French Editorial Commentary from the ACHBPT

Early cholecystectomy cannot be regarded as a mortality risk factor in moderate and severe acute biliary pancreatitis

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We read with great interest the article by Di Martino *et al.* (1) on the timing of cholecystectomy after moderately severe and severe acute biliary pancreatitis (ABP). In this retrospective study, the authors analyzed data from the MANCTRA-1 database. Of 5,304 patients, 3,696 met the inclusion criteria (cholecystectomy performed and stage of pancreatitis known) and were included in the analysis. The aim of this study was to assess the impact of early cholecystectomy (EC) on morbidity and mortality in ABP, particularly in moderately severe and severe forms according to the modified Atlanta classification (2). EC was defined as removal of the gallbladder within 14 days of admission, and was compared with delayed cholecystectomy (DC).

The authors found that EC increased the risk of postoperative mortality (1.4% versus 0.1%, P<0.001) and morbidity (7.7% versus 3.7%, P<0.001) compared with DC. In multivariate analysis, they showed among patients who had had an EC that moderately severe or severe ABP was associated with a higher risk of mortality [odds ratio (OR) =361.46; 95% confidence interval (CI): 2.28–57,212.31; P=0.02] and morbidity (OR =2.64; 95% CI: 1.35–5.19; P=0.05) compared with mild ABP.

They also compared patients with moderately severe or severe ABP who had undergone EC with those who had undergone DC. Here again, they found that EC was associated with higher mortality (15.6% versus 1.2%, P<0.001) and morbidity (30.3% versus 10.3%, P<0.001) than DC.

Finally, multivariate analysis also showed that patient age and American Society of Anesthesiologists (ASA) score were associated with an increased risk of mortality (OR =1.12; 95% CI: 1.02–1.36; P=0.03 and OR =5.91; 95% CI: 1.06–32.78; P=0.04 respectively). Severe complications of ABP (necrosis requiring surgical necrosectomy, compartment syndrome, intestinal fistula or perforation) were associated with a higher risk of mortality and morbidity.

The authors conclude that the results suggest that EC should not be performed in patients with moderately severe or severe ABP, as it is associated with increased postoperative morbidity and mortality.

Nevertheless, several points can be raised with regard to the following conclusions.

Surgical issue

We raise a crucial question concerning the relevance of the analyses carried out by the authors to answer the question

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"Is EC associated with an increase in morbidity and mortality in moderately severe or severe ABP or not?" The retrospective nature of the data makes it impossible to know whether cholecystectomy in the EC group was performed alone or in association with another surgical procedure. The increased morbidity and mortality in these patients may simply be related to the severity of the ABP (3-5), since in the EC group there were more surgical necrosectomies (7.8% of patients in the DC group versus 25% in the EC group) or surgery for compartment syndrome/intestinal fistula/intestinal perforation (4.1% in the DC group versus 21.3% in the EC group) than in the DC group. This fact is not discussed in any way by the authors; at most, it is mentioned in the very last sentence of the discussion, "Some ECs could have been performed during surgical necrosectomy or other surgical interventions", even though it is of vital importance for the methodological validity of the study.

General methodology

We would also like to add a few comments on the methodology of this study.

It's good practice to announce all the planned analyses in the Methods section. This is not the case with the various comparisons and sub-group analyses carried out by the authors, which we discover directly in the Results section.

In addition, there was no multiple tests correction (134 analyses carried out in all). In fact, the more tests are performed, the greater the chance of obtaining a statistically significant result, but wrongly so: this is known as alpha risk inflation. If you run more than 20 tests, it is better to perform a Bonferroni-type correction. These points may suggest HARKing (hypothesizing after the results are known) (6,7).

A second remark concerns the statistical validity of certain results. The multivariate model for morbidity and mortality includes 13 variables. For mortality, however, there are only 16 events, i.e., too many variables in relation to the number of events. This leads to aberrant adjusted ORs (aORs): the stage of ABP according to the revised Atlanta classification has an aOR of 361.46, and the confidence interval is between 2.28 and 57,212.31. It is worth remembering that a multivariate logistic regression model requires a minimum number of 5 to 10 events per variable to be included in the model, otherwise the validity of the results is questionable (8,9). One solution would have been to use a propensity score (10). Moreover, the area under the curve (AUC) for morbidity is 0.668, but for mortality it is 0.997. The AUC is a parameter that indicates whether or not the multivariate model is discriminant (i.e., effectively predicts the event), and ranges from 0.5 (no more discriminant than chance) to 1 (perfect discrimination). An AUC too close to 1 suggests overfitting. The model is too adapted to the sample and the results may be difficult to generalize.

Conclusions

This study attempts to answer a relevant clinical question, as it is established that a DC in moderately severe or severe ABP incurs the risk of recurrence of lithiasis migration and hence recurrence of pancreatitis. We believe that the results of this study do not allow us to conclude with certainty whether EC is safe or harmful in these patients. A comparison should be made between patients who have had EC, excluding those for whom surgery for another cause was indicated. This is a confounding bias that is impossible to overcome in a retrospective study.

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Footnote

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