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ORIGINAL RESEARCH

Relevance of Procalcitonin Levels as a Marker of Severity and Predictor of Mortality, Initiation and Duration of Antibiotics in Patients Admitted with Acute Pancreatitis: A Retrospective Cohort Study

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Introduction: Procalcitonin levels have been studied to predict the benefit of adding antibiotics in a patient with acute pancreatitis. Through this study, we are searching for any possible correlation between serum procalcitonin levels and the severity of acute pancreatitis (included acute on chronic cases) to determine whether procalcitonin levels can predict a benefit from antibiotic therapy in acute pancreatitis.

Methods: This is a retrospective cohort study involving patients with acute pancreatitis and acute on chronic pancreatitis. We included all hospitalized patients admitted to Kern Medical from January 2020 to October 2022 with a diagnosis of acute pancreatitis in a consecutive manner. The primary outcome studied was mortality related to the pancreatitis episode. Logistic regression was used to control numerous confounders.

Results: Based on univariate analysis of procalcitonin, we found starting antibiotics on the day of admission statistically significant. We also found the median differences in mortality to be mildly significant (difference = 0.79, p = 0.0640) based on procalcitonin values. In a multivariate analysis of ln(procalcitonin), we found lipase (p = 0.0249), duration of antibiotics (p = 0.0009), multi-organ failure (p = 0.0045) to be statistically significant, and lactate being mildly significant in the multivariate model (p = 0.0643).

Conclusion: The procalcitonin level can predict the initiation of antibiotics, duration of antibiotics, multi-organ failure, and mortality in patients with acute pancreatitis.

Keywords: procalcitonin, pancreatitis, acute pancreatitis

Introduction

Background

The course of illness for acute pancreatitis can range from self-limiting to extremely protracted, ending in sepsis, multiple-organ dysfunction syndrome, and death.[1] Laboratory studies, including lipase levels, assist in confirming the diagnosis of pancreatitis. A serum lipase level three times the normal's upper limit is 100% indicative of acute pancreatitis.[2] Because of large variations in the hospital course of acute pancreatitis, several scoring systems have been developed to aid physicians in the clinical assessment of acute pancreatitis. The Ranson criteria is one of the oldest and most well-known.[3] Another score used for the severity of acute pancreatitis is The Acute Physiology and Chronic Health Evaluation (APACHE II), which includes complex calculations correlating with mortality and severity of the disease.[4] The Bedside Index for Severity of Acute Pancreatitis (BISAP) score was developed specifically to be calculated at the bedside and to predict the severity of the disease.[5] One meta-analysis found that the BISAP score was more sensitive and specific than the Ranson or APACHE-II.[6] Finally, the computed tomography (CT) scoring index or

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Balthazar score uses contrast CT scans to measure the amount of pancreatic inflammation and necrosis.[2] Several inflammatory markers have been implicated in the pathophysiology of acute pancreatitis. One study found that patients with acute pancreatitis who had elevated procalcitonin levels early in the course of the disease were more likely to develop necrotic infectious pancreatitis.[7] Another study found that procalcitonin levels were significantly elevated in patients with pancreatic infections and were associated with multi-organ dysfunction.[8]

Objectives

Through this study, we are searching for any possible correlation between serum procalcitonin levels and the severity of acute pancreatitis (included acute on chronic cases) to determine whether procalcitonin levels can predict a benefit from antibiotic therapy in acute pancreatitis. We also evaluated for a correlation between procalcitonin levels and measured inflammatory markers, BISAP score, and Modified CT severity index.

Methods

Study Design

This is a retrospective cohort study involving patients with acute pancreatitis and acute on chronic pancreatitis.

Setting

Kern Medical is a safety net hospital serving the community of Kern County in Central California. The hospital is a referral center for multiple peripheral health care centers. Physicians at Kern Medical are involved in the management of acute pancreatitis on a daily basis. A significant proportion of patients presenting to Kern Medical with acute pancreatitis are clinically ill and often have evidence of pancreatic necrosis. Our study included all of the inpatients who were admitted from January 2020 to October 2022 with the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes indicative of acute pancreatitis in a consecutive manner. The Kern Medical Center Institutional Review Board approved the study (Approval # 22138). Patient informed consent was waived because anticipated number of patients was 200 and the study needed records from the past (since January 2020), but patient data including HIPAA-specified individual identifiers were kept confidential in compliance with the Declaration of Helsinki. The manuscript was written based on the STROBE (Strengthening the Reporting of observational studies in Epidemiology) checklist.

Participants

Data was collected from Electronic Medical Records with the following eligibility criteria:

Inclusion Criteria

- Any patient greater than 16 years of age admitted to the hospital for acute pancreatitis or acute on chronic pancreatitis.

Exclusion Criteria

- Patients less than 16 years of age
- Incarcerated patients
- Procalcitonin not available within 48–72 hours of admission
- Chronically elevated lipase levels in patients with chronic pancreatitis or patients with elevated lipase levels who were hospitalized for other reasons, such as cholecystitis, bowel perforation, pancreatic cancer, trauma to the pancreas, intra-abdominal abscesses, septic shock, CKD, chronic alcoholism, peptic ulcer disease, s/p ERCP/ choledocholithiasis, cirrhosis in the absence of symptoms of pancreatitis

Variables

The primary outcome of the study was mortality related to the pancreatitis episode. The other secondary outcomes were multi-organ failure, length of stay, and number of subsequent admissions. The exposures were considered if a patient was

admitted to the Intensive Care Unit (ICU), initiating antibiotics on the day of admission, and the duration of antibiotics. The predictor variables were procalcitonin, amylase, lipase, biliary etiology, the neutrophil ratio on the day of admission, ESR, CRP, lactate, LDH, D-Dimer, triglyceride levels, alcohol use, acute on chronic cases, BISAP score, and modified CT severity index. The potential confounders were other active infections, age, and gender. According to the revised Atlanta Classification, diagnostic criteria for acute pancreatitis included a serum lipase value three times the upper limit of normal with clinical symptoms of epigastric pain with/without associated symptoms of nausea/vomiting.[9]

Participants were enrolled based on the algorithm in Figure 1. The characteristics of categorical and continuous variables are shown in Table 1 and Table 2, respectively. Our patients had >60% missing values for LDH, amylase, D-Dimer, ESR, and CRP. Therefore, these variables were excluded from the statistical analysis. None of the categorical variables had missing data. Only ten patients had antibiotics initiated on subsequent days, but we only studied patients with the initiation of antibiotics on the day of admission.

Data Sources

BISAP score was calculated based on BUN, impaired mental status on admission, SIRS criteria ≥2, age >60 years, and presence of pleural effusion on chest X-ray. The modified CT severity Index was calculated based on CT findings wherever available (localized fluid collections, ascites, percentage of pancreatic necrosis, etc.).

Bias

The study can have selection bias as we enrolled only patients with a procalcitonin level available. No follow-up was needed; thus, our study did not have information bias due to the loss of follow-up. The confusion bias due to confounding was minimized using the multivariate technique, ie, logistic regression.

Study Size

The sample size was calculated based on Sample Size Calculator (clincalc.com), and it was found that 132 individuals were needed for an anticipated incidence of mortality of 8% for our study group with a known incidence of mortality of 16.3[10] in severe acute pancreatitis. [statistical power 80%, Type I error rate 0.05, Type II error rate 0.2.]

Quantitative Variables

Many of the continuous variables, including procalcitonin, lipase, neutrophil ratio, and triglyceride levels, were found to be heavily skewed. Therefore, these were categorized based on their values. The procalcitonin levels were categorized in four sets of 0.10–0.49 ng/mL: Minor or no significant inflammatory response; 0.50–1.99 ng/mL: Moderate risk for

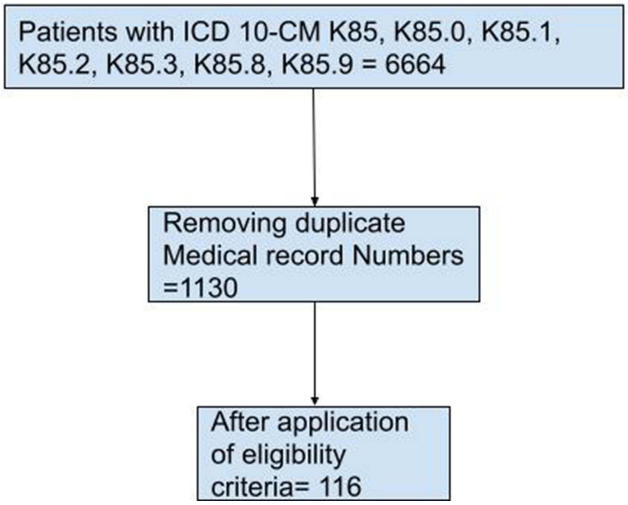

Figure 1 The algorithm shows the strategy involved in the enrollment of the patients and the inclusion and exclusion criteria followed to obtain the patients of interest.

Table 1 Proportions of Categorical Variables (There Were No Missing Elements)

Categorical Variable Studied			Proportions of Patients (%)
Gender	Females	38	33
	Males	78	67
Biliary etiology of pancreatitis	Present	39	34
	Absent	77	66
Presence of ketoacidosis (elevated beta hydroxybutyrate)	Present	35	30
	Absent	81	70
History of alcoholism	Present	43	37
	Absent	73	63
Antibiotics used on the day of admission	Yes	53	46
	No	63	54
Mortality due to pancreatitis	Yes	9	8
	No	107	92
Intensive care Unit (ICU) admission	Present	38	33
	Absent	78	67
Multi-organ failure	Present	27	23
	Absent	89	77
Acute on chronic pancreatitis	Yes	26	22
	No	90	78
Concomitant other infection	Present	49	43
	Absent	67	57

progression to severe systemic infection; Procalcitonin level 2.00–9.99 ng/mL: Severe systemic inflammatory response; Procalcitonin level > or = 10.00 ng/mL: high likelihood of severe sepsis or septic shock. Lipase values were categorized into low lipase elevation group (200–400 U/L), moderate elevation group (400–600 U/L), and high elevation group (≥600 U/L). Neutrophil ratio values were coded as <50% low, 50–75% normal, and more than 75% high. Triglycerides were grouped as normal <150 mg/dL, mild hypertriglyceridemia: 150–199 mg/dL, moderate hypertriglyceridemia: 200–499 mg/dL and severe hypertriglyceridemia: ≥500 mg/dL.

Statistical methods

The collected data was compiled in a Microsoft Excel sheet. The variables were identified as continuous or categorical. The continuous variables were studied using descriptive statistics and were expressed as mean ± standard deviation and quartiles. The p-value of ≤0.05 was considered significant for the study. Mild statistical significance was noted for p-values greater than 0.05 but less than 0.10. The missing data underwent deletion via dropping variables if the data was missing more than 60% of the observations and those variables were insignificant. Logistic regression was used to control numerous confounders by which the adjusted odds ratio was produced. The adjusted odds ratio was controlled and adjusted for multiple confounders or covariates.[11,12]

Table 2 Mean and Standard Deviation Value for the Continuous Variables Along with Missing Elements

Continuous Variable	Mean Value± Standard Deviation (SD)	Number of Missing Elements
Age	46.19 ± 16.10	0
Lipase (units/L)	5854.41 ± 7687.63	0
Neutrophil Ratio	79.32 ± 14.19	0
Lactate (mmol/L)	3.07 ± 3.31	11
Procalcitonin (μg/L)	2.73 ± 9.84	0
Triglyceride (mg/dL)	625.53 ± 1433.79	9
Length of stay (days)	6.34 ± 7.14	0
BISAP score	1.53 ± 1.3	10
CT Index	2.52 ± 1.88	39
Number of days antibiotics used	4.7 ± 7.35	0
ESR (mm/hr)	43.43 ± 33.06	86
CRP (mg/dL)	6.45 ± 8.17	73

Results

The univariate analysis for procalcitonin is shown in Table 3. The natural log transformation of variable procalcitonin [ln(procalcitonin)] was taken to address severe violations of model assumptions needed for linear regression and ANOVA, not necessarily for all univariate analyses completed. Since even with the log transformation, the data were

Table 3 Univariate Analysis for Procalcitonin. P-values for Categorical Variables with More Than Two Levels Reflect P-values Based on Ln(Procalcitonin) for Both Permutation Based ANOVA (Means) and Kruskal-Wallis (Medians)

Variable Included in Analysis		n	Mean Value ± SD	Median	Mean P-value	Median P-value
Gender	Female	38	2.58 ± 10.79	0.49	0.92	0.12
	Male	78	2.79 ± 9.41	1.49		
Biliary etiology	Yes	39	4.9 ± 15.72	0.20	0.06	0.66
	No	77	1.62 ± 4.38	0.26		
Presence of ketoacidosis	Yes	35	1.65 ± 2.91	0.69	0.50	0.03
	No	81	3.19 ± 11.61	0.16		
History of alcoholism	Yes	43	1.12 ± 2.96	0.18	0.19	0.24
	No	73	3.67 ± 12.13	0.31		
Antibiotics used on the day of admission	Yes	53	4.93 ± 13.97	0.79	0.005	0.0000
	No	63	0.87 ± 2.88	0.13		
Mortality	Present	9	3.95 ± 4.95	0.97	0.74	0.06
	Absent	107	2.62 ± 10.15	0.18		

(*Continued*)

Table 3 (Continued).

Variable Included in Analysis		n	Mean Value ± SD	Median	Mean P-value	Median P-value
ICU admission	Yes	38	3.97 ± 12	0.81	0.38	0.0000
	No	78	2.12 ± 8.62	0.14		
Multiorgan failure	Present	27	5.56 ± 14.04	1.52	0.06	0.0000
	Absent	89	1.87 ± 8.06	0.14		
Acute on chronic pancreatitis	Yes	26	0.56 ± 1.04	0.10	0.13	0.11
	No	90	3.35 ± 11.09	0.31		
Presence of concomitant infection	Present	49	3.84 ± 11.54	0.42	0.34	0.01
	Absent	67	1.91 ± 8.38	0.14		
Triglyceride levels	Mild	14.00	1.38 ± 2.04	0.65	0.0012	0.0020
	Moderate	16.00	3.21 ± 5.24	1.35		
	Normal	56.00	2.36 ± 9.94	0.12		
	Severe	21.00	0.87 ± 1.37	0.26		
Neutrophil Ratio	High	93.00	2.32 ± 8.11	0.24	0.008	0.06
	Low	6.00	14.43 ± 28.84	3.67		
	Normal	17.00	0.81 ± 1.29	0.13		
Lipase level	High	101.00	3.09± 10.5	0.24	0.19	0.12
	Low	7.00	0.36± 0.24	0.31		
	Moderate	8.00	0.26± 0.40	0.10		

still skewed with clear violations of the normality assumptions, the analysis was turned to a permutation approach for ANOVA to address group means, and a post hoc multiple comparison Kruskal–Wallis test with Bonferroni p-value adjustments was performed for medians.

Based on univariate analysis of Procalcitonin, we found the starting of antibiotics on the day of admission to be statically significant for the difference in means (difference = 4.06, p = 0.0051) and medians (difference = 0.66, p = 0.0000). We also found the median differences in mortality to be mildly significant (difference = 0.79, p = 0.0640). We also found the medians of procalcitonin to be statistically significant based on mortality (difference = 1.38, p = 0.0640).

A permutation ANOVA based on ln(procalcitonin), comparing levels of hypertriglyceridemia, neutrophil level, and lipase level, also showed statistical significance. Hypertriglyceridemia indicated a statistically significant difference between means (p = 0.0012). Two-way comparisons of the means indicate a statistically significant difference between the levels Moderate and Normal (p = 0.0065) triglyceride levels, indicating Moderate > Normal. No other two-way comparison was found to be statistically significant. A Kruskal-Wallis test indicated statistically significant differences between the medians of triglyceride levels, indicating that Normal is lower than Mild (p = 0.04) and Moderate (p = 0.0080) (Figure 2). Neutrophil levels indicate a statistically significant difference between the means of ln(procalcitonin) (p = 0.0086). A permutation post hoc multiple comparisons indicate a statistical significance between the differences of Normal-Low (difference = −2.25, p = 0.0099), High–Low (difference = −1.95, p = 0.0125) neutrophil levels.

In a multivariate analysis of ln(procalcitonin), we found lipase (p = 0.0249), duration of antibiotics (p = 0.0009), multi-organ failure (p = 0.0045) to all be statistically significant, and lactate being mildly significant in the multivariate model (p = 0.0643). For every unit increase in lipase, we expect an increase in the natural log of procalcitonin of

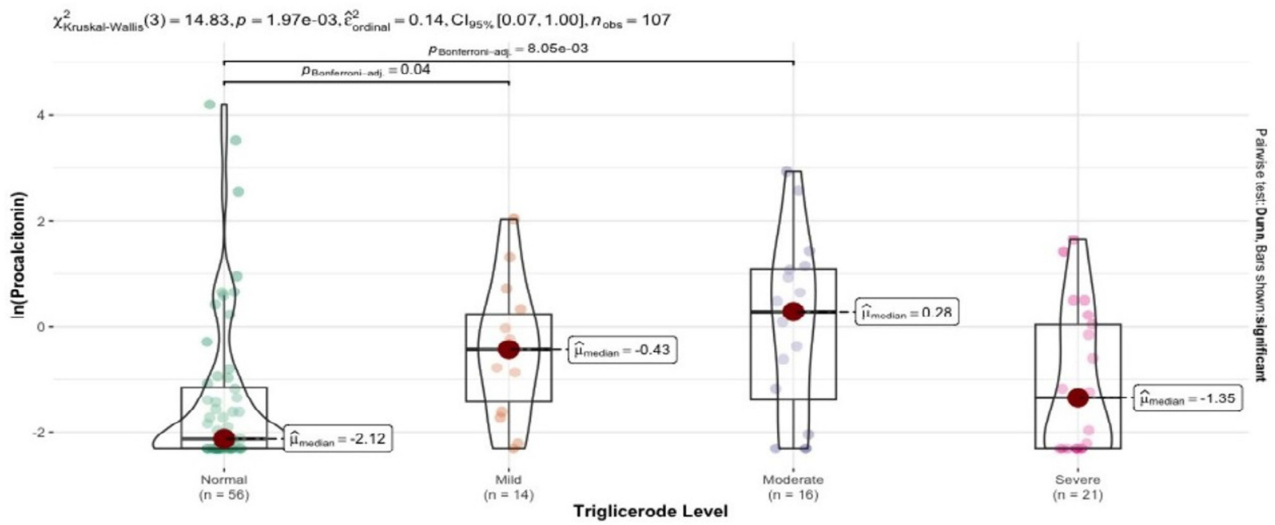

Figure 2 Kruskal–Wallis test indicates higher median procalcitonin values in mild (p=0.04) and moderate hypertriglyceridemia (p=0.0080).

0.040802. We found no relationship between procalcitonin values and BISAP score. The comparison of the lowest levels of procalcitonin to the highest levels recorded suggests an increase (based on the model) of one day in the duration of antibiotics. A 5 unit increase in lactate is expected to increase ln(Procalcitonin) by (0.0861*5 = 0.4305) or roughly 1.5380 on the original Procalcitonin scale. A linear model of log_procalcitonin predicting the initiation of antibiotics showed statistical significance $p < 0.05$ and suggested a mean difference of approximately 3.66 ng/mL between the procalcitonin of patients who were started antibiotics on the day of admission and those who were not.

Multivariate analysis was also performed for other outcomes using seven models (such as antibiotic used on the day of admission, duration of antibiotics, mortality related to pancreatitis and length of stay in the hospital, number of subsequent admissions, ICU admission, and multi-organ failure) to decrease the effect of confounding variables. Nonparametric bootstrap linear regression was applied for multivariate analysis of outcome length of stay instead of multiple linear regression technique.[13] Modeling suggested the following:

1. A patient with an underlying active infection was 15.95 times more likely to have antibiotics started on the day of admission, and we expect to see an increased duration of antibiotics by 5.7 days.
2. For every unit increase in lactate, there is an increase in the odds of antibiotic on the day of admission of 1.22, and we expect to see an increase in the odds of multi-organ failure of 1.30 over the previous lactate value.
3. For every unit increase in BISAP, there is an increase in the odds of mortality by 2.76, duration of antibiotics by 1.7 days, length of stay by 2.37 days, ICU admission by 8.46, and multi-organ failure by 5.52 over the previous BISAP value.
4. For every unit increase in the modified CT Severity Index, we expect to see an increase in the duration of antibiotics by 0.8140 days.
5. Patients with severe hypertriglyceridemia are expected to have 2.97 days longer stay and are 73.67 times more likely to be admitted to ICU than those with normal levels. Moderate hypertriglyceridemia is 26 times more likely to be admitted to the ICU than normal levels.
6. Patients with alcoholism have an increase in odds of readmission of 3.45 compared to patients without a history of alcoholism. Chronicity increases the odds of readmission by 3.88.
7. The odds of a patient with alcoholic/diabetic ketoacidosis being admitted to the ICU is 8.64 times, and multi-organ failure is 8.64 times higher than a patient without ketoacidosis.

Discussion

Acute pancreatitis is a common diagnosis for patients admitted to the hospital. Elevated inflammatory markers and diagnostic tools have evolved over time to predict its severity and clinical outcomes. PCT is a 116-amino acid polypeptide primarily used for diagnosing bacterial infections, but it is now used in patients with metastatic diseases and neuroendocrine tumors.[14]

The literature supports the use of procalcitonin to promote the judicial use of antibiotics in cases of pancreatitis.[15,16] It is also used to address the serious concerns regarding infection with Carbapenem-resistant organisms (CRO) that has become an evolving cause of mortality in acute pancreatitis. Procalcitonin and lactic acid represent two independent risk factors for mortality in acute pancreatitis with CRO infection.[17] The importance of procalcitonin also lies in need for ERCP if pancreatitis has concomitant cholangitis, in which case the initiation of antibiotics can be crucial.[18] A cut-off value of >0.5 ng/mL for plasma PCT was 100% sensitive and 80% specific for predicting antibiotic requirements.[19] A ROC analysis suggested a cut-off threshold of 0.36 ng/mL for procalcitonin when the antibiotics were started (sensitivity 66%, specificity 79%).

The main objective of our study was to identify the potential correlation between procalcitonin levels and the severity of acute pancreatitis and determine if serum levels of procalcitonin help identify patients that would benefit from antibiotic therapy in acute pancreatitis. We also analyzed various other variables that could affect clinical outcomes in acute pancreatitis.

Based on univariate analysis of Procalcitonin, we found the starting of antibiotics on the day of admission to be statically significant for the difference in mean (difference = 4.06, p = 0.0051) and median (difference = 0.66, p = 0.0000) procalcitonin values. We also found the median differences in mortality to be mildly significant (difference = 0.79, p = 0.0640). We also found the medians of procalcitonin to be statistically significant based on mortality (difference = 1.38, p = 0.0640). A permutation ANOVA based on ln(procalcitonin), comparing levels of hypertriglyceridemia, neutrophil level, and lipase level, also showed statistical significance.

In a multivariate analysis of ln(procalcitonin), we found lipase (p = 0.0249), duration of antibiotics (p = 0.0009), multi-organ failure (p = 0.0045) to all be statistically significant, and lactate being mildly significant in the multivariate model (p = 0.0643). A linear model of log_procalcitonin showed a mean difference of approximately 3.66 ng/mL between the procalcitonin of patients who started antibiotics on the day of admission and those who were not.

Multivariate analysis was also performed for various clinical outcomes in acute pancreatitis. The seven models suggested few significant conclusions about the predictor variables in acute pancreatitis. The most interesting finding in these results was that with every unit increase in BISAP, there is an increase in the odds of mortality, duration of antibiotics, length of stay, and the likelihood of ICU admission with multi-organ failure. For every unit increase in the modified CT Severity Index, there were increased odds of increasing antibiotic duration. Patients with severe hypertriglyceridemia are more likely to have a more extended stay with a higher likelihood of admission to the ICU.

The internal validity of our study was maximized by controlling the confounding variables. Other indicators of internal validity include the BISAP, which is a significant and well-known predictor of mortality, duration of antibiotics, ICU admission, length of stay, and multi-organ failure.[6] To improve the external validity/generalizability, we included clear eligibility criteria and collected multiple variables. We were able to collect an appropriate sample size. Intraobserver and interobserver variability were decreased by reviewing all the data twice by the same observer and cross-checking all the data by two observers. This resulted in increased reliability of the study. The limitations of our study include possible selection bias since this was a retrospective cohort.

Conclusions

The procalcitonin level can predict the initiation of antibiotics, duration of antibiotics, multi-organ failure, and mortality in patients with acute pancreatitis. A ROC analysis suggested a cut-off threshold of 0.36 ng/mL for procalcitonin when the antibiotics were started (sensitivity 66%, specificity 79%). Procalcitonin should always be included in the workup of acute pancreatitis. Procalcitonin levels may also help to predict triglyceride levels which may otherwise be unavailable on the day of admission.

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Disclosure

The authors report no conflicts of interest in this work.

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