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COMMENT & RESPONSE

Optimal Timing of Cholecystectomy for Severe Acute Pancreatitis and Understanding Complications and Comorbidities

To the Editor We read with interest the article by Di Martino and colleagues.[1] The timing of cholecystectomy after admission with moderately severe or severe acute biliary pancreatitis remains unclear, and the authors are to be congratulated for presenting such a large multinational study.

The authors have shown that patients admitted with moderately severe or severe pancreatitis who undergo cholecystectomy within 14 days of admission have a significantly higher risk of morbidity (30 patients [30.3%] vs 57 patients [5.5%]; $P < .001$) and mortality (16 patients [15.6%] vs 0 patients; $P < .001$). However, these results need to be interpreted with caution.

First, of the 3696 patients, data for only 108 patients (2.9%) with moderately severe or severe pancreatitis were captured. This percentage is much lower than the published literature, and reasons for this are not identified. While it is likely that these 2 patient cohorts were combined to provide sufficient numbers for analysis, this approach is fundamentally flawed. They are 2 distinct patient groups. A UK study demonstrated that the mortality rates differ significantly (8% for moderately severe vs 25.4% for severe).[2] In addition, the authors did not report on data validation, and with centers from a number of countries contributing patients, this is an important consideration.

Second, no data have been provided from this study to demonstrate whether or not organ dysfunction had resolved by the time of cholecystectomy or the number of patients in the moderately severe group. The absence of these confounding variables means that morbidity and mortality rates between the groups cannot be compared as they may simply reflect disease severity, and early intervention in severe pancreatitis is associated with poorer outcomes.[3,4] Further data that would be helpful are those identifying the cause of death in patients with early cholecystectomy and the rate of conversion to an open procedure.

The conclusion that cholecystectomy within 14 days of admission should be considered carefully in this patient group is not confirmed from these data. It is also not possible to conclude that older, more fragile patients with complications should not be considered for early cholecystectomy when 991 patients were excluded from the analysis because of age or comorbidity. Our recent experience suggests that patients with severe acute pancreatitis remain sarcopenic even 12 months postdischarge,[5] and any surgical intervention will be poorly tolerated. The optimal timing in patients with moderately severe acute pancreatitis remains to be elucidated, but earlier cholecystectomy may be warranted, and further longitudinal studies are required.

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To the Editor A study conducted by Di Martino et al[1] involving 3696 patients with moderately severe and severe acute biliary pancreatitis (ABP) assessed the safety of early cholecystectomy (EC) and concluded that EC should be considered carefully in those patients because it increased postoperative morbidity and mortality. Despite the strengths of this study, several issues require further discussion.

In Table 2 in the article, delayed cholecystectomy (DC) and EC were significantly different in terms of surgical necrosectomy, regardless of whether they were for moderately severe or severe ABP (P = .02 and P < .001, respectively). Time of surgical intervention remains controversial when pancreatitis is accompanied by gallstones and pancreatic necrosis. Fong et al[2] concluded that single-stage cholecystectomy at the time of pancreatic necrosectomy is safe in selected patients. But American Gastroenterological Association clinical practice guidelines[3] indicated that pancreatic debridement should be avoided in the early, acute period (first 2 weeks) because it has been associated with increased morbidity and mortality. And Maurer et al[4] found more than 20% of patients with necrotizing pancreatitis treated by a minimally invasive step-up approach developed gallstone-related complications while awaiting cholecystectomy. Would it be possible to know whether surgical necrosectomy preceded, followed, or occurred along with cholecystectomy in this study? In addition, is it associated with any postoperative morbidity or mortality?

The Charlson Comorbidity Index (CCI), first proposed by Charlson in 1987,[5] contains 19 indicators related to mortality, including chronic pulmonary disease, diabetes, kidney disease, etc. Despite the fact that some of the 3 indicators above differ statistically, we are not sure why the authors repeated these comparative statistics under the premise that significant differences in CCI have already existed between mild, moderately severe, and severe ABP, as well as DC vs EC for moderately severe and severe ABP (P = .001 and P = .006, respectively) in their Table 1 and Table 2. We would appreciate if the authors could offer an explanation.

Errors appeared in both the text and the numerical data in the article. Table 2 had duplicate column headings for "Moderately severe ABP only." It seems the second one should be changed to "Severe ABP only." There were 16 deaths and 103 enrollments in the group of patients with moderately severe and severe ABP receiving EC, which should be 15.5%, not 15.6%. The difference will not affect the statistical results, but it has an adverse effect on the rigor despite it being only 0.1%.

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In Reply We appreciate the valuable correspondence from Robertson et al and Zhu and Wei regarding our article, which has allowed us to further clarify the strengths and limitations of our findings.

The primary goal of cholecystectomy in acute biliary pancreatitis (ABP) is to prevent recurrent attacks. While early cholecystectomy (EC) is established as safe for mild ABP, its safety for moderately severe and severe ABP lacks robust evidence.[1] Our study is a post hoc analysis of the MANCTRA-1, originally designed to assess guideline compliance and related outcomes.[2] Our analysis reveals that EC in patients with moderately severe and severe ABP should be approached cautiously.

As noted by our colleagues, significant differences in baseline characteristics between the study and control groups were apparent. These differences were highlighted through the analysis of specific patient-related comorbidities, including cardiac, pulmonary, kidney, or endocrinological disorders, and composite outcomes such as the Charlson Comorbidity Index. Given the intrinsic relationship between these differences and the nature of ABP, achieving perfectly balanced study and control groups with sufficient statistical power is unlikely. To address these limitations, we conducted subgroup and adjusted statistical analyses using multivariable regression models.

We agree that, despite the inclusion of several international centers, our cohort may be inconsistent with earlier reports on acute pancreatitis, with only 108 patients having moderately severe or severe ABP.[3] A possible explanation may be found in the fact that we enrolled only patients with ABP. Another important limitation also highlighted in the article is that some EC procedures may have coincided with other interventional procedures in patients with unresolved organ dysfunction, making it impossible to draw firm conclusions about the specific cause of death in those cases. Therefore, we concur that the nature of the study does not permit us to make strong definitive statements regarding the causal relationship between EC and postoperative complications.

Nevertheless, it is important to note that patients with moderately severe and severe ABP exhibited not only increased morbidity and mortality but also more cholecystectomy-related complications, such as bile leakage (2.4%), when compared with patients with mild ABP. This indicated an elevated postoperative risk for the study group. Additionally, we conducted subgroup analyses for patients with both moderately severe and severe ABP and adjusted analyses aimed at providing insights into patients at higher risk of complications. These analyses indicated that patients with more complex cases and a pronounced inflammatory response, potentially leading to a sarcopenic state, were at higher risk of complications.

Additionally, we thank Zhu and Wei for pointing out the typographical errors in the Results and Table 2 column headings. The article has been corrected online, and a correction notice appears in this issue.[4]

In conclusion, our study highlights the association between EC and complications in patients with moderately severe and severe ABP based on real-life data. The safety of EC for these patients remains unestablished. Caution is warranted in routinely recommending EC for this subgroup of patients, as the reduction in ABP episodes does not seem to be supported by a commensurate level of safety. Current recommendations for EC in moderately severe and severe ABP rely on expert opinion and small, low-quality retrospective studies.[5,6] Large-scale international studies designed to assess the causal relationship between EC and postoperative complications are needed to clarify whether the disadvantages of EC outweigh the reduced risk of recurrent ABP attacks.

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Examining Gender Disparities Among Physicians When Sample Sizes Differ

To the Editor We are writing in response to the article titled "Surgeon Sex and Long-Term Postoperative Outcomes Among Patients Undergoing Common Surgeries," by Wallis et al.[1] The study has illuminated a significant issue within our industry, and we would like to contribute to the research.

Although some studies indicate that female surgeons experience fewer complications than their male counterparts, conflicting findings have emerged. For example, a study conducted in Japan over a 7-year period reported no gender disparity in surgical outcomes.[2] Understanding why such disparities exist is complex, and we must consider factors such as differences in medical education, variations in surgical training, and the specific surgical field.

In the article published by Wallis et al,[1] it is not mentioned if the authors considered differences in sample sizes between male and female surgeons. Given the substantial sample size of male surgeons, it is plausible that they may have reported more complications. Additionally, we must consider that there are fewer females working in the field, which often compels patients to choose male surgeons. A study conducted by Stanford Medicine[3] found that patients were less likely to assign higher satisfaction scores to female obstetrician-gynecologists compared with their male counterparts. This surprising finding was due to the stereotype that males perform better in surgeries or exhibit greater technical proficiency.

However, it is important to note that numerous studies support the idea that female physicians achieve better outcomes than male physicians. A study by Firth-Cozens[4] reported that women physicians tend to allocate more time to patient care and excel in communication when compared with their male colleagues. This study also underscored that physicians often work in teams, with the senior consultant, typically male, assuming significant responsibility. Another study published in *JAMA Internal Medicine*[5] highlights variations in medical practice between female and male physicians, which could contribute to outcome disparities. While multiple studies report similar outcomes, the reasons for such outcomes remain unknown, whether attributed to differences in operative technique, individual skills, or attitudes.

In conclusion, the issue of gender inequality within our industry is multifaceted and demands our unwavering attention and concerted efforts for redress. We must collectively strive toward a future where gender disparities are relegated to the annals of history, and all professionals in our field are accorded the respect and opportunities they rightfully deserve.

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