ORIGINAL ARTICLE

The role of procalcitonin as a prognostic factor for acute cholangitis and infections in acute pancreatitis: a prospective cohort study from a European single center

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Abstract

Background: Infection in acute pancreatitis will worsen the disease prognosis. The aim of our study was to analyze the role of procalcitonin as a prognostic biomarker for infections and clinical severity.

Method: A prospective single-cohort observational study of patients diagnosed of acute pancreatitis (n = 152) was designed. PCT determination was tested on admission (first 72 h). Infections (biliary, extrapancreatic and infected pancreatic necrosis), need for antibiotics, urgent ERCP and severity scores for acute pancreatitis was assessed. ROC curves were designed and the area under the curve was calculated. Logistic regression for multivariate analysis was performed to evaluate the association between procalcitonin optimal cut-off level and major complications.

Results: PCT >0.68 mg/dL had higher incidence of global infection, acute cholangitis, bacteraemia, infected pancreatic necrosis, use of antibiotics in general, and need for urgent ERCP. In the multivariate regressions analysis, PCT >0.68 mg/dL at admission demonstrated to be a strong risk factor for complications in acute pancreatitis.

Discussion: PCT levels can be used as a reliable laboratory test to predict infections and the clinical severity of acute pancreatitis. High levels of PCT predict antibiotics prescription as well as the need for urgent ERCP in patients with concomitant clinically severe cholangitis.

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Background

Infections in acute pancreatitis (AP) are present in 25%[1,2] and the most frequent are acute cholangitis (AC), bacteremia, lung infection, urinary infection and catheter line related infections.[3] From these, cholangitis has relevance due to the fact that it requires prompt and specific treatment. It is demonstrated that both AC and AP could coexist.[4–8] Regarding the other type of infections in AP, it has been largely assumed and recently confirmed in the literature, that its presence will worsen the disease prognosis, increasing the risk for organ failure and sepsis, or even developing a secondary infection of pancreatic necrosis.[3]

In AP, antibiotics are only indicated in case of a proven infection or in case of a very strong clinical suspicion of either infected necrosis, extrapancreatic infection, and cholecystitis or associated cholangitis. In the latter case, biliary drainage is mandatory.[9] It is therefore imperative to identify patients with AP in whom AC is also present, who require broad spectrum antibiotics and emergent biliary drainage for acute cholangitis at an early stage of disease onset.[10] Therefore, to find a test to diagnose early infections and AC in the context of AP is crucial.

Serum procalcitonin (PCT) has recently been proposed as an effective biomarker for infections that offers high specificity and positive predictive value differentiating systemic

inflammatory response syndrome (SIRS) versus sepsis.[11] When tested in other clinical scenarios, and compared to C-reactive protein (CRP), PCT is more sensitive and specific in discriminating bacterial from non-infectious causes of inflammation.[12] The increased serum PCT correlates narrowly with the inflammatory response of a host to microbial infections.[12,13] In addition, serum PCT levels can decrease with clinical improvement.[14]

The aim of our study was to analyze the role of procalcitonin as a prognostic biomarker for infections in AP, including: acute cholangitis, cholecystitis, extrapancreatic infections and infected pancreatic necrosis in patients with AP.

Methods

Study design

A prospective single-cohort observational study of adult patients diagnosed of acute pancreatitis in a third level referral center was designed in order to evaluate the role of PCT.

Inclusion criteria

Patients with acute pancreatitis and PCT determination on admission (first 72 h) were included.

AP was defined according to the revised Atlanta Classification in 2012, requiring two or more criteria: (a) typical abdominal pain (epigastralgia radiating to the back), (b) at least a threefold increase in serum amylase levels, (c) indicative findings on computed tomography scans (CT), magnetic resonance imaging (MRI), or abdominal ultrasound (US) studies.

To diminish the risk of including pure cholangitis patients in our study cohort, a radiological confirmation of acute pancreatitis was mandatory.

Exclusion criteria

We exclude patients with no pancreatitis on imaging test. Renal chronic disease stage V and ERCP as cause of AP were also excluded.

PTC analysis/determination and cut-offs

Procalcitonin was tested using electrochemiluminescence immunoassay. Additionally, based on previous studies we are considering healthy individual levels <0.5 ng/mL (low risk for progression to sepsis). Levels between 0.5 ng/mL and 2 ng/mL are considered positive with an intermediate risk for progression to sepsis whilst levels >2 ng/mL are considered the cut-off value for predicting severe sepsis.[15–17] Additionally, we analyze the best cut-off value of PCT in predicting overall infections (biliary infections, extrapancreatic infection and infected pancreatic necrosis) in our cohort, in order to compare it with the classical cut-offs explained above. This calculation was made using Youden's index of the ROC curve.

Variables and outcomes

Infection

It was considered when one of the following infections was present: A. Biliary infection, B. Extrapancreatic infection, C. Infected pancreatic necrosis.

A. - Biliary infection could either be AC or cholecystitis. Acute cholangitis was defined according to previous reports due to TG13 has not been validated in the context of AP[18] (supplementary image 1). Cholecystitis was defined according to Tokyo Guidelines 2013[19] and/or a demonstrated gallbladder infection after drainage (positive bile culture) or surgery.

B. - Extrapancreatic infection was considered when a culture for bacteria or yeast was detected. The following extrapancreatic infections were analyzed: bacteremia, urinary tract infection, pneumoniae and catheter line infection. For bacteremia, blood samples were drawn when temperature reached ≥38 °C (for coagulase negative cocci at least 2 samples have to be positive). For pneumoniae, a positive sputum culture plus coughing, dyspnea, infiltrates on X-ray and low arterial blood gas was required. When intubated, a positive endotracheal secretion culture was mandatory.

C. - Infected pancreatic necrosis (IPN) was defined as a positive culture for microorganisms after necrosectomy or interventional (radiological or endoscopic) drainage. A suspicion of IPN was thought when persistent sepsis without extrapancreatic origin despite negative fine needle puncture; patients with pancreatic necrosis and gas with clinical deterioration unresponsive to intensive care support irrespective of fine needle puncture.[3] However, IPN usually occurs after 2 weeks so this event was rarely seen during admission.

Need for antibiotics

Broad spectrum antibiotics were initiated after clinical suspicion and/or after positive culture. We divided the use in two groups: early (first 72 h) or late (>72 h) after admission. Therapy regime, starting day and reason to initiate were registered in all cases.

Antibiotics were initiated after clinical suspicion or diagnostic of cholecystitis according to TG13 guidelines, and according to APEC trial definition (supplementary image 1) for acute cholangitis due to the lack of validation of TG13 guidelines for acute cholangitis in AP patients. For IPN we started antibiotics when suspected or confirmed IPN after a positive culture. In case of bacteriemia, catheter line infection, urinary tract infection, antibiotics were started when a positive culture was found (positive of gram staining or culture). For respiratory infections, antibiotics were started when confirmed infection after positive culture or suspected respiratory infection (definitions of suspected pneumonia was based on clinical deterioration of basal respiratory vital signs (respiratory rate, oxygen saturation, and radiological findings) in a patient with inflammatory markers CRP or elevated WBC). No prophylactic antibiotics were used.

Antibiotics were stopped when there were no signs of sepsis, normalization of leukocytes, and/or significant reduction (less than 3 cm) in size of infected collections or necrosis. In case of cholangitis, it was mandatory to resolve the cause of CBD obstruction to stop antibiotics. In case of cholecystitis if clinically remission of gallbladder inflammation, fever and normalization of WBC, antibiotics were continued after completed 14 days. In urinary tract infection, a regimen of 10 days of antibiotics was prescribed. In bacteraemia cases, a minimum of 5 days of antibiotics by intravenous route was needed, and negativization of blood culture was mandatory."

Need for urgent ERCP

The criteria to perform urgent ERCP was suspected severe cholangitis[20] or bile duct stones confirmed on MRI or US with clinical deterioration.

Severity AP scores

AP severity was defined according to Atlanta Classification[21]: mild acute pancreatitis requires no organ failure neither local or systemic complications, moderately severe acute pancreatitis requires the presence of transient organ failure (<48 h) and/or local or systemic complications, severe acute pancreatitis requires the present of persistent (>48 h) of single or multiple organ failure. Organ failure was defined according to Marshall scoring system (cardiovascular, respiratory or renal failure). Finally, local complications included fluid and acute necrotic collections, while systemic complications relate to comorbidity exacerbation.

Severity classical scoring systems include the Acute Physiology and Chronic Health Evaluation (APACHE-II), Bedside Index for Severity in Acute Pancreatitis (BISAP), and C-reactive protein (CRP). Other severity parameters collected were: need for intensive care unit (ICU), need for mechanical ventilation, persistent SIRS and mortality.

Risk factors for severe AP

For the multivariate analysis, we evaluate potential risk factors previously described in the literature, such: age, diabetes disease (insulin or non-insulin-dependent), high blood pressure, and C-reactive protein $\geq$15 mg/dL. Risk factors at admission evaluated were: C-reactive protein $\geq$15 mg/dL, APACHE-II $\geq$ 8 points, BISAP $\geq$3 points.[22–25]

Management of AP

Management of AP patients was done according to international guidelines: initial fluid-therapy was installed according to patient characteristics (ringer lactate, sodium physiological solution) for a urinary output of $\geq$0.5 ml/kg/h. No empirical use of ATB. When severe AP was suspected, the patient was referred to the ICU team for management and counselling. Moreover, this study did not influence the physician decision to indicate an early ERCP or prescribe antibiotics.

CT scan was ordered when moderate/severe or severe AP was suspected, when persistent SIRS was present, as well as differential diagnostic for suspected cholecystitis, bowel perforation, gastric ulcer, among others causes of abdominal pain in the emergency setting. For non-biliary AP, a CT scan was done in order to discard a different aetiology. For mild AP cases with biliary aetiology on the ultrasound, a CT scan was not done by routine.

Ethics

The present study and the prospective database was approved by our local Ethical Committee (PR (AG)02/2017) following the principles of the Declaration of Helsinki for human investigations. Informed consent was signed by all patients participating in our prospective study.

Statistical analysis

Descriptive statistics were used for baseline patients' characteristics and clinical parameters outcomes. Chi-square or Fisher's exact tests were used to compare qualitative variables. For quantitative variables, t-student test was used. To test the predicting accuracy of procalcitonin levels during admission, the receiver operating characteristic (ROC) curves was designed and the area under the curve (AUC) was calculated. The optimal cutoff values for procalcitonin in the ROC curves were determined on the basis of the Youden index. The AUC were compared using the Delongs test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) analysis was made according the best cut-off value. Logistic regression for multivariate analysis was performed to evaluate the association between procalcitonin optimal cut-off level and major complications. A p-value of <0.05 was considered to be statistically significant. Statistical analysis was performed using commercial software SPSS version 21 (Licenced by Universidad Autonoma de Barcelona).

Results

From December 2015 to January 2020, 233 patients meet the inclusion criteria. Eighty one were excluded so 152 patients were prospectively enrolled (Supplementary image 2). There were no statistical differences between the initial cohort and after applying exclusion criteria on main basal characteristics (sex, age) and main outcomes (severity, mortality and length of hospitalization). Main clinical basal, laboratory and radiological characteristics are shown in Table 1.

After de ROC analysis and calculation of Youden's index, a value of PCT >0.68 mg/dL has the best power in predicting overall infections.

Severity parameters and local complications in acute pancreatitis

The incidence of clinical severity parameters was higher in the PCT >0.5 mg/dL group, compared to the PCT <0.5 mg/dL group

for: severe AP, organ failure, multiorgan failure, persistent organ failure, persistent multiorgan failure, persistent SIRS, need of ICU, and mortality (see Table 2).

Local complications such as the need to intervention against necrosis was not statistical significant between groups.

Similar results were obtained after calculating PCT's optimal cut-off value according to Youden's Index (PCT>0.68 mg/dL group versus PCT<0.68 mg/dL group) (see Table 2).

Early infection, need for antibiotics and ERCP

Fifty-four patients developed an infection during hospital stay. The most common was acute cholangitis in 20 patients (37%) followed by infected pancreatic necrosis in 13 (24.1%) and bacteraemia in 12 (22.2%). A detail of type of infection, and pathogen according to PCT value is shown in Supplementary image 3.

The following infections occurred later on during the disease: IPN 39.8 ± 35 days, urinary tract infections 11,55 ± 10 days, catheter line infections 23.4 ± 15 days, respiratory infections 25.3 ± 53 days, while acute cholangitis, cholecystitis and bacteraemia occurred mainly early at the admission (0.9 ± 1.97 days, 2.5 ± 3.1 days, 1.8 ± 3.4 days, respectively).

When analysing the patients by group of PCT >0.5 mg/dL or PCT >0.68 mg/dL, both had higher incidence of global infection, acute cholangitis, bacteraemia, and infected pancreatic necrosis (Table 2). In the subgroup population analysis of patients who developed pancreatic necrosis (n = 38), the median of PCT was higher in the infected necrosis group than in the sterile necrosis group (PCT median: 2.64 mg/dL vs 0.34 mg/dL, p = 0.01, respectively).

Regarding the use of antibiotics, both groups (PCT >0.5 mg/dL and PCT >0.68 mg/dL) had higher incidence of use of antibiotics in general although both did not show more incidence of use of early antibiotics (first 72 h) compared with inferior levels of PCT (Table 2).

Urgent ERCP was higher in patients with PCT >0.68 mg/dL (22.2% vs. 8.2% p = 0.015, OR: 3.179 CI95%:1.20–8.35) compared with PCT<0.68 mg/dL, but no statistical significance was found in cases with PCT>0.5 mg/dL versus PCT<0.5 mg/dL (Table 2).

ROC analysis for laboratory tests and scoring systems

Both PCT at admission and BISAP showed a higher area under curve (AUC) for all disease severity parameters and local complications (see Table 3). Interestingly the value of AUC for AC was higher for PCT (AUC: 0.738) than the scores compared (Fig. 1).

In the comparative study of AUC performed by Delong's test, there was no statistical significant difference between PCT and BISAP for global infection, acute cholangitis, need for antibiotics, urgent ERCP, mortality and intervention against necrosis. There was a significant statistical difference in benefit of BISAP against PCT for persistent organ failure (p = 0.010), persistent multiorgan failure (p = 0.002) and need for ICU (p = 0.04).

When comparing PCT and CRP at admission after performing DeLong's test, PCT showed superiority over CRP for cholangitis

Table 1 Patient, laboratory and radiological characteristics and pathological background

Number of patients	152
Age (mean ± SD)	65.95 (±17.92)
Sex (Male/Female)	84/68 (55.3%/44,7%)
BMI (kg/m2) ± SD	28.42 (±4.57)
Co-morbidity	
Arterial hypertension	89 (58.6%)
Diabetes Mellitus	38 (25%)
Cardiovascular disease	35 (23%)
Respiratory disease	25 (16,4%)
Chronic renal disease	6 (3,9%)
Dyslipemia	54 (35.5%)
Clinical, laboratory and radiological characteristics	
Pancreatitis etiology	
Biliary	130 (85.5%)
Alcoholism	10 (6.6%)
Other	12 (8,1%)
Laboratory	
Amylase U/L, mean ± SD	1309.97 ± 1939.4
Hematocrit %, mean ± SD	42.25 ± 5.95
Leukocytes 103/mL, mean ± SD	13,787.78 ± 5556.46
Platelets 103/mL, mean ± SD	244.12 ± 84.19
PCT mg/dL, mean ± SD	3.51 ± 8.69
CRP mg/dL, mean ± SD	6.07 ± 8.97
Bilirubin mg/dL, mean ± SD	2.04 ± 1.88
ALT U/L, mean ± SD	217.54 ± 260.32
Alkaline phosphatase U/L, mean ± SD	146.75 ± 102.81
GGTP mg/dL, mean ± SD	315.97 ± 376.87
Creatinine mg/dL, mean ± SD	1.04 ± 0.53
Clinical Score	
APACHE II	7.02 ± 3.54
BISAP	1.74 ± 1.31
Radiological Score	
CTSI	3.93 ± 2.80
MCTSI	5.62 ± 3.03

CRP: C-reactive protein; ALT: alanine aminotransferase; GGTP: gamma-glumatyl transpeptidase; BISAP: Bedside Index Severity in Acute Pancreatitis.
PCT: procalcitonin; APACHE-II: Acute Physiology and Chronic Health Evaluation II; CTSI: CT severity Index; MCTSI: Modified CT severity index.

Table 2 Outcomes according to PCT values

2.1 Severity parameters and local complications								
Clinical severity parameters	PCT <0.5 mg/dL	PCT ≥0.5 mg/dL	*p*	OR (95% CI)	PCT<0,68 mg/dL	PCT >0,68 mg/dL	*p*	OR (95% CI)
Atlanta Classification (SAP)	5 (5,7%)	16 (32,7%)	**0,001**	5350 (1847–15,530)	7 (7,2%)	14 (25,9%)	**0,001**	4500 (1688–11,999)
Organ failure	7 (8%)	30 (46,2%)	**0**	9796 (3929–24,243)	9 (9,3%)	28 (51,9%)	**0**	10,530 (4415–25,113)
Multiorgan failure	5 (5,7%)	15 (23,1%)	**0,002**	4920 (1685–14,365)	7 (7,2%)	13 (24,1%)	**0,003**	4077 (1514–10,974)
Persistent organ failure	5 (5,7%)	18 (78,3%)	**0**	6281 (2190–18,015)	7 (7,2%)	16 (29,6%)	**0**	5414 (2061–14,220)
Persistent multiorgan failure	5 (5,7%)	12 (18,5%)	**0,014**	3713 (1237–11,144)	7 (7,2%)	10 (18,5%)	**0,035**	2922 (1042–8193)
Persistent SIRS	8 (9,2%)	18 (27,7%)	**0,003**	3782 (1526–9374)	10 (10,3%)	16 (29,6%)	**0,003**	3663 (1524–8807)
Need of ICU	4 (4,6%)	14 (21,5%)	**0,001**	5696 (1777–18,254)	5 (5,2%)	13 (24,1%)	**0,001**	5834 (1952–17,441)
Need of mechanical ventilation	1 (1,1%)	5 (7,7%)	0,084*	7167 (0,816–62,906)	2 (2,1%)	4 (7,4%)	0,188*	3800 (0,673–21,468)
Mortality	3 (3,4%)	10 (15,9%)	**0,009**	5091 (1341–19,331)	5 (5,2%)	8 (14,8%)	0,066*	3200 (0,991–10,322)
Local Complications								
Intervention against infected necrosis								
a. Radiological	2 (2,3%)	5 (7,7%)	0,138*	3542 (0,665–18,867)	2 (2,1%)	5 (9,3%)	0,098*	4874 (0,907–25,894)
b. Endoscopic	2 (2,3%)	4 (6,2%)	0,403*	2787 (0,495–15,703)	2 (2,1%)	4 (7,4%)	0,188*	3800 (0,673–21,468)
c. Surgical	0 (0%)	4 (6,2%)	**0,032***	0,412 (0,340–0,500)	1 (1%)	3 (5,6%)	0,131*	5647 (0,573–55,681)
SAP: Severe Acute Pancreatitis; ICU: intensive care unit; *: Fisher's exact test								
2.2 Infections	22 (25,3%)	32 (49,2%)	**0,002**	2865 (1443–5687)	25 (25,8%)	29 (53,7%)	**0,001**	3341 (1655–6743)
Biliary								
Acute cholangitis	4 (4,6%)	16 (24,6%)	**0**	6776 (2143–21,423)	5 (5,2%)	15 (27,8%)	**0**	7077 (2405–20,822)
Acute cholecystitis	2 (2,3%)	3 (4,6%)	0,652*	2056 (0,334–12,678)	2 (2,1%)	3 (5,6%)	0,349*	2794 (0,452–17,267)
Extrapancreatic								
Bacteriemia	3 (3,4%)	9 (13,8%)	**0,019**	4500 (1167–17,353)	4 (4,1%)	8 (14,8%)	**0,028***	4043 (1157–14,129)
Urinary tract	5 (5,7%)	5 (7,7%)	0,745*	1367 (0,379–4933)	6 (6,2%)	4 (7,4%)	0,746*	1213 (0,327–4503)
Pneumoniae	3 (3,4%)	7 (10,7%)	0,099*	3379 (0,839–13,612)	5 (5,2%)	5 (9,6%)	0,331*	1878 (0,518–6801)
CVC infection	2 (2,3%)	6 (9,2%)	0,074*	4322 (0,843–22,156)	3 (3,1%)	5 (9,6%)	0,135*	3197 (0,733–13,940)
Infected pancreatic necrosis	3 (3,4%)	10 (15,9%)	**0,009**	5091 (1341–19,331)	4 (4,1%)	9 (16,7%)	**0,014***	4650 (1359–15,915)
CVC: central venous catheter; *: Fisher's exact test								
2.3 Use of (early) antibiotics								
Prescription of antibiotics	22 (25,3%)	40 (61,5%)	**0**	4727 (2359–9475)	26 (26,8%)	36 (66,7%)	**0**	5462 (2652–11,248)
Early prescription (<72 h)	13 (14,9%)	11 (16,9%)	0,74	1160 (0,483–2785)	15 (15,5%)	9 (16,7%)	0,846	1093 (0,443–2697)
2.4 Need of urgent (<72 h) ERCP								
Early ERCP	8 (9,2%)	12 (18,5%)	0,095	2236 (0,856–5839)	8 (8,2%)	12 (22,2%)	**0,015**	3179 (1209–8359)

ERCP: endoscopic retrograde cholangiopancreatography.
Bold was used to highlight when statistical significance was achieved.

(AUC: 0.738 vs 0.501, p = 0.0387), need for antibiotics (AUC: 0.698 vs 0.576, p = 0.0394) and the presence of persisting organ failure (AUC: 0.717 vs 0.426, p = 0.0451). For the rest of severity parameters and clinical complications analysed, there was no statistical significance difference between PCT and CRP.

Sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV) analysis

Similarly to AUC, the best S/E/PPV and NPV values of PCT correspond to acute cholangitis (S: 75,0% (CI 53,1%–88.8%)/E: 70.2% (CI 61.9–77.4)/PPV: 27.8% (CI 17.6–40.9)/NPV: 94.8% (CI 88.5–97.8%) and infected pancreatic necrosis (S: 76.9% (CI 49.7–91.8)/E: 68.4% (CI 60.2–75.6)/PPV: 18.9% (CI 10.6–31.4)/NPV: 96.9% (CI 91.2–98.9).

Multivariate regressions of risk factors for complications in acute pancreatitis

Multivariate regressions analysis demonstrated that PCT >0.68 mg/dL at admission was a strong risk factor for complications in acute pancreatitis. Procalcitonin >0.68 mg/dL was independently associated with: global infections (OR: 2.878, CI 95%: 1.33–6.21), acute cholangitis (OR: 6.206, CI 95% 1.92–19.99), intervention against necrosis (OR: 5.826, CI 95% 1.40–24.14), antibiotic prescription (OR: 4.357, CI 95% 1.98–9.58), urgent ERCP (OR: 3.480, CI 95% 1.16–10.43) and organ failure (OR: 7.627, CI 95% 3.00–19.33) as shown in Table 4. For PCT >0.5 mg/dL the results were similar but with less power regarding the OR values in comparison with PCT >0.68 mg/dL.

Discussion

The results of our prospective study showed that a PCT value > 0.68 mg/dL at admission was a risk factor for infections in acute pancreatitis (acute cholangitis, bacteraemia and infected pancreatic necrosis. Additionally, patients with PCT>0.68 mg/dL, exhibited higher need of antibiotics, urgent ERCP and developed a clinically severe AP. This new cut-off (PCT

Table 3 ROC curve and area under the curve (AUC) for laboratory tests and scoring systems

	PCT			CRP			Leukocytes			APACHE II			BISAP		
Severity parameters and clinical complications	**AUC**	***p***	**CI**	**AUC**	***p***	**CI**	**AUC**	***p***	**CI**	**AUC**	***p***	**CI**	**AUC**	***p***	**CI**
Global infection	**0,642**	0026	0,522 −0762	0,602	0109	0,477 −0727	0,528	0663	0,402 −0654	0,654	0016	0,534 −0773	**0,676**	0006	0,561 −0791
Acute cholangitis	**0,738**	0,02	0,555 −0920	0,501	0988	0,305 −0698	0,489	0914	0,288 −0690	0,678	0083	0,514 −0842	**0,685**	0071	0,550 −0820
Need for antibiotics	**0,698**	0002	0,584 −0812	0,576	0232	0,452 −0700	0,531	0625	0,406 −0656	0,663	0,01	0,545 −0781	**0,719**	0001	0,610 −0829
Need for early use of antibiotics	**0,581**	0275	0,444 −0718	0,552	0488	0,395 −0708	0,576	0306	0,424 −0729	0,668	0024	0,529 −0806	**0,606**	0153	0,467 −0745
Urgent ERCP	**0,722**	0071	0,475 −0970	0,573	0555	0,332 −0814	0,519	0876	0,312 −0726	0,607	0385	0,448 −0766	**0,671**	0165	0,463 −0879
Persistent organ failure	**0,717**	0003	0,596 −0837	0,426	0309	0,273 −0579	0,664	0025	0,544 −0785	0,729	0002	0,604 −0854	**0,807**	0	0,715 −0898
Persistent multiorgan failure	**0,646**	0,07	0,507 −0785	0,341	0049	0,176 −0506	0,634	0096	0,498 −0770	0,699	0014	0,554 −0844	**0,778**	0001	0,674 −0881
Need for ICU	**0,711**	0006	0,585 −0837	0,384	0134	0,232 −0537	0,489	0877	0,346 −0633	0,592	0235	0,446 −0737	**0,768**	0001	0,660 −0875
Mortality	**0,692**	0034	0,562 −0822	0,429	0436	0,243 −0615	0,654	0089	0,521 −0756	0,725	0013	0,589 −0861	**0,766**	0003	0,646 −0887
Local complications															
Intervention against infected necrosis	**0,68**	0,04	0,530 −0827	0,625	0153	0,463 −0787	0,534	0697	0,367 −0701	0,663	0064	0,480 −0845	**0,695**	0026	0,541 −0849

ERCP: endoscopic retrograde cholangiopancreatography; ICU: intensive care unit; PCT: procalcitonin, CRP: C-reactive protein, APACHE-II: Acute Physiology and Chronic Health Evaluation II, BISAP: Bedside Index Severity in Acute Pancreatitis.
Bold was used to highlight PCT and BISAP values.

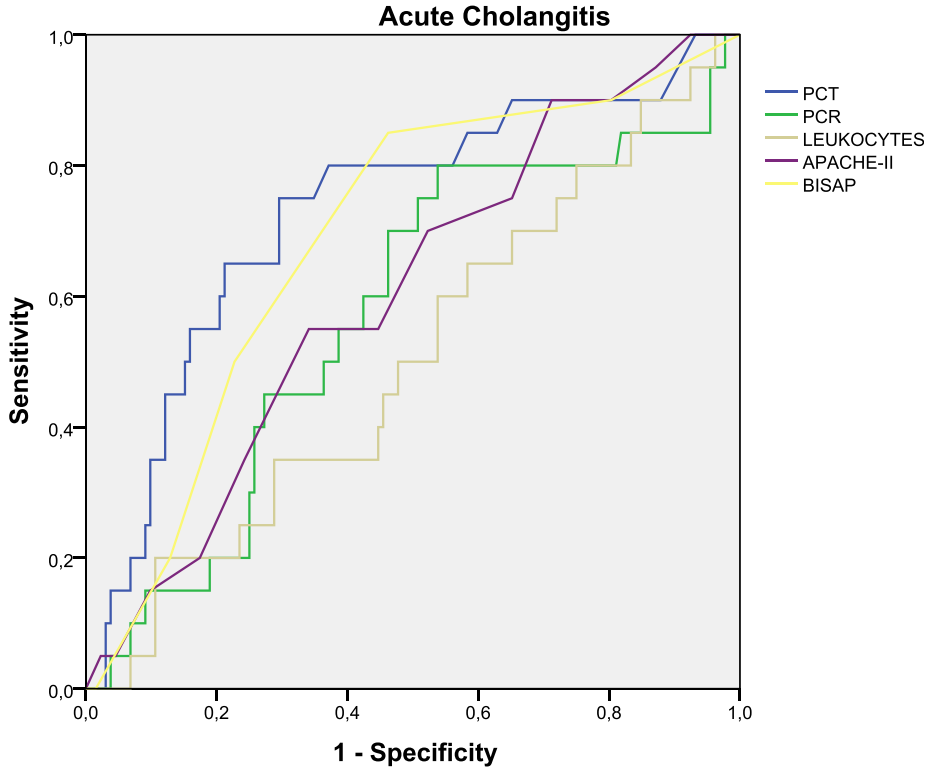

Figure 1 Receiver operating characteristic (ROC) and area under the curve (AUC) of laboratory tests and scoring systems for Acute Cholangitis

Table 4 Multivariate binary regressions of risk factors for complications in acute pancreatitis

	Global infection		**Acute cholangitis**		**Intervention against infected necrosis**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1004 (0,981–1029)	0,72	1009 (0,971–1049)	0,633	0950 (0,907–0,996)	0,032
HTA	1160 (0,493–2729)	0,733	1020 (0,267–3901)	0,977	1873 (0,337–10,396)	0,473
DM	0,767 (0,333–1767)	0,533	0638 (0,199–2050)	0,45	2371 (0,636–8835)	0,198
CRP >15 mg/dL (48 h)	1935 (0,922–4059)	0,81	1917 (0,609–6041)	0,266	1740 (0,457–6621)	0,416
PCT > 0,68 mg/dL at admission	**2878 (1333–6210)**	**0,007**	**6206 (1926–19,991)**	**0,002**	**5826 (1406–24,141)**	**0,015**
	ATB used global		**Urgent ERCP**		**Organ Failure**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0,993 (0,968–1018)	0,565	1022 (0,988–1057)	0,201	1016 (0,984–1049)	0,342
HTA	1991 (0,824–4814)	0,126	0340 (0,105–1105)	0,073	1116 (0,374–3332)	0,844
DM	1075 (0,461–2509)	0,867	1502 (0,510–4424)	0,46	1619 (0,631–4156)	0,317
CRP >15 mg/dL (48 h)	2398 (1128–5097)	0,023	1120 (0,400–3137)	0,829	3209 (1208–8525)	0,019
PCT > 0,68 mg/dL at admission	**4357 (1981–9583)**	**0**	**3480 (1161–10,438)**	**0,026**	**7627 (3009–19,337)**	**0**

HTA: Arterial hypertension; DM: diabetes mellitus; CRP: C-reactive protein; PCT: procalcitonin.
Bold was used to highlight PCT and BISAP values.

>0.68 mg/dL) outperformed the classical value of PCT>0.5 mg/dL in our cohort.

Our study gives new data regarding the relation of elevated serum values of PCT in acute pancreatitis patients and its relation with infections and complications. Additionally, we analyzed every type of infection and its relation with PCT values.

Few studies in the literature have investigated the role of PCT in patients with acute pancreatitis, and its role in predicting the

most prevalent infections related to AP (biliary tract infections, extrapancreatic infections) has not well elucidated, or has been made in the pre-era of the new Atlanta classification.[26]

In relation with our hypothesis, high levels of PCT at admission (>0.68 mg/dL) was an independent risk factor for use of antibiotics in general (OR: 4.357). However, higher levels of procalcitonin were not associated with the early prescription of antibiotics due to that most of infections usually happen after admission and not readily occur during the first 72 h. In consequence, if we consider the relation with the occurrence of overall infections with the presence of higher levels of PCT, we can hypothesize, that patients with higher levels of PCT could have had benefited from early ATB regimens. This hypothesis is in agreement to the PROCAP protocol study,[27] where a procalcitonin guided-algorithm according to a PCT level (during admission) will help support on the use of antibiotics during AP course and will serve as a follow-up test to deescalate and stop antibiotics. Additionally, Cai et al.[28] demonstrated that serum PCT is valuable to monitor clinical response and have a role in deescalating antibiotic therapy in AP.

In consequence, our results puts into relevance the role of procalcitonin in differentiating whether AP is related with infections in early phases. This dilemma has been thought for many years and has gained interest recently, especially when acute cholangitis is suspected. It is difficult to differentiate whether AP is associated with AC, due to the same variations in lab test are seen in most cases (cholestasis, increased bilirubin levels, leukocytosis, etc). In acute biliary AP, impacted stone in common bile duct motivates biliary stasis, inhibiting the flushing activity of bile and bacteriostatic effect of bile salts, which preserve bile sterility. In AC, elevated intraductal pressure favors bacterial translocation and toxins out of the ducts and into the systemic circulation, which can result in sepsis, shock, and death without timely intervention.[29] Without biliary decompression and antibiotics, the mortality rate of severe AC associated with septic shock approaches 100%.[30] Early endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (ES) is mandatory for patients with gallstone pancreatitis associated with acute cholangitis.[4,6,31–33]

There are few reports reporting the coexistence of AC and AP, and there are no studies on the role of PCT in differentiating both entities. Previous literature suggests that PCT levels >0.5 mg/dL[34] are associated with higher incidence of acute cholangitis (not in AP settings), bacteremia[35] and infected pancreatic necrosis.[14,26] Our study is the first prospective study in the literature showing the relation with procalcitonin and acute cholangitis in a scenario of AP and its capacity to predict the occurrence of AC (AUC: 0.738).

Regarding the need of ERCP in AP context, there is little evidence on the role of PCT as a prognostic factor for the need of urgent biliary decompression. Our study is one of the few in the literature, showing that PCT >0.68 mg/dL is an independent risk factor for urgent ERCP in acute pancreatitis scenario. Previous reports were based on pure cholangitis patients, where PCT seems to predict severe acute cholangitis better than other biomarkers[10] and identify high-risk patients who will not respond to initial medical therapy.[36] It is of vital importance to discriminate between both AC and AP and start a prompt and specific treatment, even if invasive procedures such as ERCP are needed.

For the occurrence of IPN, using the cut-off level of PCT >0.68 mg/dL, we found a positive relation between PCT and IPN (OR: 5826). The Hungarian pancreatic study group found similar results, concluding that low PCT levels appear to be strong negative predictor of IPN with acceptable sensitivity and specificity.[37] Furthermore, our results are in accordance to Rau et al.[26] on the matter than PCT was superior than C-reactive protein on predicting major complications such as infected pancreatic necrosis and mortality.

Likewise, PCT was compared to other biochemical markers (CRP and leukocytes) and classical scoring systems (APACHE-II and BISAP) at admission for prediction of infections, and others systemic complications as well of severity of AP. Procalcitonin and BISAP achieved the best AUC when plotting ROC curves for infections in general, as well as for every severity parameter, clinical complication and local complication. For infections in general PCT, APACHE-II and BISAP score showed higher AUC values, with little superiority between them, but all scores outperformed CRP and Leukocytes values. Regarding AC prediction and need for urgent ERCP, procalcitonin showed the best value of the AUC (0.738 and 0.722 respectively) compared to the other scores, however, no significant differences when comparing with BISAP and APACHE-II.

The performance of BISAP score in predicting severe AP has been confirmed in many studies[38–40] and our results corroborate this affirmation. Besides, our results are in agreement with Hagjer et al.[41] as we show that PCT is a promising test with prediction rates similar to BISAP. Finally, PCT >0.68 mg/dL on admission after multivariate analysis proved to be the most important independent risk factor for the presence organ failure in agreement with Khanna et al.[42] who found a 100% sensitivity of PCT for predicting organ failure and mortality.

For the past decades, serum PCT has gained attention as an effective biomarker for AP that offers high specificity and positive predictive values for SIRS, systemic infections,[11,43,44] developing infected pancreatic necrosis[34,45] and organ failure within 24 h of symptoms onset or hospital admission.[46,47] Our study seems to be the first that evaluates the role of PCT in pure AP patients, exploring the most important infections: acute cholangitis, IPN and extrapancreatic infections, and the need for specific treatment such as antibiotics use and early ERCP.

One of the strengths of this study is the fact that this study it was designed according the 2012 Atlanta classification, while others were based in outdated definitions of AP severity. Moreover, we analyzed in detailed the most frequent types of infections complications in AP, and our data was obtained from a prospective cohort designed specifically for this purpose.

Our study has some limitations. PCT levels were only measured upon admission. Changes in PCT concentrations were not taken into consideration and no further analysis could be made (i.e. response to targeted therapies such as urgent ERCP or antibiotics prescription). Second, most infection phenomena usually occurs late during AP hospitalization, especially infected pancreatic necrosis, so consecutive PCT determinations would have help to support our outcomes more strongly. Thirdly, the fact that PCT screening could not be extended for all the AP patients, due to our exclusion criteria of patients with well-known end stage renal disease. Additionally, in our cohort, the development of AKI, as a complication of AP, could increase the rate of PCT false positives. Moreover, only patients with a radiological confirmation of acute pancreatitis were taken into consideration for analysis. This was thought to avoid the bias of including pure cholangitis patients. It is evident that mild symptomatic patients with AP do not require an imaging study, so our results may tend to be inclined towards a more severe scenario. Finally, regarding survival sepsis guidelines, in which PCT value of 0.5 or above are the cut-off in patients with sepsis in ICU and 0.25 in ward, we didn't validate this result in our cohort, but have higher values of the cut-off point (0.68). One explanation is the fact that, elevation of PCT early stages of AP is a phenomena explained in most cases due to increased permeability of the intestinal barrier by itself[48] having or not a well-defined source of infection. This mechanism could explain the increase in the PCT cut-off in these patients.

In conclusion, our prospective study revealed that PCT levels on admission can be used as a reliable laboratory test to predict infections and the clinical severity of acute pancreatitis. Moreover, high levels of PCT predict antibiotics prescription as well as the need for urgent ERCP in patients with concomitant clinically severe cholangitis.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.10.016.