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The prognostic role of procalcitonin in predicting mortality after early cholecystectomy in patients with acute calculous cholecystitis

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Abstract

Recent studies have shown that Procalcitonin (PCT) can predict severity, difficult laparoscopic cholecystectomy, open conversion, and post-operative morbidity after Early Cholecystectomy (EC) in patients with Acute Calculous Cholecystitis (ACC). However, these studies are limited by their small sample sizes and lack of statistical power. The present study is a post-hoc analysis of a large prospective study (the S.P.Ri.M.A.C.C. study) to evaluate the value of PCT, as a predictor for mortality after EC. The S.P.Ri.M.A.C.C. study is an observational multicentre prospective study endorsed by the World Society of Emergency Surgery (WSES). 1253 patients from 79 locations in

19 countries were enrolled between September 1, 2021, and September 1, 2022. In this post-hoc analyses, patients with incomplete information regarding PCT value were excluded. The Receiving Operating Characteristic (ROC) curve and Area Under the Curve (AUC) were used to study the diagnostic ability of PCT. Exact logistic regression model was used to define the Odds Ratio (OR). 612 patients were included in this post-hoc analysis. The AUC of the PCT value as a continuous variable in predicting 30-day mortality was 0.926 (95% CI 0.874-0.978). The best cut-off in predicting 30-day mortality was 4 ng/mL with a sensitivity of 90.9% (95% CI 58.7%-99.8%) and a specificity of 88% (95% CI 85.1%-90.5%). The negative predicting value for mortality was 99.8% (95%CI 98.9%-100%), while the positive predicting value was 12.2% (95%CI 6.01%-21.3%). Patients with a PCT≥4 ng/mL had 72.19 (95%CI 10.01-3175.90) times higher odds to die after EC than patients with a PCT<4 ng/ml. The present study demonstrated the prognostic value of pre-operative PCT in predicting 30-day mortality after EC in patients with ACC.

Introduction

The lifetime prevalence of a healthy adult having gallstones is estimated to be about 15–20%, with a wide geographic variation, with 20% of these patients developing Acute Calculous Cholecystitis (ACC).[1,2] The most cited guidelines[1,3-9] agree to identify Early Cholecystectomy (EC) as the first-line therapy for ACC. However, cholecystectomy in the setting of ACC is a surgical intervention in which complications may arise. Indeed, significant data in the literature show mortality rates up to 3-4% for patients older than 80 years old[10] or with Charlson Comorbidity Index (CCI) >5,[11] up to 15.5% for patients with perforated gallbladder[12] and up to 46.3% for patients with American Society of Anaesthesiologists – Performance Status (ASA-PS) of III-IV.[13]

Accordingly, new endoscopic procedures have recently emerged as alternative methods for high-risk patients having ACC.[1,14] Still, some questions remain unanswered, especially about which patients are suitable for these treatments and how they may be selected.

To address this issue, the Validation and comparison of Scores for Prediction of RIsk for postoperative major Morbidity after cholecystectomy in Acute Calculous Cholecystitis (S.P.Ri.M.A.C.C.)[15] study was performed, which was a prospective multicentre observational study on patients with ACC who were candidates to EC. It aimed to prospectively validate and compare the performance of pre-operative risk prediction models for mortality and morbidity after EC in patients with ACC.

A total of 1253 patients from 79 centres located in 19 different countries were included, finding the POSSUM Physiological Score (PS) as the best risk prediction model for a complicated course after EC for ACC. The CHOLE-POSSUM was defined as the POSSUM PS with a cut-off of 25, tailored to predict major morbidity and mortality after EC in patients with ACC. According to the abovementioned study, the CHOLE-POSSUM has proved to be a valuable tool to select patients with ACC for safe early cholecystectomy with minimum risk of postoperative mortality and with an acceptable risk of major complications.

Recent studies have shown that Procalcitonin (PCT) can predict severity, difficult laparoscopic cholecystectomy, open conversion, and post-operative morbidity in ACC.[16]

Starting from these premises, we performed a post-hoc analysis of the S.P.Ri.M.A.C.C. study to evaluate the prognostic value of PCT in predicting 30-day mortality after EC in patients with ACC. Given the observational and post-hoc nature of the present analysis, causal inference cannot be established, and the study is intended to explore a prognostic association rather than a causal relationship.

Material and Methods

Ethical considerations

The medical ethics board of the trial coordinating centre IRCCS San Matteo Hospital, Pavia, Italy, approved the S.P.Ri.M.A.C.C. study protocol. All regional ethics committees of the participating centres provided secondary approval. Before enrollment, patients provided both verbal and written informed consent. The S.P.Ri.M.A.C.C. trial was carried out in line with the Helsinki Declaration.

Design

The S.P.Ri.M.A.C.C. study is an observational multicenter prospective study endorsed by the World Society of Emergency Surgery (WSES). A total of 1253 patients from 79 centers in 19 countries were enrolled between September 1, 2021, and September 1, 2022.[15] The study was registered on ClinicalTrials.gov under the identifier NCT04995380.

The present study is a post-hoc analysis of the S.P.Ri.M.A.C.C. cohort focusing on the prognostic role of preoperative PCT in patients with ACC undergoing EC. After exclusion of patients with incomplete PCT data, 612 participants were included in the analysis. EC was performed in all patients within 10 days from symptom onset.

Preoperative PCT levels were measured within 24 hours before surgery according to local laboratory protocols. The exact timing of surgery within this interval, as well as the use and duration of preoperative antibiotic therapy, were not standardized and were left to the discretion of the treating teams. Consequently, potential variability in procalcitonin levels related to these factors cannot be ruled out and is acknowledged as an inherent limitation of this post-hoc analysis.

Studied variables

30-day mortality rate after EC for patients with ACC was the primary objective of the study.

Inclusion and exclusion criteria

The following criteria were required for a patient to be included in the study: i) have a diagnosis of ACC according to the 2018 Tokyo Guidelines; ii) be a candidate for EC during the index admission; iii) be older than 18 years of age; iv) have a preoperative PCT value (within 24 hours before surgery); v) sign a written informed consent form, inclusive of the date and vi) be willing to comply with all study protocol rules and be available for the duration of the investigation.

Exclusion criteria included pregnancy or lactation, acalculous acute cholecystitis, symptoms starting more than 10 days before cholecystectomy, concurrent cholangitis or pancreatitis, intraoperative treatment of common bile duct stones, or anything else that would prevent full compliance with or completion of the study were the exclusion criteria.

Statistical analysis

The Receiving Operating Characteristic (ROC) curve and Area Under the Curve (AUC) were used to study the diagnostic ability of PCT. The nearest point of the curve to the left upper corner of the graph was the best cut-off prediction point of the variable having the best-balanced sensitivity and specificity. Exact logistic regression model was used to define the Odds Ratio (OR) of the studied variables. Statistical Package for the Social Sciences (IBM-SPSS version 28, Chicago, IL) and STATA (Statistics / Data analysis) were used for analyses. A $p \leq 0.05$ was accepted as statistically significant.

Results

A total of 612 patients were included in the post-hoc analysis. Table 1 shows patients characteristics. The 30-day mortality rate was 1.8%. The mean preoperative procalcitonin level was 3.50 ng/mL (SD 13.25, median 0.34, IQR 1.12).

The AUC of PCT for predicting 30-day mortality was 0.926 (95% CI 0.874–0.978) (Figure 1). The optimal cut-off was 4 ng/mL, yielding 90.9% sensitivity (95% CI 58.7–99.8%) and 88% specificity (95% CI 85.1–90.5%). The negative predictive value was 99.8% (95% CI 98.9–100%) and the positive predictive value 12.2% (95% CI 6.0–21.3%).

Patients with PCT ≥ 4 ng/mL had 72.2 times higher odds of death within 30 days after EC compared to those with PCT < 4 ng/mL (95% CI 10.01–3175.9). In patients with PCT ≥ 4 ng/mL, the absolute 30-day mortality risk was 12.2% (95% CI 6.0–21.3%), whereas in those with PCT < 4 ng/mL it was 0.2% (95% CI 0–1.1%).

Discussion

According to recent literature, PCT is increasingly used to differentiate bacterial infections from non-infective causes of inflammation. It shows higher sensitivity (88% vs. 75%) and specificity (81% vs. 67%) than C-Reactive Protein (CRP)[16] and rapidly increases in the presence of bacterial infections, but not viral infections or non-infectious inflammation.[17,18]

The pathogenesis of ACC is primarily inflammatory, resulting from obstruction of biliary outflow by a gallstone. Gallbladder distension compresses blood vessels in the wall, potentially causing local gangrene, while infection is typically a secondary phenomenon.[19] In this context, PCT may serve as a useful marker of ACC stage and severity.

Several studies have reported correlations between PCT levels and difficult laparoscopic cholecystectomy, major postoperative complications, and ACC severity.[20,23] These studies, however, were limited by small sample sizes and low statistical power, underscoring the need for larger prospective investigations. A recent systematic review[16] confirmed that PCT may predict ACC severity, operative difficulty, risk of open conversion, and postoperative morbidity, but heterogeneity in study design and cut-offs prevents firm conclusions.

This post-hoc analysis of a large international prospective study demonstrated that preoperative PCT, measured within 24 hours before surgery, has prognostic value for 30-day mortality after EC in patients with ACC. At a cut-off of 4 ng/mL, PCT showed 91% sensitivity and 88% specificity. While PCT has slightly lower sensitivity but higher specificity than the CHOLE-POSSUM score, its positive predictive value at this cut-off is relatively low (12%). Therefore, PCT should not be

used alone to withhold EC, but rather interpreted alongside established risk stratification tools, such as CHOLE-POSSUM, to identify patients at genuinely high risk.

Although the AUC of 0.926 indicates excellent discriminatory ability, the relatively low number of deaths in the cohort introduces a risk of over-optimism. Therefore, these findings should be interpreted with caution and confirmed in larger prospective studies.

PCT has limitations, as it is not routinely available in many developing countries. For this reason, it was not included among the prognostic factors analysed in the S.P.Ri.M.A.C.C. study. While understanding its prognostic value in ACC may encourage further research and adoption in centres where the biomarker is available, policy implications cannot be drawn from this post-hoc analysis. Additionally, PCT testing is generally more expensive than standard inflammatory markers, such as CRP, and costs vary by region and assay platform. Given the high incidence of ACC, widespread use of PCT as a screening biomarker would substantially increase testing costs. These factors—limited availability and high cost—may restrict the universal applicability of PCT for risk stratification in ACC.

A limitation of this study is its retrospective nature, despite being based on prospectively collected data. To address this, we have initiated a prospective study to investigate the prognostic value of PCT combined with CHOLE-POSSUM in ACC. The "CHOLE-POSSUM PRO: Validation for Prediction of Mortality after Cholecystectomy for Acute Calculous Cholecystitis" is a multicentre observational study proposed by the WSES Biomarkers in Acute Care Surgery & Trauma Initiative (WSES-BACS&TI). It has been approved by the Ethical Committee of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) and enrolment began on 1 March 2024, with an expected duration of approximately two years. More information is available at https://www.wses-bacseti.com/.

Conclusions

The present study demonstrated that preoperative PCT predicts 30-day mortality after EC in patients with ACC. Patients with a PCT ≥ 4 ng/mL had 72.19 times higher odds of death within 30 days after surgery compared to those with PCT < 4 ng/mL (95% CI 10.01–3175.90).

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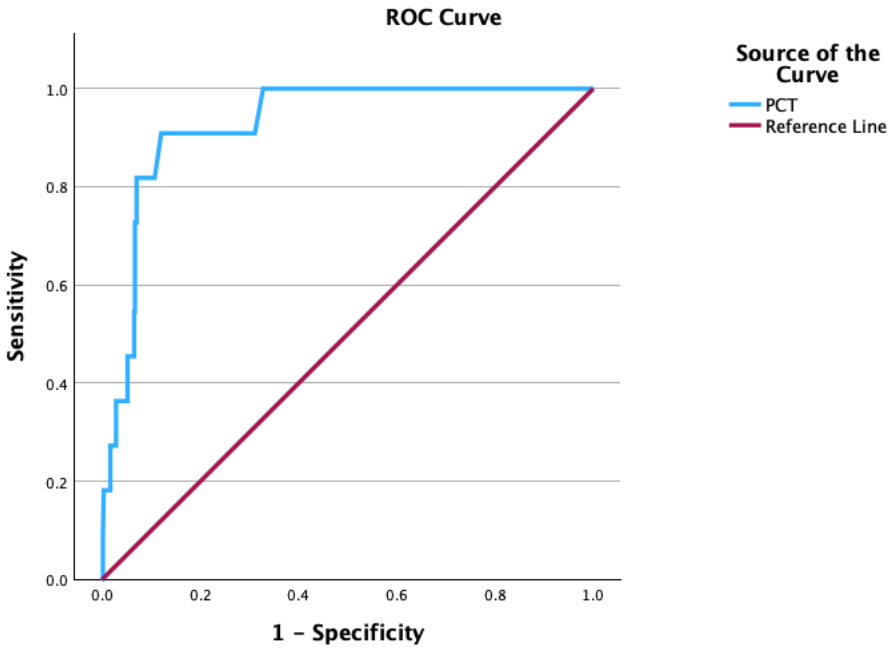
Table 1. Patients characteristics (SD, standard deviation; ACC, acute calculous cholecystitis; ASA, American Society of Anesthesiologists; PCT, procalcitonin; LOS, length of stay; CD, Clavien-Dindo).

Variable	**Value** **mean±SD** **median (IQR)**
Charlson Comorbidity Index	2.69±2.75 2.00 (4.00)
ACC grade (Tokyo Grade)	1.69±0.49 2.00 (1.00)

ASA score	2.22±0.87 2.00 (1.00)
Chole Risk score	1.31±0.95 1.00 (1.00)
POSSUM Physiological Score	20.77±7.21 19.00 (9.00)
Frailty Index	1.16±1.54 1.00 (2.00)
APACHE II	6.76±5.71 6.00 (6.00)
PCT (ng/ml)	3.50±13.25 0.34 (1.12)
Laparotomic cholecystectomies	8.2%
Laparoscopic cholecystectomies converted to open	10.7%
Bail-out procedures	8.2%
Intraoperative complications	4.1%
30-day major complications (CD>2)	8.9%
30-day mortality	1.8%
LOS>10 days	13.2%

Figure 1. ROC curves of PCT for 30-day mortality after EC in patients with ACC (ROC, Receiver Operating Characteristic; PCT, procalcitonin; EC, Early Cholecystectomy; ACC, Acute Calculous Cholecystitis).



Contributions: Luca Ansaloni, Paola Fugazzola: study conception; Paola Fugazzola, Luca Ansaloni, Andrea Dagnoni, Lorenzo Cobianchi, Francesca Dal Mas, Fikri M Abu-Zidan, Catherine Klersy: manuscript conception and draft and contribute to important scientific knowledge; Catherine Klersy, Fikri M Abu-Zidan statistical analysis of the data. Paola Fugazzola, Andrea Dagnoni, Lorenzo Cobianchi, Francesca Dal Mas, Carlo Bianchi, Fikri M Abu-Zidan, Matteo Tomasoni, Fausto Catena, Catherine Klersy, Ahmed Ghaly, Enrico Cicuttin, Simone Frassini, Valeria Musella, Jacopo Viganò, Fausto Catena, Luca Ansaloni gave substantial contributions to the interpretation of data for the work and critically revised the manuscript; Paola Fugazzola, Andrea Dagnoni, Valeria Musella, Walter Biffi, Massimo Sartelli and S.P.Ri.M.A.C.C. Collaborative Group: substantial contributions to the acquisition of data and draft critically revised. All authors gave the final approval and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: the authors declare that they have no competing interests.

Consent for publication: not applicable

Availability of data and materials: the datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author at reasonable request.

Ethics approval and consent to participate: the study protocol was approved by the medical Ethics Board of the trial coordinating centre at the IRCCS San Matteo Hospital, Pavia (Italy) (Prot. 20210057631). Patients gave oral and written informed consent before inclusion.

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Online supplementary materials

S.P.Ri.M.A.C.C. Collaborative Group