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Timing of Cholecystectomy After Moderate and Severe Acute Biliary Pancreatitis

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Invited Commentary

Supplemental content

IMPORTANCE Considering the lack of equipoise regarding the timing of cholecystectomy in patients with moderately severe and severe acute biliary pancreatitis (ABP), it is critical to assess this issue.

OBJECTIVE To assess the outcomes of early cholecystectomy (EC) in patients with moderately severe and severe ABP.

DESIGN, SETTINGS, AND PARTICIPANTS This cohort study retrospectively analyzed real-life data from the MANCTRA-1 (Compliance With Evidence-Based Clinical Guidelines in the Management of Acute Biliary Pancreatitis) data set, assessing 5304 consecutive patients hospitalized between January 1, 2019, and December 31, 2020, for ABP from 42 countries. A total of 3696 patients who were hospitalized for ABP and underwent cholecystectomy were included in the analysis; of these, 1202 underwent EC, defined as a cholecystectomy performed within 14 days of admission. Univariable and multivariable logistic regression models were used to identify prognostic factors of mortality and morbidity. Data analysis was performed from January to February 2023.

MAIN OUTCOMES Mortality and morbidity after EC.

RESULTS Of the 3696 patients (mean [SD] age, 58.5 [17.8] years; 1907 [51.5%] female) included in the analysis, 1202 (32.5%) underwent EC and 2494 (67.5%) underwent delayed cholecystectomy (DC). Overall, EC presented an increased risk of postoperative mortality (1.4% vs 0.1%, *P* < .001) and morbidity (7.7% vs 3.7%, *P* < .001) compared with DC. On the multivariable analysis, moderately severe and severe ABP were associated with increased mortality (odds ratio [OR], 361.46; 95% CI, 2.28-57 212.31; *P* = .02) and morbidity (OR, 2.64; 95% CI, 1.35-5.19; *P* = .005). In patients with moderately severe and severe ABP (n = 108), EC was associated with an increased risk of mortality (16 [15.6%] vs 0 [0%], *P* < .001), morbidity (30 [30.3%] vs 57 [5.5%], *P* < .001), bile leakage (2 [2.4%] vs 4 [0.4%], *P* = .02), and infections (12 [14.6%] vs 4 [0.4%], *P* < .001) compared with patients with mild ABP who underwent EC. In patients with moderately severe and severe ABP (n = 108), EC was associated with higher mortality (16 [15.6%] vs 2 [1.2%], *P* < .001), morbidity (30 [30.3%] vs 17 [10.3%], *P* < .001), and infections (12 [14.6%] vs 2 [1.3%], *P* < .001) compared with patients with moderately severe and severe ABP who underwent DC. On the multivariable analysis, the patient's age (OR, 1.12; 95% CI, 1.02-1.36; *P* = .03) and American Society of Anesthesiologists score (OR, 5.91; 95% CI, 1.06-32.78; *P* = .04) were associated with mortality; severe complications of ABP were associated with increased mortality (OR, 50.04; 95% CI, 2.37-1058.01; *P* = .01) and morbidity (OR, 33.64; 95% CI, 3.19-354.73; *P* = .003).

CONCLUSIONS AND RELEVANCE This cohort study's findings suggest that EC should be considered carefully in patients with moderately severe and severe ABP, as it was associated with increased postoperative mortality and morbidity. However, older and more fragile patients manifesting severe complications related to ABP should most likely not be considered for EC.

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Acute pancreatitis (AP) is an acute inflammation of the pancreas; gallstones and biliary sludge are the most common cause of the disease, accounting for approximately 50% of the cases.[1] Although AP follows a mild and self-limited course in approximately 80% of cases, it can progress to moderately severe or severe AP,[2] with a mortality rate of 20% to 40%.[3,4] Additionally, acute biliary pancreatitis (ABP) presents a significant risk of recurrence of up to 33% when cholecystectomy is not performed.[5-9] Therefore, it is paramount to identify the cause of the disease as early as possible and propose a timely cholecystectomy to reduce the risk of recurrent attacks.[10-17]

Several aspects of the definitive treatment for ABP have been debated during the past decades, and credible evidence has started to emerge only recently.[18,19] The multicenter PONCHO (Same-Admission Vs Interval Cholecystectomy for Mild Gallstone Pancreatitis) randomized clinical trial[19] showed that same-admission cholecystectomy reduced the rate of recurrent gallstone-related complications in patients with mild gallstone pancreatitis, with a very low risk of postoperative complications, compared with delayed cholecystectomy (DC).

Nevertheless, whether a same-admission or early cholecystectomy (EC) should be indicated in patients with moderately severe and severe ABP is still debatable. There are conflicting data,[5,20,21] based on a few small retrospective studies,[22-28] as reflected by a previous systematic review of current guidelines,[29] which demonstrated that current recommendations are based on a quality of evidence not above level 2C, according to the Oxford Centre for Evidence-Based Medicine.[30] Therefore, considering the lack of equipoise on the timing of cholecystectomy in patients with moderately severe and severe ABP, it is critical to assess the safety and outcomes of EC in such patients.

The aim of this study was to assess the safety of EC in patients with moderately severe and severe ABP. Factors associated with increased morbidity and mortality were identified from the overall cohort of patients undergoing EC. Then, the outcomes of patients with moderately severe and severe ABP undergoing EC were compared with those with mild ABP undergoing EC and with those with moderately severe and severe ABP undergoing DC. Finally, factors that were potentially associated with mortality and morbidity exclusively in patients with moderately severe and severe ABP who underwent EC were identified.

Key Points

Question Is performing early cholecystectomy in patients with moderately severe and severe acute biliary pancreatitis (ABP) safe?

Findings This cohort study of 3696 patients hospitalized for ABP found that early cholecystectomy in those with moderately severe and severe ABP had an increased risk of mortality and morbidity compared with patients with mild ABP undergoing early cholecystectomy and with patients with moderately severe and severe ABP undergoing delayed cholecystectomy.

Meaning This study suggests that older and more fragile patients with severe complications of moderately severe and severe ABP should not be considered for early cholecystectomy.

Methods

Study Design

The cohort study interrogated the MANCTRA-1 (Compliance With Evidence-Based Clinical Guidelines in the Management of Acute Biliary Pancreatitis) data set, including patients with AP from centers in 42 countries in Europe, Asia, Africa, South America, and Oceania.[31-33] Ethical approval of the MANCTRA-1 study was granted by the institutional review board of the University of Cagliari[32] and local boards of the participating centers. Informed consent was waived for this retrospective study design because it involved the use of deidentified data. The study was conducted in compliance with the guidelines and regulations set by the Central Ethics Committee of the University of Cagliari. The study was conducted under the principles of the Declaration of Helsinki[34] and was developed and presented according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[35]

A retrospective analysis was performed on all consecutive patients hospitalized between January 1, 2019, and December 31, 2020, with a diagnosis of AP who subsequently underwent cholecystectomy. The exclusion criteria included the following: age younger than 16 years, AP with a cause other than gallstones, history of chronic pancreatitis, pregnancy, or breastfeeding. Additionally, patients with residual bile duct stone after cholecystectomy, refusal of cholecystectomy by the patient, cholecystectomy not indicated because of age or comorbidity, and an unclear classification of mild, moderately severe, and severe ABP were excluded from the analysis.

Definitions

Early cholecystectomy was defined as a cholecystectomy performed within 14 days of hospital admission, whereas DC was defined as a cholecystectomy performed more than 14 days after hospital admission.[36] Comorbidities were assessed on admission using the Charlson Comorbidity Index,[37] and the preoperative anesthetic risk was evaluated using the American Society of Anesthesiologists (ASA) score.[38] The patients were classified as having mild, moderately severe, or severe ABP according to the revised Atlanta classification (eFigure 1 in Supplement 1).[2] In-hospital mortality was defined as death occurring during hospitalization for ABP. Postoperative complications were recorded according to the Clavien-Dindo classification[39] and the Comprehensive Complication Index[40]; infectious complications were described in accordance with the US Centers for Disease Control and Prevention definitions.[41,42]

Variables of Interest and Outcomes

For each patient, the following variables were analyzed: demographic data and baseline characteristics, stage of AP according to revised Atlanta classification, laboratory data, concomitant findings and ABP complications (bowel ischemia, bowel fistula, and abdominal compartmental syndrome were grouped as severe ABP complications that required surgical intervention), and postcholecystectomy outcomes. Additional information on the variables of interest is available in the eMethods in Supplement 1.

The study's primary end points were postoperative mortality and morbidity in patients with moderately severe and severe ABP undergoing EC. In addition, the following clinical outcomes were assessed: postoperative complications according to the Clavien-Dindo classification and Comprehensive Complication Index, postoperative hemorrhage, bile leakage, infectious complications, incisional site infection, organ or space infection, postoperative length of stay, and readmission rate within 30 days after cholecystectomy.

Statistical Analysis

Baseline characteristics of the study population were expressed as numbers (percentages) for qualitative variables, whereas means (SDs) or medians (IQRs) were used for the quantitative variables. The differences between the qualitative variables of the groups were determined using the χ^2 or Fisher exact test as appropriate. The 2 groups' quantitative variables were compared using the 2-tailed *t* test and the Wilcoxon signed rank test.

Univariable and multivariable logistic regression models were used to identify prognostic factors of mortality and morbidity. Variables yielding *P* < .10 by univariable analysis and clinical factors associated with mortality and complications were added to a multivariable logistic analysis. The strength of association between a risk factor identified in univariable and multivariable analyses for mortality and complications was determined by calculating the unadjusted odds ratios (ORs) and adjusted odds ratios (AORs) with 95% CIs. The receiver operating characteristic (ROC)[12] curve was plotted to test model quality and its prognostic performance. A 2-sided *P* < .05 was considered statistically significant. All the statistical analyses were performed using Stata software, version 16.0 (StataCorp).[43] Data analysis was performed from January 2022 to February 2023.

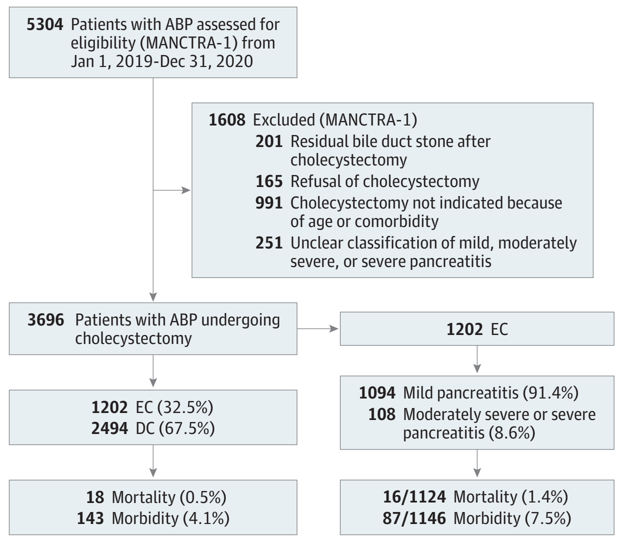
Results

Of the 5304 patients, 3696 (mean [SD] age, 58.5 [17.8] years; 1907 [51.5%] female and 1789 [48.4%]) were hospitalized for ABP between 2019 and 2020, underwent cholecystectomy, and were included in the analysis. A total of 1202 patients (32.5%) underwent EC and 2494 (67.5%) underwent DC (**Figure 1**).

Comparison of EC and DC

When compared with those who underwent DC, patients undergoing EC were younger (mean [SD] age, 57.2 [17.9] years for EC vs 59.7 [17.7] years for DC; *P* < .001) and more frequently had a clinical background of ischemic heart disease (144 [11.9%] vs 211 [8.4%], *P* < .001) (eTable 1 in Supplement 1). Patients undergoing EC had higher values of platelets, total bilirubin, γ-glutamyltransferase, lactate dehydrogenase, and C-reactive protein on admission, but with limited clinical relevance. Still, the EC group accounted for a higher percentage of endoscopic retrograde cholangiopancreatographies (ERCPs) (329 [27.3%] vs 517 [20.7%], *P* < .001), surgical necrosectomy (27 [2.2%] vs 21 [0.8%], *P* < .001), and severe ABP complications requiring surgical intervention (24 [1.9%] vs 15 [0.6%], *P* < .001).

Figure 1. Study Flow Diagram



ABP indicates acute biliary pancreatitis; DC, delayed cholecystectomy; EC, early cholecystectomy; and MANCTRA-1, Compliance With Evidence-Based Clinical Guidelines in the Management of Acute Biliary Pancreatitis.

Overall, the EC group had higher postcholecystectomy mortality (16 [1.4%] vs 2 [0.1%], *P* < .001), morbidity (87 [7.7%] vs 56 [3.7%], *P* < .001), complications with a Clavien-Dindo classification of IIIa or higher (15 [1.3%] vs 6 [0.4%], *P* = .007), a higher median (IQR) Comprehensive Complication Index (26.2 [8.7-31.65] vs 8.7 [8.7-26.2], *P* = .04), overall infectious complications (16 [1.4%] vs 7 [0.5%], *P* = .008), incisional site infections (10 [0.9%] vs 2 [0.1%], *P* = .004), and organ or space infections (12 [1.1%] vs 3 [0.2%], *P* = .002) (eTable 2 in Supplement 1). Because the study and control group presented significant heterogeneities in demographic and ABP characteristics, an adjusted analysis of factors associated with mortality and morbidity after EC was performed as described below.

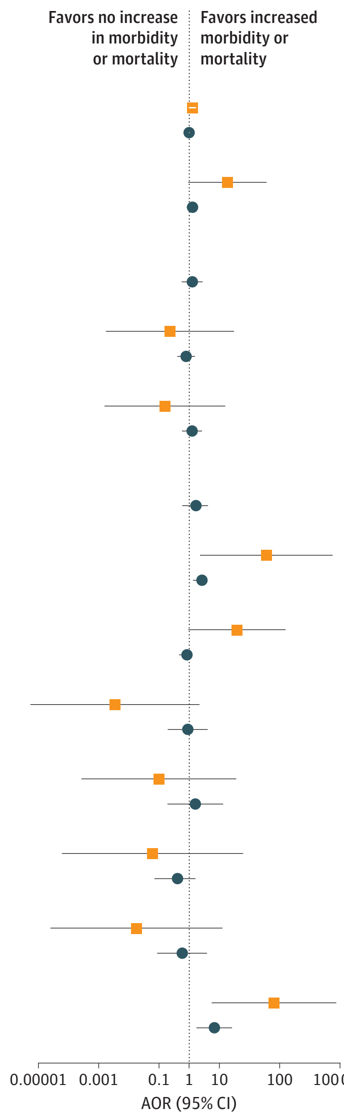
Factors Associated With Morbidity and Mortality After EC

Morbidity

An unadjusted analysis demonstrated a significant association between several demographic factors and post-EC morbidity (eTable 3 in Supplement 1). In the multivariable analysis, the presence of moderately severe and severe ABP (AOR, 2.64; 95% CI, 1.35-5.19; *P* = .005) and severe complications of the ABP requiring surgical intervention (AOR, 6.77; 95% CI, 1.74-26.36; *P* = .006) were independently associated with increased morbidity after EC (**Figure 2**). The ROC curve plotted to assess the performance of the multivariable model showed an area under the curve (AUC) of 0.668 (eFigure 2 in Supplement 1).

Figure 2. Factors Associated With Postoperative Mortality and Morbidity in Patients With Acute Biliary Pancreatitis (ABP) Undergoing Early Cholecystectomy

Variable	AOR (95% CI)	*P* value
Patient age		
Mortality	1.29 (0.98-1.70)	.07
Morbidity	1.01 (0.99-1.03)	.49
ASA III and IV vs I and II		
Mortality	18.61 (0.93-371.14)	.06
Morbidity	1.28 (0.83-1.98)	.26
Clinical history of chronic pulmonary disease		
Mortality	NA	NA
Morbidity	1.27 (0.57-2.85)	.56
Clinical history of hypertension		
Mortality	0.23 (0.002-30.78)	.56
Morbidity	0.80 (0.40-1.58)	.51
Clinical history of ischemic heart disease		
Mortality	0.16 (0.002-15.70)	.43
Morbidity	1.66 (0.59-4.64)	.57
Clinical history of chronic kidney disease		
Mortality	NA	NA
Morbidity	1.66 (0.59-4.63)	.34
RAC		
Mortality	361.46 (2.28-57 212.31)	.02
Morbidity	1.66 (0.59-4.63)	.005
Choledocholithiasis		
Mortality	38.09 (0.93-1567.94)	.06
Morbidity	0.84 (0.47-1.51)	.58
Pseudocyst		
Mortality	0.03 (0.00-2.21)	.09
Morbidity	0.90 (0.19-4.13)	.89
Infected necrosis		
Mortality	0.10 (0.00-36.21)	.44
Morbidity	1.60 (0.19-13.37)	.67
Endoscopic or percutaneous drainage		
Mortality	0.06 (0.00-61.69)	.43
Morbidity	0.42 (0.07-2.47)	.34
Surgical necrosectomy		
Mortality	0.02 (0.00-12.69)	.23
Morbidity	0.58 (0.09-3.93)	.58
ABP complications requiring surgical intervention		
Mortality	646.44 (5.55-75 261.08)	.008
Morbidity	6.77 (1.74-26.36)	.006



The patients were classified as having mild, moderately severe, or severe ABP according to the revised Atlanta classification (RAC). Complications of ABP include abdominal compartment syndrome, bowel ischemia, and bowel fistula. Vertical line indicates the line of no effect. AOR indicates adjusted odds ratio; ASA, American Society of Anesthesiologists; and NA, not available.

Mortality

The findings of the unadjusted analysis are described in eTable 4 in Supplement 1, and they are consistent with the previous analysis. In the multivariable analysis, the presence of a moderately severe and severe ABP (AOR, 361.46; 95% CI, 2.28-57 212.31; *P* = .02) and severe complications of the ABP requiring surgical intervention (eg, abdominal compartment syndrome, bowel ischemia, and bowel fistula) (AOR, 646.44; 95% CI, 5.55-75 261.08; *P* = .008) were independently associated with increased mortality after EC. The ROC curve presented an AUC of 0.997 (eFigure 3 in Supplement 1).

Postoperative Outcomes of EC in Patients With Moderately Severe and Severe ABP vs Those With Mild ABP

Because the revised Atlanta classification was independently associated with post-EC mortality and morbidity, a comparison of patients with mild ABP and moderately severe or severe ABP undergoing EC was performed. A total of 108 patients with moderately severe and severe ABP underwent EC. The analysis of demographic and baseline characteristics is given in **Table 1** and eTable 5 in Supplement 1. Patients with moderately severe and severe ABP who underwent EC were older and had a more complex clinical background and more complications related to ABP.

Patients with moderately severe and severe ABP who underwent EC had higher postcholecystectomy mortality (16 [15.6%] vs 0, *P* < .001) and morbidity (30 [30.3%] vs 57 [5.5%], *P* < .001), more complications with a Clavien-Dindo classification of IIIa or higher (9 [11.0%] vs 6 [0.7%], *P* = .001), a higher median (IQR) Comprehensive Complications Index (49.6 [26.2-100] vs 20.9 [8.7-26.2], *P* = .001), more bile leakage (2 [2.4%] vs 4 [0.4%], *P* = .02), more overall infectious complications (12 [14.6%] vs 4 [0.4%], *P* < .001), more incisional site infections (8 [9.8%] vs 2 [0.2%], *P* < .001), more organ or space infec-

Table 1. Comparison of Patients With Mild and Moderately Severe to Severe Acute Biliary Pancreatitis (ABP) Undergoing Early Cholecystectomy[a]

Characteristic	Mild vs moderately severe and severe ABP			Mild vs moderately severe ABP		Mild vs severe ABP	
	Mild (n = 1094)	Moderately severe and severe (n = 108)	P value[b]	Moderately severe only (n = 76)	P value[b]	Severe only (n = 32)	P value[b]
Patient age, mean (SD), y	56.6 (18.0)	63.6 (15.1)	<.001	63.6 (14.9)	.001	63.7 (15.8)	.03
Sex							
Female	635/1094 (58.0)	44/108 (40.7)	<.001	30/76 (39.5)	.002	14/32 (43.8)	.11
Male	459/1094 (42.0)	64/108 (59.3)		46/76 (60.5)		18/32 (56.2)	
CCI, median (IQR)	2 (0-4)	3.5 (2-5)	<.001	4 (2-5)	<.001	3 (1.5-5.5)	.006
ASA score III-IV	232/897 (25.8)	42/86 (48.8)	<.001	26/61 (42.6)	.004	16/25 (48.8)	<.001
Clinical history of diabetes	179/1094 (16.4)	39/108 (36.1)	<.001	30/76 (39.5)	<.001	9/32 (28.1)	.07
Clinical history of chronic pulmonary disease	89/1094 (8.1)	27/108 (25.0)	<.001	17/76 (22.4)	<.001	10/32 (31.3)	<.001
Clinical history of chronic kidney disease	42/1094 (3.7)	12/108 (11.1)	<.001	8/76 (10.5)	.004	4/32 (12.5)	.01
ERCP	298/1094 (26.1)	45/108 (41.7)	<.001	31/76 (40.8)	.005	14/32 (43.8)	.02
Pseudocyst	0/1094 (0)	24/108 (22.2)	<.001	17/76 (22.4)	<.001	7/32 (21.9)	<.001
Infected necrosis	0/1094 (0)	35/108 (32.4)	<.001	14/76 (18.4)	<.001	21/32 (65.6)	<.001
Endoscopic or percutaneous drainage	0/1094 (0)	30/108 (27.8)	<.001	17/76 (22.4)	<.001	13/32 (40.6)	<.001
Surgical necrosectomy	0/1094 (0)	27/108 (25.0)	<.001	11/76 (14.5)	<.001	11/32 (14.5)	<.001
Severe complications requiring surgical intervention[c]	0/1094 (0)	23/76 (21.3)	<.001	9/76 (11.8)	<.001	14/32 (43.8)	<.001
Postcholecystectomy mortality	0/1037 (0)	16/103 (15.6)	<.001	16/72 (8.3)	<.001	10/31 (32.3)	<.001
Postcholecystectomy morbidity	57/1034 (5.5)	30/99 (30.3)	<.001	17/72 (23.6)	<.001	13/27 (28.1.6)	<.001
Clavien-Dindo classification of IIIa or higher	6/996 (0.7)	9/82 (11.0)	<.001	6/64 (9.4)	<.001	3/18 (16.7)	<.001
Comprehensive Complication Index, median (IQR)	20.9 (8.7-26.2)	49.6 (26.2-100)	.001	60 (26.2-100)	.010	46.2 (17.4-100)	.04
Bile leakage	4/994 (0.4)	2/82 (2.4)	.02	2/64 (3.1)	.005	0/18 (3.1)	.79
Hemorrhage	1/994 (0.1)	2/82 (2.4)	<.001	1/64 (1.6)	.009	1/18 (5.6)	.009
Infectious postoperative complications	4/994 (0.4)	12/82 (14.6)	<.001	8/64 (12.5)	<.001	4/18 (22.2)	<.001
Incisional site infection	2/994 (0.2)	8/82 (9.8)	<.001	5/64 (7.8)	<.001	3/18 (16.7)	<.001
Organ or space infection	3/994 (0.3)	9/82 (11)	<.001	7/64 (10.9)	<.001	2/18 (11.1)	<.001
Postoperative length of stay, mean (SD), d	5 (4.3)	13.3 (9.9)	.007	12.4 (9.9)	.008	15.5 (10.8)	.003
Readmission rate within 30 d after cholecystectomy	44/1036 (4.2)	11/96 (11.5)	.002	6 (8.6)	.002	5 (19.2)	<.001

Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; ERCP, endoscopic retrograde cholangiopancreatography.

[a] Data are presented as number/total number (percentage) of patients unless otherwise indicated.

[b] $P < .05$ is considered statistically significant.

[c] This includes complications of ABP, such as abdominal compartment syndrome, bowel ischemia, and bowel fistula.

tions (9 [11.0%] vs 3 [0.3%], $P < .001$), and a higher readmission rate within 30 days after cholecystectomy (11 [11.5%] vs 44 [4.2%], $P = .002$). Additional data from the subgroup analysis comparing outcomes of mild vs moderately severe ABP only and mild vs severe ABP only are provided in Table 1 and eTable 5 in Supplement 1.

Postoperative Outcomes of Patients With Moderately Severe and Severe ABP Undergoing EC vs Those Undergoing DC

The study then compared the outcomes of the 108 patients with moderately severe and severe ABP who underwent EC with those who were deferred to DC. The demographic and baseline characteristics of both groups are given in **Table 2** and eTable 6 in Supplement 1. Again, patients who underwent EC had a more complex clinical background and more complications associated with ABP compared with the control group.

Patients who underwent EC also had higher postoperative mortality (16 [15.6%] vs 2 [1.2%], $P < .001$) and morbidity (30 [30.3%] vs 17 [10.3%], $P < .001$), more complications with a Clavien-Dindo classification of IIIa or higher (9 [11.0%] vs 3 [1.9%], $P = .002$), more overall infectious complications (12 [14.6%] vs 2 [1.3%], $P < .001$), more incisional site infections (8 [9.8%] vs 1 [0.6%], $P < .001$), and more organ or space infections (9 [11.0%] vs 1 [0.6%], $P < .001$). Further data on subgroup analysis comparing the outcomes of EC vs DC in pa-

Table 2. Comparison of Patients With Moderately Severe and Severe Acute Biliary Pancreatitis (ABP) Undergoing DC vs EC[a,b]

	Moderately severe and severe ABP			Moderately severe ABP only			Moderately severe ABP only		
Characteristic	DC (n = 270)	EC (n = 108)	*P* value[c]	DC (n = 197)	EC (n = 76)	*P* value[c]	DC (n = 73)	EC (n = 32)	*P* value[c]
Patient age, mean (SD), y	62.1 (17.1)	63.6 (15.1)	.40	63.8 (16.5)	63.6 (14.9)	.94	57.4 (17.6)	63.7 (15.8)	.09
Sex									
Female	110/270 (40.7)	44/108 (40.7)	>.99	83/197 (42.1)	30/76 (39.5)	.69	27/73 (37.0)	14/32 (43.8)	.51
Male	160 (59.3)	64 (59.3)		114 (57.9)	46 (60.5)		46 (63.0)	18 (56.2)	
CCI, median (IQR)	3 (1-4)	3.5 (2-5)	.006	3 (1-4)	4 (2-5)	.051	2 (0-4)	3 (1.5-5.5)	.03
ASA score III-IV	82/176 (46.6)	42 (48.8)	.73	62/117 (53.0)	26/61 (42.6)	.19	20/59 (34)	16/25 (64)	.01
Clinical history of diabetes	66/270 (24.4)	39/108 (36.1)	.02	49/197 (24.9)	30/76 (39.5)	.02	17/73 (23)	9/32 (28)	.60
Clinical history of chronic pulmonary disease	33/270 (12.2)	27/108 (25.0)	.002	25/197 (12.7)	17/76 (22.4)	.047	8/73 (11)	10/32 (31)	.01
Clinical history of chronic kidney disease	20/270 (7.4)	12/108 (11.1)	.24	15/197 (7.6)	8/76 (10.5)	.44	5/73 (7)	4/32 (13)	.34
ERCP	65/270 (24.1)	35/108 (32.4)	.10	29/197 (14.7)	14/76 (18.4)	.45	36/73 (49)	21/32 (66)	.12
Pseudocyst	67/270 (24.8)	45/108 (41.7)	.001	48/197 (24.4)	31/76 (40.8)	.007	19/73 (26)	14/32 (44)	.07
Infected necrosis	67/270 (24.8)	24/108 (22.2)	.59	48/197 (24.4)	17/76 (22.4)	.73	19/73 (26)	7/32 (22)	.65
Endoscopic or percutaneous drainage	54/270 (20.0)	30/108 (27.8)	.10	30/197 (15.2)	17/76 (22.4)	.16	24/73 (33)	13/32 (41)	.44
Surgical necrosectomy	21/270 (7.8)	27/108 (25.0)	<.001	11/197 (5.6)	11/76 (14.5)	.02	10/73 (14)	16/32 (50)	<.001
Severe complications requiring surgical intervention	11/270 (4.1)	23/108 (21.3)	<.001	4/197 (2.0)	9/76 (11.8)	<.001	7/73 (10)	14/32 (44)	<.001
Postcholecystectomy mortality	2/168 (1.2)	16/103 (15.6)	<.001	2/115 (1.7)	6/72 (8.3)	.03	0/53 (0)	10/31 (32)	<.001
Postcholecystectomy morbidity	17/165 (10.3)	30/99 (30.3)	<.001	8/113 (7.1)	17/72 (23.6)	.001	9/52 (17)	13/27 (48)	.004
Clavien-Dindo classification of IIIa or higher	3/156 (1.9)	9/82 (11.0)	.002	1/107 (0.9)	6/64 (9.4)	.007	2/49 (4)	3/18 (17)	.08
Comprehensive Complication Index, median (IQR)	26.2 (8.7-26.2)	29.6 (26.2-100)	.08	26.9 (26.2-27.6)	60 (26.2-100)	.40	20.9 (8.7-26.2)	26.2 (17.4-45.6)	.30
Bile leakage	2/156 (1.3)	2/82 (2.4)	.51	1/107 (0.9)	2/64 (3.1)	.29	1/49 (2)	0/18 (0)	.54
Hemorrhage	0/156 (0.0)	2/82 (2.4)	.050	0/107 (0.0)	1/64 (1.6)	.19	0/49 (0)	1/18 (6)	.10
Infectious postoperative complications	2/156 (1.3)	12/82 (14.6)	<.001	1/107 (0.9)	8/64 (12.5)	.001	1/49 (2)	4/18 (22)	.005
Incisional site infection	1/156 (0.6)	8/82 (9.8)	<.001	0/107 (0.0)	5/64 (7.8)	.003	0/49 (0)	3/18 (17)	.003
Organ or space infection	1/156 (0.6)	9/82 (11.0)	<.001	0/107 (0.0)	7/64 (10.9)	<.001	1/49 (2)	2/18 (11)	.11
Postoperative length of stay, mean (SD), d	6.6 (3.9)	13.3 (9.9)	.08	7.5 (3.5)	12.4 (9.9)	.52	6.3 (4.4)	15.5 (10.8)	.10
Readmission rate within 30 d after cholecystectomy	33/196 (16.8)	11/96 (11.5)	.23	18/138 (13.0)	6/72 (8.6)	.34	15/58 (26)	5/26 (19)	.51

Abbreviations: ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; DC, delayed cholecystectomy; EC, early cholecystectomy; ERCP, endoscopic retrograde cholangiopancreatography.

[a] This includes complications of ABP, such as abdominal compartment syndrome, bowel ischemia, and bowel fistula.

[b] Data are presented as number/total number (percentage) of patients unless otherwise indicated.

[c] $P < .05$ is considered statistically significant.

tients with moderately severe ABP only and severe ABP only are provided in Table 2 and eTable 6 in Supplement 1.

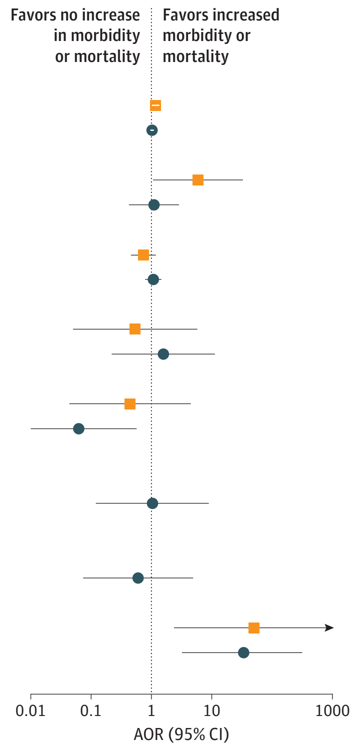
Factors Associated With Morbidity and Mortality After EC in Patients With Moderately Severe and Severe ABP

Morbidity

The unadjusted analysis demonstrated a significant association between post-EC morbidity and an increased ASA score (OR, 2.38; 95% CI, 1.31-4.33; $P = .005$), Charlson Comorbidity Index value (OR, 1.17; 95% CI, 1.01-1.35; $P = .04$), increased presence of severe AP (vs moderately severe AP) (OR, 3.00; 95% CI, 1.18-7.62; $P = .02$), having had infected necrosis (OR, 2.48; 95% CI, 1.01-6.07; $P = .047$), a surgical necrosectomy (OR, 3.17; 95% CI, 1.21-8.27; $P = .02$), severe complications of the ABP requiring surgical intervention (eg, abdominal compartment syndrome, bowel ischemia, and bowel fistula) (OR, 8.03; 95% CI,

Figure 3. Variables Associated With Postoperative Mortality and Morbidity in Patients With Moderately Severe and Severe Acute Biliary Pancreatitis (ABP) Undergoing Early Cholecystectomy

Variable	AOR (95% CI)	P value
Patient age		
Mortality	1.12 (1.02-1.14)	.03
Morbidity	1.03 (0.96-1.20)	.42
ASA III and IV vs I and II		
Mortality	5.91 (1.07-32.78)	.04
Morbidity	1.10 (0.42-2.88)	.84
Charlson Comorbidity Index		
Mortality	0.74 (0.46-1.18)	.21
Morbidity	1.08 (0.78-1.47)	.65
RAC		
Mortality	0.54 (0.50-5.76)	.61
Morbidity	1.58 (0.22-11.30)	.65
ERCP		
Mortality	0.44 (0.04-4.50)	.49
Morbidity	0.06 (0.01-0.57)	.01
Infected necrosis		
Mortality	NA	NA
Morbidity	1.04 (0.12-8.97)	.97
Surgical necrosectomy		
Mortality	NA	NA
Morbidity	0.61 (0.07-4.97)	.64
ABP complications requiring surgical intervention		
Mortality	50.04 (2.37-1058.01)	.01
Morbidity	33.64 (3.19-354.73)	.003



The patients were classified as having mild, moderately severe, or severe ABP according to the revised Atlanta classification (RAC). Complications of ABP include abdominal compartment syndrome, bowel ischemia, and bowel fistula. Vertical line indicates the line of no effect. AOR indicates adjusted odds ratio; ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; and NA, not available.

2.66-24.26; *P* < .001), and not having had an ERCP (OR, 0.35; 95% CI, 0.13-0.93; *P* = .04) (eTable 7 in Supplement 1).

In the multivariable analysis, the presence of severe complications requiring surgical intervention (eg, abdominal compartment syndrome, bowel ischemia, and bowel fistula) (AOR, 33.64; 95% CI, 3.19-354.73; *P* = .003) and not having had an ERCP (AOR, 0.06; 95% CI, 0.001-61.69; *P* = .01) were presented as independent factors associated with increased morbidity after EC in patients with moderately severe and severe ABP (**Figure 3**). The ROC curve plotted to assess the performance of the above-mentioned prognostic factors for post-EC morbidity showed an AUC of 0.838 (eFigure 4 in Supplement 1).

Mortality

The unadjusted analysis demonstrated a significant association between post-EC mortality and older age (OR, 1.05; 95% CI, 1.00-1.20; *P* = .03), higher ASA score (OR, 6.49; 95% CI, 1.99-21.23; *P* = .002), presence of severe AP (vs moderately severe AP) (OR, 5.24; 95% CI, 1.70-16.13; *P* = .004), and severe complications of the ABP requiring surgical intervention (eg, abdominal compartment syndrome, bowel ischemia, and bowel fistula) (OR, 6.70; 95% CI, 2.14-20.99; *P* = .001) (eTable 8 in Supplement 1).

In the multivariable analysis, the patient's age (AOR, 1.12; 95% CI, 1.02-1.36; *P* = .03), ASA score (AOR, 5.91; 95% CI, 1.06-32.78; *P* = .04), and presence of severe complications of the ABP requiring surgical intervention (eg, abdominal compartment syndrome, bowel ischemia, and bowel fistula) (AOR, 50.04; 95% CI, 2.37-1058.01; *P* = .01) were independently associated with increased mortality after EC (Figure 3). The ROC curve presented an AUC of 0.961 (eFigure 5 in Supplement 1).

Discussion

The absence of high-quality data on patients with moderately severe and severe ABP makes it challenging to provide a conclusive recommendation regarding the ideal timing for cholecystectomy in this subgroup of patients. A recent meta-analysis by Prasanth et al[21] did not identify enough patients with moderately severe and severe ABP to perform a subgroup analysis assessing the effect of the timing of cholecystectomy in these patients.

With this in mind, we assessed the timing of cholecystectomy in patients from the MANCTRA-1 data set with moderately severe and severe ABP. The analysis showed that moderately severe and severe ABP was independently associated with increased postoperative mortality and morbidity after EC. Patients with moderately severe and severe ABP who underwent EC had poorer postoperative outcomes compared with patients with mild ABP undergoing EC and patients with moderately severe and severe ABP undergoing DC. The patient's age, ASA score, absence of bile duct clearance by ERCP, and severe complications of the ABP requiring surgical intervention were the specific factors associated with morbidity and mortality in patients with moderately severe and severe ABP who underwent EC.

Although current guidelines recommend that EC should be performed in patients with mild ABP with level of evidence 1A[10,11,44] of the Oxford Centre for Evidence-Based Medicine,[30] there is a lack of conclusive evidence on the timing of cholecystectomy in patients with moderately severe and severe ABP. Current recommendations suggest delaying cholecystectomy until the procedure can be performed safely, considering the location of the remaining collections and the estimated technical difficulty with cholecystectomy.[10-14] However, this issue needs more careful consideration because delaying cholecystectomy in patients with ABP increases the risk of recurrence.

The risk of gallstone-related events progressively increases with time if cholecystectomy is not performed. A systematic review of current guidelines by Hughes et al[29] showed that it is common practice not to recommend surgery until peripancreatic collections have completely resolved or at least 6 weeks after onset. However, data from the Dutch Pancreatitis Study Group[5] showed that the risk of biliary events in patients with necrotizing pancreatitis increased when cholecystectomy was postponed, with a turning point at 8 weeks after discharge for recurrent pancreatitis and at 10 weeks for recurrent biliary events overall. The risk for the latter increased significantly from 19% before 10 weeks to 31% after 10 weeks from discharge.

However, EC could be associated with an increased risk of perioperative complications in patients with moderately severe and severe ABP. Data on complications after EC for patients with moderately severe and severe ABP are heterogenous and superficial. Published studies[22-28] are primarily retrospective in design with small sample sizes, having been published 1 to 2 decades ago, when the management of AP was substantially different from the current trends. Fong et al[20] reported some reassuring data favoring EC performed during surgical necrosectomy in patients with necrotizing pancreatitis, showing no significant differences in postoperative mortality, overall morbidity, or bile duct injury compared with the control group. Similarly, Ackerman et al[45] compared 56 patients with moderately severe or severe ABP with 299 patients with mild ABP and showed that laparoscopic cholecystectomy could be performed safely, irrespective of severity. However, Nealon et al[26] assessed 78 patients with moderately severe or severe ABP who underwent EC and 109 patients who underwent DC, finding a complication rate after cholecystectomy of 44% in the former vs 5.5% in the latter.

To our knowledge, the current study is the largest one to confirm that moderately severe and severe ABP is independently associated with increased post-EC mortality and morbidity. The analysis highlighted a mortality rate of 15.6% and a morbidity rate of 30.3% in patients with moderately severe and severe ABP undergoing EC. However, these patients had relevant comorbidities more frequently compared with both control groups. Although the analysis confirmed the higher risk associated with EC in moderately severe and severe ABP, it identified some factors associated with detrimental outcomes in this subgroup of patients. The presence of severe complications of the ABP requiring surgical intervention, such as abdominal compartment syndrome, bowel ischemia, and bowel fistula, was independent associated with increased postoperative morbidity and mortality after EC. Similarly, the patient's age and the ASA score were independently associated with post-EC mortality. Additionally, the absence of preoperative bile duct clearance by ERCP was independently associated with postoperative morbidity.

Strengths and Limitations

This study has several distinct strengths. It represents the most extensive series, to our knowledge, assessing the impact of the timing of EC in patients with moderately severe and severe ABP. Additionally, as a multinational study with 151 participating centers across 42 different countries, the applicability of its results is high.

The study also has several limitations pertaining to the retrospective nature of the analysis. The MANCTRA-1 data set included centers with different levels of experience in treating ABP. Rates of cholecystectomy could be affected by local resources, with a possible underrepresentation of patients with EC. The influence of alcohol abuse as a potential confounder was not investigated. Inflammatory markers reported are those obtained at the diagnosis of ABP, but it was not possible to assess inflammatory markers at the time of the cholecystectomy. Some ECs could have been performed during surgical necrosectomy or other surgical interventions.

Conclusions

This cohort study of the MANCTRA-1 data set provided real-life data on a gray area of the literature, namely, the treatment of patients with moderately severe and severe ABP. It confirmed that moderately severe and severe ABP affected more frail patients and was associated with increased mortality and morbidity compared with patients with mild ABP undergoing EC and patients with moderately severe and severe ABP undergoing DC. Consequently, these patients should be treated carefully.

The presence of severe complications in patients with ABP requiring surgical intervention was independently associated with increased postoperative morbidity and mortality after EC. Similarly, the patient's age and the ASA score were independently associated with post-EC mortality, whereas the absence of a preoperative bile duct clearance by ERCP was independently associated with postoperative morbidity.

Future studies should investigate the outcomes of EC in comparable groups of patients, assessing the precise timing of the cholecystectomy and considering the risk of recurrent episodes of ABP. It will be important to analyze separately those patients undergoing EC concurrently with surgical interventions (ie, necrosectomy) vs those undergoing EC exclusively. However, based on the current evidence, it is recommended that older and more fragile patients with severe complications of moderately severe and severe ABP or those without bile duct clearance should not be considered for EC.

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