aspartate amino transferase, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

Similarly, in this study, it was concluded that a lactate value greater than 2.2 mmol/L was successful in predicting mortality with 0.821 AUC. In fact, there are several hypotheses that can explain that increased lactate levels in AP may be associated with mortality. First, increased lactate level is one of the first signs of ischemia, and the gastrointestinal tract is very sensitive in terms of hypoxia and ischemia.[23] In addition, the serum lactate level is an early biomarker reflecting the seriousness of the systemic inflammatory response in the sepsis.[24] Eventually, when the infection occurs, the leukocytes increase the anaerobic glucose mechanism; and as a result, the lactate level increases.[25] In line with these mechanisms, serum lactate level will increase in parallel with local or systemic complications in acute pancreatitis. Therefore, the authors think that it is reasonable to use serum lactate level as a predictive value for early detection of mortality.

As in any retrospective study, this study has some limitations. The current study was carried out in a single centre and with a comparatively small number of patients. Since routine blood gas measurement was not performed in patients with acute pancreatitis, the present serum lactate value of all patients could not be reached. Therefore, those patients were excluded from the study. Thus, the patients' number, who could be included in the study, decreased.

CONCLUSION

Early recognition of patients with AP and initiation of appropriate treatment without delay will reduce mortality and morbidity. According to these results of the study, the lactate elevation, measured at the time of admission, can be used as a useful, fast and simple method in estimating mortality in patients with AP.

ETHICAL APPROVAL:

The study was approved by the Ethics Committee of the Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey.

PATIENTS' CONSENT:

Because this study was retrospective, the patients' consents were waived.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

FD: Project development, data collection and/or processing, analysis and/or interpretation, literature search, manuscript writing, critical reviews.

RA: Project development, analysis, literature search, manuscript writing, critical reviews.

EY: Data collection and/or processing, literature search, critical reviews.

REFERENCES

1. Mederos MA, Reber HA, Girgis MD. Acute pancreatitis: A review. *JAMA* 2021; **325**: 382-90. doi:10.1001/jama.2020.20317.
2. Leppäniemi A, Tolonen M, Tarasconi A. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J*

Emerg Surg 2019; **14**:1-20. doi: 10.1186/s13017-019-0247-0.

3. Portelli M, Jones CD. Severe acute pancreatitis: Pathogenesis, diagnosis and surgical management. *Hepatobiliary Pancreat Dis Int* 2017; **16**:155-9. doi: 10.1016/S1499-3872(16) 60163-7.
4. Sarri G, Guo Y, Iheanacho I. Moderately severe and severe acute pancreatitis: A systematic review of the outcomes in the USA and European Union-5. *BMJ Open Gastroenterol* 2019; **6**:248. doi: 10.1136/bmjgast-2018-000248.
5. Crockett SD, Wani S, Gardner TB. American gastro-enterological association institute guideline on initial management of acute pancreatitis. *Gastroenterol* 2018; **154**:1096-101. doi: 10.1053/j.gastro.2018.01.032.
6. Erdogan MO, Hokenek NM. How to score acute pancreatitis in the emergency setting: Five systems against ED-SAS. *Signa Vitae* 2021; **1**:8. doi: 10.22514/sv.2021.147.
7. Wu BU, Johannes RS, Sun X. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterol* 2009; **137**:129-35. doi: 10.1053/j.gastro. 2009.03.056.
8. Muddana V, Whitcomb DC, Khalid A. Elevated serum creatinine as a marker of pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol* 2009; **104**:164-70. doi: 10.1038/ajg.2008.66.
9. Silva-Vaz P, Abrantes AM, Castelo-Branco M. Multifactorial scores and biomarkers of prognosis of acute pancreatitis: Applications to research and practice. *Int J Mol Sci* 2020; **21**:338. doi: 10.3390/ijms21010338.
10. Sakal C, Ak R, Tasci A. Admission blood lactate levels of patients diagnosed with cerebrovascular disease effects on short-and long-term mortality risk. *Int J Clin Prac* 2021; e14161. doi.org/10.1111/ijcp.14161.
11. Ibrahim A, Bayramoglu B, Hokenek NM. Lactate clearance during the first 2 hours after hospital admission: A useful biomarker for predicting 30-day mortality in patients with diabetic ketoacidosis. *Int Clin Practice* 2020; e14204. doi.org/10.1111/ijcp.14204.
12. Höokenek NM, Seyhan AU, Erdogan MO. Evaluation of blood gas analysis as a mortality predictor. *Southern Clin Istanbul Eurasia* 2019; **30**:228-31. doi: 10.14744/scie.2019.44365.
13. Banks PA, Bollen TL, Dervenis C. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**:102-11. doi: 10.1136/gutjnl-2012-302779.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988; **44**:837-45.
15. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med* 2000; **45**: 23-41. doi: 10.1016/S0167-5877(00)00115-X.
16. Zhu Y, Pan X, Zeng H. A study on the etiology, severity, and mortality of 3260 patients with acute pancreatitis according to the revised Atlanta classification in Jiangxi, China over an 8-year period. *Pancreas* 2017; **46**:504-9. doi: 10.1097/MPA. 0000000000000776.
17. Peery AF, Crockett SD, Barritt AS. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterol* 2015; **149**:1731-41. doi: 10.1053/j.gastro.2015.08.045.
18. Shu W, Wan J, Chen J. Elevated arterial lactate level as an independent risk factor for pancreatic infection in moderately severe acute pancreatitis. *Pancreatology* 2019; **19**: 653-7. doi: 10.1016/j.pan.2019.06.001.
19. Staubli SM, Oertli, D, Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. *Crit Rev Clin Lab Sci* 2015; **52**:273-83. doi: 10.3109/10408363.2015. 1051659.
20. Valverde-Lopez F, Matas-Cobos AM, Alegria-Motte C. Bisap, Ranson, lactate and others biomarkers in prediction of severe acute pancreatitis in a European cohort. *J Gastroenterol Hepatol* 2017; **32**: 1649-56. doi: 10. 1111/ jgh.13763.
21. Khosravani H, Shahpori R, Stelfox HT. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care* 2009; **13**:1-5. doi: 10.1186/cc7918.
22. Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: A systematic review. *Scand J Trauma Resusc Emerg Med* 2011; **19**:1-12. doi: 10.1186/1757-7241-19-74.
23. Rahman SH, Ammori BJ, Holmfield J. Intestinal hypoper-fusion contributes to gut barrier failure in severe acute pancreatitis. *J Gastrointestinal Surg* 2003; **7**:26-36. doi: 10.1016/S1091-255X(02)00090-2.
24. Mikkelsen ME, Miltiades AN, Gaieski DF. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; **37**: 1670-7. doi: 10.1097/CCM.0b013e31819fcf68.
25. Cicalese L, Sahai A, Sileri P. Acute pancreatitis and bacterial translocation. *Dig Dis Sci* 2001; **46**:1127-32. doi: 10.1023/A: 1010786701289.