

Benefits of Therapeutic Endoscopic Retrograde Cholangiopancreatography in Patients Admitted
with Acute Gallstone Pancreatitis: A Nationwide Cohort Study

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ABSTRACT:

Benefits of Therapeutic Endoscopic Retrograde Cholangiopancreatography in Patients Admitted with Acute Gallstone Pancreatitis: A Nationwide Cohort Study

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Introduction:

Acute gallstone pancreatitis is the most common gastrointestinal cause for hospital admission. Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and/or stone extraction from the common bile duct could be beneficial in preventing recurrence. However, previous trials showed mixed results, with no effect on in-hospital outcomes such as mortality, complications, severity, and length of stay.

Aim:

To examine the association between ERCP during an admission for acute gallstone pancreatitis and subsequent emergent encounters and readmissions for recurrent pancreatitis and other causes.

Methods:

We performed a retrospective cohort study using the Truven Health Marketscan Databases, which capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services for subjects with employer based health insurance. All admissions from the inpatient admissions table with a primary diagnosis of acute pancreatitis were extracted using the ICD-9-CM code for acute pancreatitis, with gallstone pancreatitis identified by using additional codes for cholelithiasis. Details regarding inpatient admissions, inpatient services used, outpatient services used, and demographic variables were collected. The exposure was having undergone a therapeutic ERCP during the admission, defined as an ERCP with sphincterotomy and/or stone extraction. The primary outcome of interest was persistent / recurrent pancreatitis following discharge from the index admission. Secondary outcomes included all-cause emergent encounters, all-cause emergent readmissions, and all-cause emergent readmission within 30 days of discharge. Survival analysis methods with Cox proportional hazards models were used to examine the primary and secondary outcomes and to adjust for potential covariates. Logistic regression was used for the secondary outcome of all-cause emergent readmission within 30 days of discharge. To further examine the relationship between ERCP and recurrent pancreatitis in patients with acute gallstone pancreatitis, propensity scores for receiving ERCP were generated, and Cox proportional hazards models, stratified by cholecystectomy status, were subsequently fit with inverse probability weighting based on propensity scores.

Results:

There were 17,348 patients in our study who met inclusion criteria, of whom 3,375 patients (19.5%) underwent a therapeutic ERCP. Compared to those who did not undergo therapeutic

ERCP, patients who received therapeutic ERCP during the index admission tended to be female, have fewer comorbidities, and have a longer length of stay. Adjusting for patient characteristics, comorbidities, severity of acute pancreatitis, clinical factors, and cholecystectomy status, patients undergoing therapeutic ERCP had a lower hazard of recurrent pancreatitis following discharge from the index admission (HR 0.71, 95% CI 0.59-0.84, $p < 0.001$). This was especially true for patients who were discharged with gallbladder *in situ* (0.64, 95% CI 0.50 – 0.82, $p < 0.001$), but not for those who underwent cholecystectomy prior to discharge. The results of the analysis using adjustment for confounders via inverse probability weighting based on propensity for therapeutic ERCP further indicate that the hazard for recurrent pancreatitis is reduced for patients as long as the gallbladder remains *in situ* (HR 0.45, 95% CI 0.30 – 0.68, $p < 0.001$), but not once the gallbladder is removed (HR 0.96, 95% CI 0.66 – 1.39). Moreover, therapeutic ERCP was associated with lower hazard of all-cause emergent encounters (HR 0.86, 95% CI 0.80-0.92, $p < 0.001$) and all-cause readmissions following discharge (HR 0.81, 95% CI 0.71-0.91, $p = 0.001$).

Conclusion:

Therapeutic ERCP is associated with reduction in recurrent pancreatitis, all-cause emergent encounters, and all-cause readmissions following discharge in patients initially admitted for acute gallstone pancreatitis. This procedure should especially be considered in patients who are being discharged with gallbladder *in situ*.

BACKGROUND / INTRODUCTION

Acute pancreatitis is one of the leading causes of admission due to gastrointestinal disease in the United States, accounting for 274,000 discharges in 2012, an increase of 30% since 2000, and costing \$2.6 billion on an annual basis.¹⁻³ The clinical presentation of acute pancreatitis can be quite variable, with 15-20% of patients experiencing severe disease.^{4,5} The two most common etiologies of pancreatitis include alcohol intake and gallstones, with gallstones accounting for 40 – 70% of cases.⁶ Acute gallstone pancreatitis results from impaction of stones or sludge material that have migrated from the gallbladder into the common bile duct, resulting in obstruction of pancreatic outflow and inflammation of the pancreas. Hence, cholecystectomy is considered the definitive treatment for acute gallstone pancreatitis as it would prevent recurrent stone formation.^{3,7}

Endoscopic retrograde cholangiopancreatography (ERCP) is a minimally invasive endoscopic procedure performed by gastroenterologists for diagnostic purposes to assess the bile ducts and therapeutic purposes such as stone extraction or widening of the sphincter of Oddi via sphincterotomy. Theoretically, this could prevent recurrent gallstone pancreatitis by extracting existing stones or preventing impaction of migrating gallstones, allowing them to pass easily from the bile duct to the duodenum.

There have been several randomized controlled trials examining therapeutic ERCP for acute gallstone pancreatitis, with varying results and short follow-up times.⁸⁻¹³ Recent meta-analyses have also examined these trials in detail, but note that the trials were small and suffered from significant heterogeneity.¹⁴⁻¹⁷ Overall, there was no decrease in in-hospital mortality in patients receiving ERCP compared to those not receiving ERCP for acute gallstone

pancreatitis.¹⁷ There is a potential for reduced rate of local and systemic complications, but only in those trials which included patients with cholangitis.^{15,16} Thus, there is a lack of consensus on the benefits of ERCP in patients presenting with acute gallstone pancreatitis.¹⁸

While the above trials examined the short-term outcomes of ERCP in patients with acute gallstone pancreatitis, studies examining the longer-term outcomes such as recurrent pancreatitis and hospital readmissions are lacking. Therefore, we sought to assess the potential long-term benefits of a therapeutic ERCP for incident acute gallstone pancreatitis requiring hospitalization using a large, national, administrative claims database.

METHODS

Study Design & Data Source

We conducted a retrospective cohort study using medical claims data from the Truven Health MarketScan Research Databases, which capture person-specific enrollment, expenditures, and clinical inpatient and outpatient utilization from commercial health plans. These databases are comprised of claims of insured active employees and their dependents, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees, and Medicare-eligible retirees with employer-provided Medicare Supplemental plans. Within this set of databases, the Commercial Claims and Encounters Database is comprised of several linked tables containing data from paid claims and encounters, and detailed patient information. The Inpatient Admission Table contains records that summarize an individual hospitalization based on discharge claims and is linked to the Inpatient Services Table, which contains individual facility and professional encounters and services for a given hospitalization. The Outpatient Services Table contains encounters and

claims for services that were rendered in a doctor's office, hospital outpatient facility, emergency room, or other outpatient facility. The Enrollment Tables contain person-level enrollment records with demographic and plan information on users and non-users of services contained in the MarketScan Commercial Claims and Encounters. The structure of the final dataset for this study included variables linked from each of these tables.

Study Population & Data Sampling

All admissions from the Inpatient Admissions Table with a primary discharge diagnosis of acute pancreatitis based on the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) code 577.0 were identified between 2008 and 2014 (Figure 1) (See Appendix for all codes used in this study). Patients were classified as having acute pancreatitis due to gallstones if they carried a secondary code for gallstone disease (574.x), which includes cholelithiasis and choledocholithiasis. To ensure that only initial cases of acute gallstone pancreatitis were being examined, patients were excluded if they did not have at least one year of enrollment in the MarketScan databases prior to the index admission date. Additionally, patients were excluded if they did not have at least 30 days of enrollment following discharge from the index hospitalization. Other exclusion criteria included concomitant diagnoses of chronic pancreatitis or pancreatobiliary malignancy. Patients who died during the index hospitalization or were transferred to hospice care were also excluded.

Exposure

Patients were identified as having received therapeutic ERCP during the index admission if ICD-9-CM procedural or Current Procedural Terminology (CPT) codes for either ERCP with

sphincterotomy (ICD-9-CM 51.85; CPT 43262, 43277) or ERCP with stone extraction (ICD-9-CM 51.88, 52.94; CPT 43265) were present in the inpatient record for that admission. Patients who only underwent a diagnostic ERCP were not classified as having received therapeutic ERCP.

Outcomes

The primary outcome of interest was recurrent pancreatitis following discharge from the index admission. Recurrent pancreatitis was defined as an outpatient emergent office visit, emergency room visit, or emergent inpatient readmission with a primary diagnosis of either acute pancreatitis, chronic pancreatitis, other pancreatitis, or cyst / pseudocyst of the pancreas. Secondary outcomes included all-cause emergent encounters, all-cause emergent readmissions, and emergent readmission within 30 days following discharge from the index admission.

Other Variables

We examined factors that could potentially confound the relationship between therapeutic ERCP and recurrent pancreatitis. Patient demographic variables included age at the time of index admission, sex, region, and insurance plan type. Insurance plan type was recoded into a three-level variable that included HMO capitated point of service plan, low out of pocket plan, and high out of pocket plan.

The Elixhauser Comorbidity Index was used to generate a measure of comorbidity for each patient.¹⁹ This index is a method for categorizing comorbid conditions of patients based on ICD-9-CM codes and consists of 30 chronic disease entities that are associated with adverse outcomes in hospitalized patients. The use of this index has been validated in large

administrative claims data.²⁰⁻²² Patients were identified as having a specific comorbidity if they experienced an outpatient or inpatient encounter for that condition in the year prior to their index admission for acute gallstone pancreatitis.

Clinical factors during the index admission that could potentially influence the occurrence of therapeutic ERCP and affect outcome were also examined in detail, and included severity of acute pancreatitis, length of hospital stay for the index admission, the presence of common bile duct obstruction, common bile duct stones without obstruction, cholangitis, and jaundice. Per the Revised Atlanta Criteria, severe acute pancreatitis is defined as the presence of persistent organ failure based on the modified Marshall scoring system.^{3,4} Patients were identified as having severe acute pancreatitis in their index admission if they carried concomitant diagnosis codes for sepsis with organ failure, systemic inflammatory response syndrome with organ failure, acute renal failure, respiratory failure, neurological failure, or myocardial infarction. The use of mechanical ventilation was also used to classify patients as having severe acute pancreatitis. See Appendix tables for all codes used in this study.

Procedure codes from inpatient and outpatient encounters dated prior to the index admission were examined to see if the patients had a history of prior cholecystectomy. Patients who carried a procedure code for cholecystectomy as part of their admission for acute gallstone pancreatitis were considered to have undergone a cholecystectomy during the index admission. Patients were, therefore, classified as post-cholecystectomy at the time of discharge if they had undergone cholecystectomy prior to the index admission for acute pancreatitis or if they underwent cholecystectomy during the index admission. For those patients who underwent cholecystectomy after discharge from the index admission, the risk of outcomes was allowed to vary between the time until cholecystectomy was performed and the time following the

cholecystectomy, at which point those patients were considered to be post-cholecystectomy. All other patients were considered to have not undergone cholecystectomy. In this way, cholecystectomy status was treated as a time-varying covariate in our analysis model.

Statistical Analysis

The overall distributions of variables were examined with respect to therapeutic ERCP status during the index admission. For continuous variables, means and standard deviations are reported. For categorical variables, proportions of patients within each category are reported. The Elixhauser comorbidity index was recoded as an ordered categorical variable with patients having either zero comorbidities, one comorbidity, two comorbidities, or greater than or equal to three comorbidities. Differences between continuous variables with respect to therapeutic ERCP status were tested with the Student T-test, while differences between proportions between the categorical variables were tested with the Chi-square test.

Patients were followed from discharge from the index admission until an emergent encounter, emergent encounter for pancreatitis, any emergent readmission, emergent readmission for pancreatitis, death if recorded, or until the end of enrollment in the MarketScan databases. Multivariable Cox proportional hazards regression models were used to examine the primary outcome and the secondary outcomes of all-cause emergent encounters and all-cause emergent readmissions. A multivariate logistic regression model was used to examine emergent readmission within 30 days of discharge. The models were adjusted for demographic variables (age, sex, region, and insurance plan type), patient comorbidities (Elixhauser index), clinical variables regarding the index admission (length of initial hospital stay, severity of pancreatitis, the presence of common bile duct obstruction, common bile duct stones, cholangitis, and

jaundice), and cholecystectomy status as a time-varying covariate. Hazard ratios and odds ratios of therapeutic ERCP for the occurrence of the outcomes were the primary measures of association of interest.

For the Cox proportional hazards models, the proportionality of hazards assumption was tested based on Schoenfeld residuals after fitting the Cox models. The Cox model was refit stratified on those variables for which the proportionality of hazards assumption was questionable to see if there was a change in the results. Additionally, Kaplan-Meier observed survival curves, Cox-predicted curves, and log-log plots were examined visually to see if the variables satisfied the proportionality of hazards assumption.

To better understand the relationship between therapeutic ERCP and the primary outcome of recurrent pancreatitis with respect to cholecystectomy status, we calculated propensity scores for each patient to undergo therapeutic ERCP. We fit a saturated logistic regression model with therapeutic ERCP as the outcome and all the same covariates as above except for cholecystectomy status, along with interactions and second order polynomials for each covariate. Inverse probability-weighted Cox proportional hazards models for recurrent pancreatitis were then fit separately for patients who were pre-cholecystectomy and post-cholecystectomy, using the propensity scores for therapeutic ERCP, while also clustering at the individual patient level. In this way, the proportionality of hazards assumption was relaxed for all the covariates as part of the propensity score model, and the hazards were observed stratified on cholecystectomy status in a time-varying way. Additionally, by clustering at the individual level, the resulting hazard ratios are adjusted for individual fixed effects, representing individual level hazard ratios. Adjusted survival curves were generated using the Kaplan-Meier method.

All statistical analyses were performed using *Stata Statistical Software: Release 14* (StataCorp LP, College Station, TX, 2015). Additional analyses and data visualization were performed using *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, Vienna, Austria, 2017).

RESULTS

Overall, there were 17,348 patients in our study who met inclusion criteria, of whom 3,375 patients (19.5%) underwent a therapeutic ERCP (Figure 1). Table 1 shows the distribution of demographic variables and clinical factors with respect to having received a therapeutic ERCP during the index admission. There were no differences between those patients who did or did not receive a therapeutic ERCP with respect to age, insurance plan type, and severity of acute pancreatitis. Compared to those who did not undergo therapeutic ERCP, patients who underwent therapeutic ERCP during the index admission tended to be female (62.3% vs 59.1%, $p < 0.001$), have overall lower number of comorbidities (42.5% with 0 vs 38.6% with 0, $p < 0.001$), and longer length of stay (mean 5.4 days vs 4.7 days, $p < 0.001$). When compared to patients who did not undergo therapeutic ERCP, a higher percentage of patients who underwent therapeutic ERCP had bile duct obstruction, bile duct stones, cholangitis, and jaundice ($p < 0.001$).

In terms of cholecystectomy status, 58.3% of patients underwent cholecystectomy during the index admission, while 3.8% had a history of prior cholecystectomy within the database. Comparing patients who underwent therapeutic ERCP to those who did not, there was no difference in proportion of patients who underwent cholecystectomy during the index admission, but a higher proportion had undergone cholecystectomy prior to admission among those who

received therapeutic ERCP (9.9% vs 2.4%, $p < 0.001$). Of the 6,575 patients who had not received a cholecystectomy prior to discharge from the index admission, 58.3% underwent cholecystectomy at some point following discharge, with 61.1% of those occurring within 30 days of the discharge (median time to cholecystectomy 22 days). A lower percentage of patients had cholecystectomy post-discharge among those who underwent therapeutic ERCP compared to those who did not (15.3% vs 23.7%, $p < 0.001$).

Univariate Outcomes

Results of the univariate analyses for the outcomes are shown in Table 2. Overall median follow-up time was 18.1 months (interquartile range (IQR) 8.1-45.8 months). 1,595 patients (9.2%) experienced an emergent encounter for recurrent pancreatitis, with a lower percentage among those who underwent therapeutic ERCP (6.2% vs 9.9%, $p < 0.001$). A lower percentage of patients experienced an emergent encounter (40.2% vs 45.7%) and an emergent readmission (13.8% vs 17.5%) for any cause among those who underwent therapeutic ERCP (both $p < 0.001$). There was no difference in the risk of emergent readmissions within 30 days between the two groups, however.

Multivariate Outcomes

Results of the Cox proportional hazards model for the primary outcome of recurrent pancreatitis are shown in Table 3. The median time at risk (follow-up time) following discharge was 16.1 months (IQR 6.4 to 32.6 months). Adjusting for demographic variables, clinical factors in the index admission, severity of acute pancreatitis, and cholecystectomy status, patients undergoing therapeutic ERCP had a lower hazard of recurrent pancreatitis following discharge

from the index admission (HR 0.71, 95% CI 0.59 to 0.84, $p < 0.001$) (Figure 2A). Refitting the model stratifying on cholecystectomy status did not alter the results.

Patients who underwent therapeutic ERCP had a lower hazard for the secondary outcome of emergent encounters for any cause compared to those who did not, adjusting for the same demographic variables, comorbidities, clinical factors, severity of acute pancreatitis, and cholecystectomy status (HR 0.86, 95% CI 0.80 to 0.92, $p < 0.001$) (Figure 2B). Patients who underwent therapeutic ERCP also had a lower adjusted hazard of emergent readmission for any cause (HR 0.81, 95% CI 0.71 to 0.91, $p = 0.001$) (Figure 2C). Refitting the models stratifying on the variables that were questionable for the proportional hazards assumption did not alter the results (data not shown). The results of the logistic regression indicate that there was no difference in adjusted odds for the outcome of readmission within 30 days for any cause between those who underwent therapeutic ERCP and those who did not (OR 0.86, 95% CI 0.68 to 1.08, $p = 0.190$) (Figure 2D).

We performed subgroup analyses for the primary outcome of recurrent pancreatitis in patients who were discharged with gallbladder *in situ* ($n = 6,575$) and in those who had a cholecystectomy during the index admission before being discharged ($n = 10,106$). Among patients who were discharged with gallbladder *in situ*, even after adjusting for interval cholecystectomy, patients who underwent therapeutic ERCP had a significantly lower hazard for recurrent pancreatitis when compared to those who did not (HR 0.64, 95% CI 0.50 to 0.82, $p < 0.001$) (Figure 3A). However, in the group of patients who had an index cholecystectomy, therapeutic ERCP was not associated with reduced recurrent pancreatitis (HR 0.81, 95% CI 0.61 to 1.08, $p = 0.148$) (Figure 3B).

The results of the inverse probability-weighted Cox proportional hazards model indicate that for patients with acute gallstone pancreatitis who were pre-cholecystectomy at any point in time post-discharge, undergoing therapeutic ERCP was associated with a significantly lower hazard of recurrent pancreatitis compared to not undergoing therapeutic ERCP (HR 0.45, 95% CI 0.30 to 0.68, $p < 0.001$) (Figure 4A). However, for patients who were post-cholecystectomy at any point in time post-discharge, there was no significant difference in hazard of recurrent pancreatitis between those who underwent therapeutic ERCP and did not undergo therapeutic ERCP (HR 0.96, 95% CI 0.66 to 1.39) (Figure 4B).

DISCUSSION

In this retrospective cohort study using commercial claims data from across the United States, the rate of recurrent pancreatitis requiring an emergent outpatient encounter or readmission is high (9.2% over a median follow-up time of 18.1 months) for patients discharged after an initial admission for acute gallstone pancreatitis. Patients undergoing therapeutic ERCP during the initial admission for acute gallstone pancreatitis had a lower hazard of recurrent pancreatitis compared to patients who did not undergo therapeutic ERCP, even after adjusting for patient characteristics, comorbidities, pancreatitis severity, clinical factors, and cholecystectomy status. Moreover, patients undergoing therapeutic ERCP had a lower adjusted hazard of emergent encounter for any cause and lower adjusted hazard for readmission for any cause.

Cholecystectomy is considered the definitive treatment for patients who are admitted with acute gallstone pancreatitis, as it should prevent further formation of gallstones and, thus, reduce the risk of recurrent pancreatitis. A meta-analysis of eight cohort studies and one

randomized trial showed a readmission rate of 0% for those patients undergoing cholecystectomy during the index admission.²³ Therefore, for patients with acute gallstone pancreatitis, current guidelines recommend that a cholecystectomy should be performed prior to discharge from the index admission and in no case beyond 2-4 weeks following discharge.^{3,24,25} A recent study using MarketScan data determined that adherence to these guidelines results in a decrease in subsequent admissions for both acute and chronic pancreatitis.²⁶

It has been hypothesized that ERCP with sphincterotomy could be a safe alternative for patients with gallbladder left in-situ, and guidelines do suggest delaying cholecystectomy in those with severe acute gallstone pancreatitis.^{27,28} In our study, while high severity of pancreatitis was associated with lower rates of guideline recommended cholecystectomy, severity of pancreatitis was not associated with occurrence of therapeutic ERCP. Among patients who did not undergo cholecystectomy prior to discharge, those who received a therapeutic ERCP had a much lower hazard of recurrent pancreatitis. However, in these patients, interval cholecystectomy was associated with an even lower adjusted hazard of recurrent pancreatitis than therapeutic ERCP (Figure 3A). Moreover, in our inverse probability weighted analysis based on propensity for therapeutic ERCP, there was no further benefit to having undergone a therapeutic ERCP once the gallbladder was removed post-discharge. This would indicate that despite the benefits seen with a therapeutic ERCP in patients discharged with gallbladder *in situ*, an interval cholecystectomy as recommended by guidelines is still essential to the prevention of recurrent pancreatitis. For those that, for whatever reason, absolutely cannot undergo a cholecystectomy, therapeutic ERCP could still reduce the risk of recurrent pancreatitis significantly.

A report presenting the findings of a recent review of acute pancreatitis cases in the United Kingdom's National Health Service (NHS) noted that 20% of patients experienced multiple admissions for acute pancreatitis, with the same etiology for acute pancreatitis in nearly all readmissions.²⁹ Gallstones were the cause of 30% of recurrent admissions during that study. Estimates of recurrence rates following acute gallstone pancreatitis vary widely.³⁰ A systematic review of observational studies found that 95 out of 515 (18%) patients who had not undergone a cholecystectomy were readmitted for recurrent biliary events, 43 of which (8% overall) were due to recurrent gallstone pancreatitis.²³ We show an overall rate of emergent encounter due to pancreatitis following discharge from the index admission as 9.2%, consistent with previous findings.

The literature examining rates of recurrent pancreatitis and other long-term outcomes following therapeutic ERCP is sparse, and limited to small, observational, descriptive studies, with variable follow-up times and heterogenous outcomes.^{27,28,31-35} Some of these studies only followed elderly patients who could not receive a cholecystectomy, with mean age greater than 70.^{27,28,35,32,31} The study with the longest follow-up time followed less than 100 patients for a median of 84 months, presented descriptive outcomes only, and did not properly account for patients lost to follow up.³² These studies show the rate of recurrent gallstone pancreatitis following ERCP ranging from 0.9 to 6.4%, but none had an appropriate comparison group.³⁰ Our study has a large sample size consisting of younger patients from across the United States. For those undergoing therapeutic ERCP, we not only show that the rate of recurrent pancreatitis following discharge from the index admission is 6.2%, but also that this rate is significantly lower than for those who did not undergo therapeutic ERCP.

The results of our study differ from prior literature. We found that therapeutic ERCP during the index admission was associated with a lower risk of emergent encounter for any cause and readmissions for any cause (40.2% vs 45.7%). This is a somewhat surprising finding given that most studies have shown that therapeutic ERCP does not in fact prevent systemic complications of acute pancreatitis and does not alter predicted severity, which is likely major determinant of long-term outcome.¹⁶ It is likely that these studies did not have the prolonged follow-up period needed to see the potential all-cause benefits of therapeutic ERCP in patients with acute gallstone pancreatitis. With regards to the all-cause emergent readmissions, almost half (47.5%) of the readmissions in our study were secondary to a pancreatic or biliary causes, and there was no influence of therapeutic ERCP when only non-biliopancreatic emergent readmissions were examined (data not shown). Thus, the primary benefit of therapeutic ERCP with respect to all-cause emergent readmissions is likely through the prevention of biliopancreatic readmissions.

Our study is not without its limitations, however. While the underlying population sampled for this study receives care from across the United States, the population is not necessarily representative of the national population overall. Given that the database is made up of insurance claims from employer-based, private insurance, the population that comprises this dataset does not include older individuals on Medicare, individuals receiving care through Medicaid, or uninsured individuals. Moreover, given the nature of claims data, important variables such as lab values and vital signs could not be assessed. The determination of severe acute pancreatitis resulted from applying ICD-9-CM codes for clinical findings that would be consistent with the Atlanta Revision.^{4,36} We were not able to assess imaging findings such as acute necrotic collections that would also contribute to severity or that might contribute to later

admissions or office visits. While we adjusted for many appropriate confounders in this retrospective cohort study, there is still a possibility of residual confounding of our associations due to unmeasured variables.

The study relies on ICD-9-CM diagnostic and procedure codes, which can be incomplete for encounters. However, this database also uses CPT codes for individual encounters, allowing us to capture more variables. With respect to our intervention, we were able to define a therapeutic ERCP specifically as it would pertain to acute gallstone pancreatitis using a combination of ICD-9-CM and CPT codes. Typically, studies defined early ERCP as ERCP within the first 72 hours following admission.^{9,13,14,37} We were not, however, able to accurately determine the timing of ERCP during the index admission for all ERCPs, and thus this was not examined.

Our definition of recurrent pancreatitis rested on the assumption that if the patient was discharged from the hospital, it was because the index episode of pancreatitis had resolved. However, it is possible that there are cases that we classify as recurrent pancreatitis that are persistence or sequelae of the original episode of pancreatitis. This is difficult to sort out in prior studies as well, though our results remain robust as they are based on emergent encounters only and are still valid in terms of interpreting these encounters as due to pancreatitis and analyzing healthcare utilization.

This is the first and largest study comparing the longer-term outcomes of patients with acute gallstone pancreatitis who did or did not undergo therapeutic ERCP. The strengths of our study lie in the fact that the data source is a large, administrative dataset, resulting in a sufficiently large sample size, representing a population of patients who receive care throughout the United States. The time course of the study allowed for patient characteristics and

comorbidities to be gleaned from a full year of data prior to the index admission, and for patients to be followed for a significant period following discharge. We performed a more thorough assessment of recurrent pancreatitis because services from both inpatient and outpatient encounters were available.

We were able to adjust for possible confounders including demographic variables, comorbidities, clinical factors, severity of acute pancreatitis, and cholecystectomy status using survival analysis, allowing us to fully capture data from patients who were either lost to follow-up or who did not experience the outcomes prior to the end of the study period. For the Cox proportional hazards model, the hazard of outcome was allowed to vary with the patient's cholecystectomy status, based on whether they were pre-cholecystectomy or post-cholecystectomy at any given time after discharge from the index admission. This allowed for a more thorough adjustment for cholecystectomy status in order to truly examine the relationship between therapeutic ERCP and the outcomes. Moreover, by using propensity scores and individual level clustering to generate a fixed-effects survival model weighted by inverse probabilities, we were able to assess the impact of therapeutic ERCP on an individual level stratified by cholecystectomy status, thereby relaxing many of the limitations of the Cox proportional hazards model, lending robustness to our results.

In conclusion, therapeutic ERCP in patients admitted for acute gallstone pancreatitis is associated with reduced rates of recurrent pancreatitis, reduced rates of all-cause emergent encounters, and reduced rates of readmissions following discharge from the index admission. There may be particular benefit to ERCP in patients who are not candidates for definitive cholecystectomy, or in whom cholecystectomy will be delayed, as cholecystectomy is still the definitive treatment. Further studies should continue to elucidate factors that would identify the

patients most likely to benefit from therapeutic ERCP, with consideration to randomized trials with long follow-up times.

1. Peery, A. F. *et al.* Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* **143**, 1179-1187.e1–3 (2012).
2. Singla, A. *et al.* National hospital volume in acute pancreatitis: analysis of the Nationwide Inpatient Sample 1998-2006. *HPB* **11**, 391–397 (2009).
3. Tenner, S., Baillie, J., DeWitt, J. & Vege, S. S. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. *Am. J. Gastroenterol.* **108**, 1400–1415 (2013).
4. Banks, P. A. *et al.* Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* **62**, 102–111 (2013).
5. Banks, P. A., Freeman, M. L. & Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am. J. Gastroenterol.* **101**, 2379–2400 (2006).
6. Gullo, L. *et al.* Acute pancreatitis in five European countries: etiology and mortality. *Pancreas* **24**, 223–227 (2002).
7. Gurusamy, K. S., Nagendran, M. & Davidson, B. R. Early versus delayed laparoscopic cholecystectomy for acute gallstone pancreatitis. *Cochrane Database Syst. Rev.* CD010326 (2013). doi:10.1002/14651858.CD010326.pub2
8. Neoptolemos, J. P. *et al.* Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet Lond. Engl.* **2**, 979–983 (1988).
9. Fan, S. T. *et al.* Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N. Engl. J. Med.* **328**, 228–232 (1993).

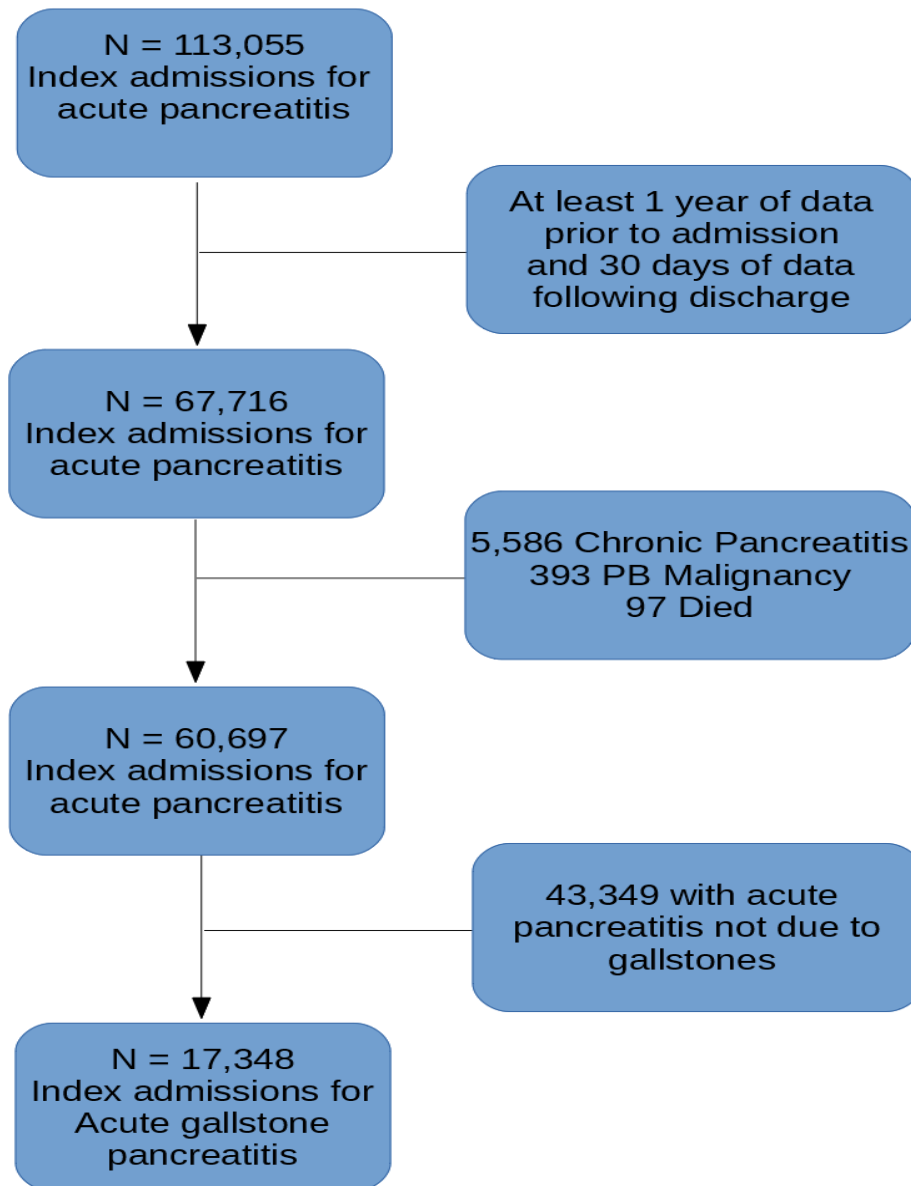
10. Fölsch, U. R., Nitsche, R., Lüdtker, R., Hilgers, R. A. & Creutzfeldt, W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N. Engl. J. Med.* **336**, 237–242 (1997).
11. Zhou, M.-Q., Li, N.-P. & Lu, R.-D. Duodenoscopy in treatment of acute gallstone pancreatitis. *Hepatobiliary Pancreat. Dis. Int. HBPD INT* **1**, 608–610 (2002).
12. Acosta, J. M. *et al.* Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. *Ann. Surg.* **243**, 33–40 (2006).
13. Oría, A. *et al.* Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Ann. Surg.* **245**, 10–17 (2007).
14. Moretti, A. *et al.* Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver* **40**, 379–385 (2008).
15. Petrov, M. S., Uchugina, A. F. & Kukosh, M. V. Does endoscopic retrograde cholangiopancreatography reduce the risk of local pancreatic complications in acute pancreatitis? A systematic review and metaanalysis. *Surg. Endosc.* **22**, 2338–2343 (2008).
16. Tse, F. & Yuan, Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst. Rev.* CD009779 (2012). doi:10.1002/14651858.CD009779.pub2
17. Burstow, M. J. *et al.* Meta-Analysis of Early Endoscopic Retrograde Cholangiopancreatography (ERCP) ± Endoscopic Sphincterotomy (ES) Versus Conservative

- Management for Gallstone Pancreatitis (GSP). *Surg. Laparosc. Endosc. Percutan. Tech.* **25**, 185–203 (2015).
18. van Geenen, E.-J. M. *et al.* Lack of consensus on the role of endoscopic retrograde cholangiography in acute biliary pancreatitis in published meta-analyses and guidelines: a systematic review. *Pancreas* **42**, 774–780 (2013).
 19. Elixhauser, A., Steiner, C., Harris, D. R. & Coffey, R. M. Comorbidity measures for use with administrative data. *Med. Care* **36**, 8–27 (1998).
 20. Southern, D. A., Quan, H. & Ghali, W. A. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. *Med. Care* **42**, 355–360 (2004).
 21. Gutacker, N., Bloor, K. & Cookson, R. Comparing the performance of the Charlson/Deyo and Elixhauser comorbidity measures across five European countries and three conditions. *Eur. J. Public Health* **25 Suppl 1**, 15–20 (2015).
 22. Fortin, Y. *et al.* External validation and comparison of two variants of the Elixhauser comorbidity measures for all-cause mortality. *PloS One* **12**, e0174379 (2017).
 23. van Baal, M. C. *et al.* Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. *Ann. Surg.* **255**, 860–866 (2012).
 24. Forsmark, C. E., Baillie, J., AGA Institute Clinical Practice and Economics Committee & AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology* **132**, 2022–2044 (2007).
 25. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol. Off. J. Int. Assoc. Pancreatol. IAP AI* **13**, e1-15 (2013).

26. Kamal, A. *et al.* Effectiveness of Guideline-Recommended Cholecystectomy to Prevent Recurrent Pancreatitis. *Am. J. Gastroenterol.* **112**, 503–510 (2017).
27. Bignell, M., Dearing, M., Hindmarsh, A. & Rhodes, M. ERCP and endoscopic sphincterotomy (ES): a safe and definitive management of gallstone pancreatitis with the gallbladder left in situ. *J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract* **15**, 2205–2210 (2011).
28. Vázquez-Lglesias, J. L. *et al.* Endoscopic sphincterotomy for prevention of the recurrence of acute biliary pancreatitis in patients with gallbladder in situ: long-term follow-up of 88 patients. *Surg. Endosc.* **18**, 1442–1446 (2004).
29. O'Reilly, D. A., McPherson, S. J., Sinclair, M. T. & Smith, N. Lessons from a national audit of acute pancreatitis: A summary of the NCEPOD report 'Treat the Cause'. *Pancreatol. Off. J. Int. Assoc. Pancreatol. IAP AI* (2017). doi:10.1016/j.pan.2017.02.010
30. van Geenen, E. J. M., van der Peet, D. L., Mulder, C. J. J., Cuesta, M. A. & Bruno, M. J. Recurrent acute biliary pancreatitis: the protective role of cholecystectomy and endoscopic sphincterotomy. *Surg. Endosc.* **23**, 950–956 (2009).
31. Uomo, G., Manes, G., Laccetti, M., Cavallera, A. & Rabitti, P. G. Endoscopic sphincterotomy and recurrence of acute pancreatitis in gallstone patients considered unfit for surgery. *Pancreas* **14**, 28–31 (1997).
32. Hammarström, L. E., Stridbeck, H. & Ihse, I. Effect of endoscopic sphincterotomy and interval cholecystectomy on late outcome after gallstone pancreatitis. *Br. J. Surg.* **85**, 333–336 (1998).
33. Gislason, H. *et al.* Endoscopic sphincterotomy in acute gallstone pancreatitis: a prospective study of the late outcome. *Eur. J. Surg. Acta Chir.* **167**, 204–208 (2001).

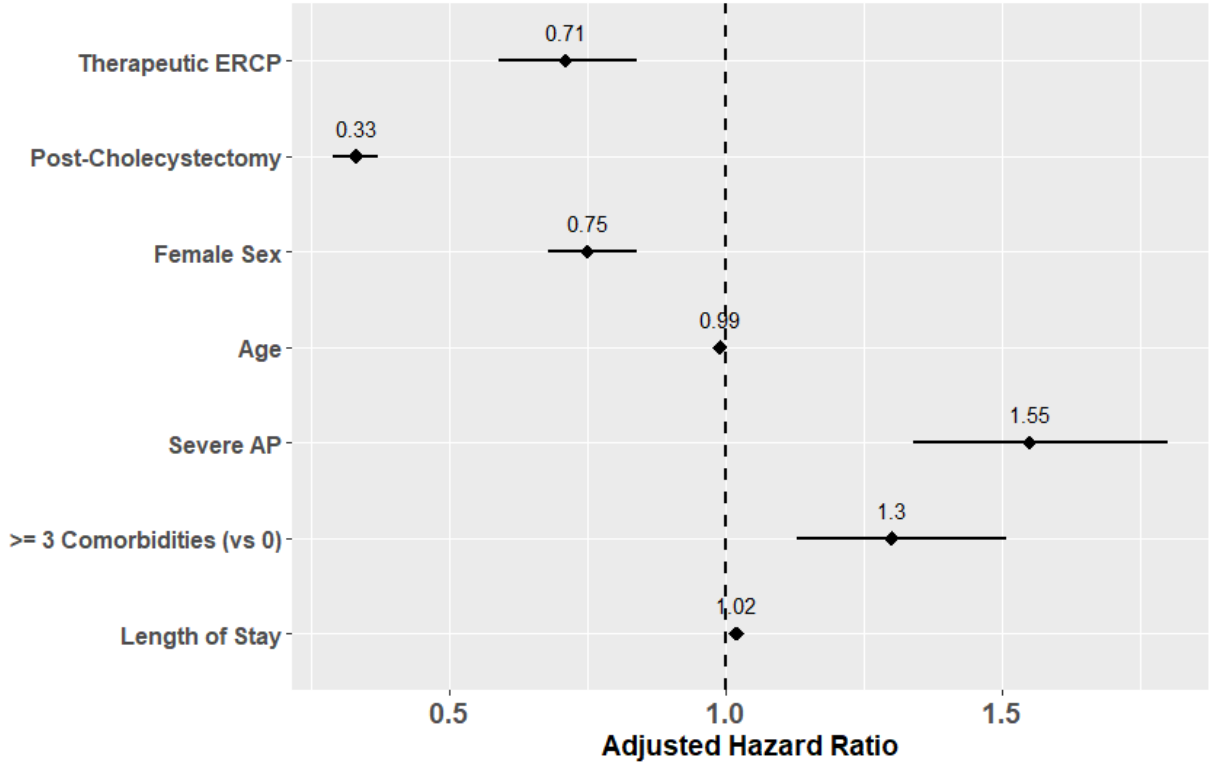
34. Kaw, M., Al-Antably, Y. & Kaw, P. Management of gallstone pancreatitis: cholecystectomy or ERCP and endoscopic sphincterotomy. *Gastrointest. Endosc.* **56**, 61–65 (2002).
35. Billi, P., Barakat, B., D'Imperio, N. & Pezzilli, R. Relapses of biliary acute pancreatitis in patients with previous attack of biliary pancreatitis and gallbladder in situ. *Dig. Liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver* **35**, 653–655 (2003).
36. Zhao, K., Adam, S. Z., Keswani, R. N., Horowitz, J. M. & Miller, F. H. Acute Pancreatitis: Revised Atlanta Classification and the Role of Cross-Sectional Imaging. *Am. J. Roentgenol.* **205**, W32–W41 (2015).
37. van Santvoort, H. C. *et al.* Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann. Surg.* **250**, 68–75 (2009).

Figure 1: Creation of dataset from MarketScan



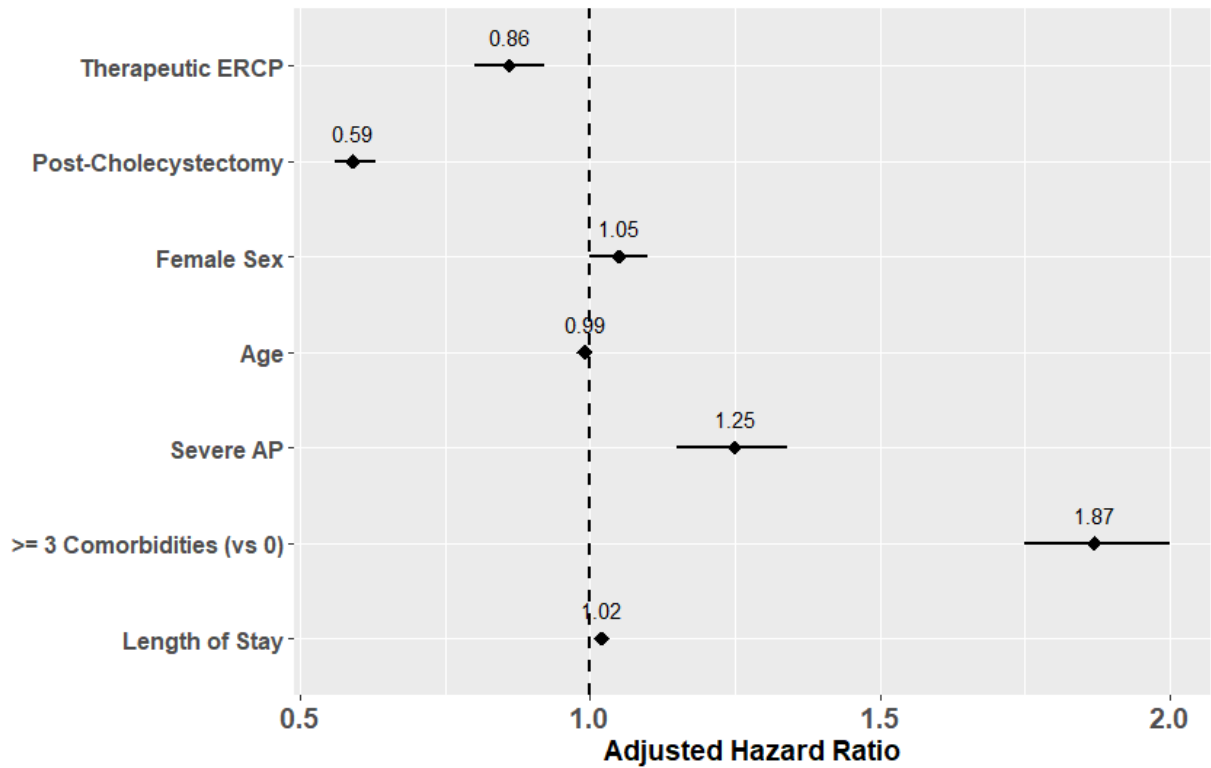
Abbreviations: PB, pancreaticobiliary

Figure 2A: Hazard ratios for selected covariates from the Cox proportional hazards model for the primary outcome of recurrent pancreatitis. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



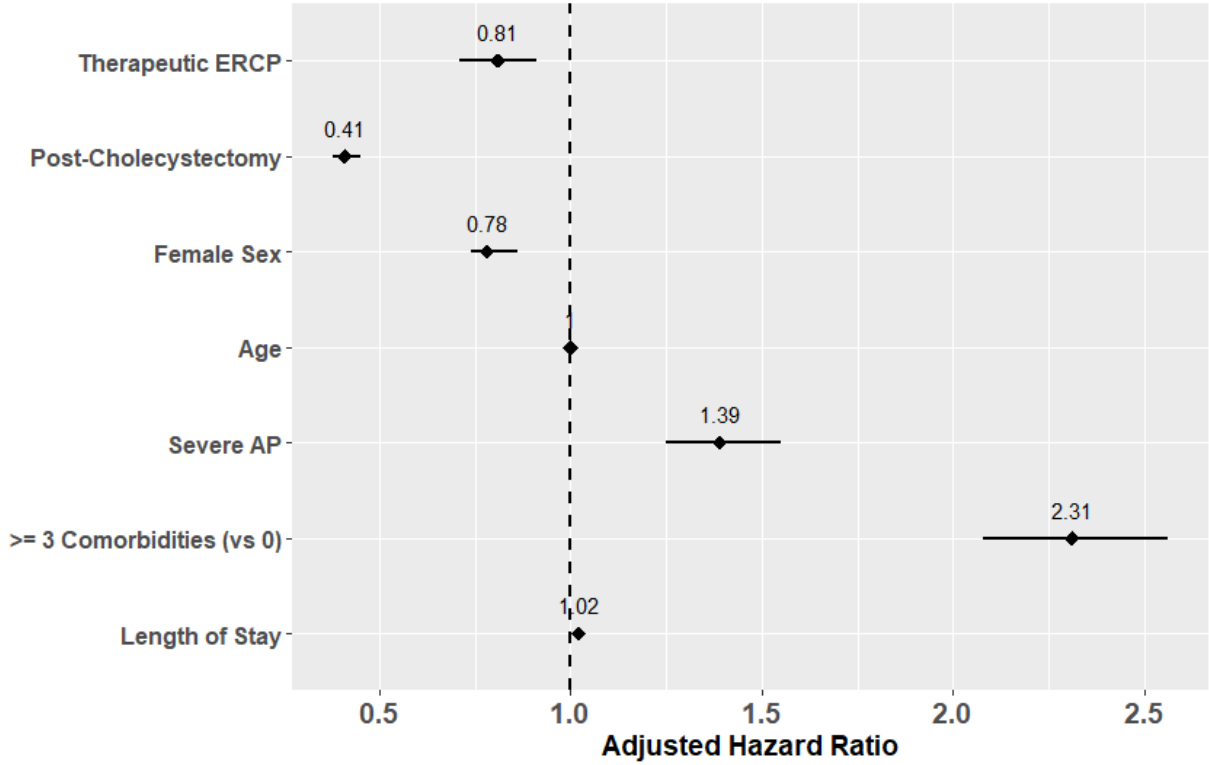
Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 2B: Hazard ratios for selected covariates from the Cox proportional hazards model for the secondary outcome of any emergent encounter. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



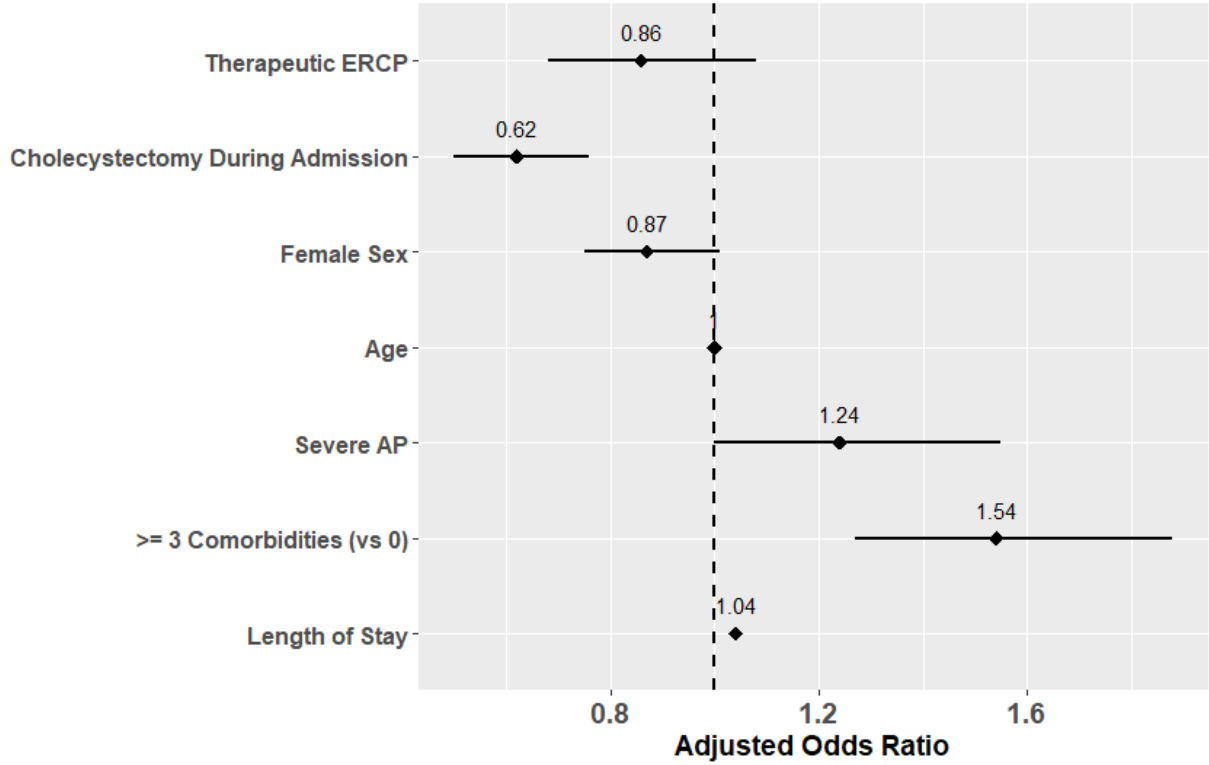
Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 2C: Hazard ratios for selected covariates from the Cox proportional hazards model for the secondary outcome of all-cause emergent readmission. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



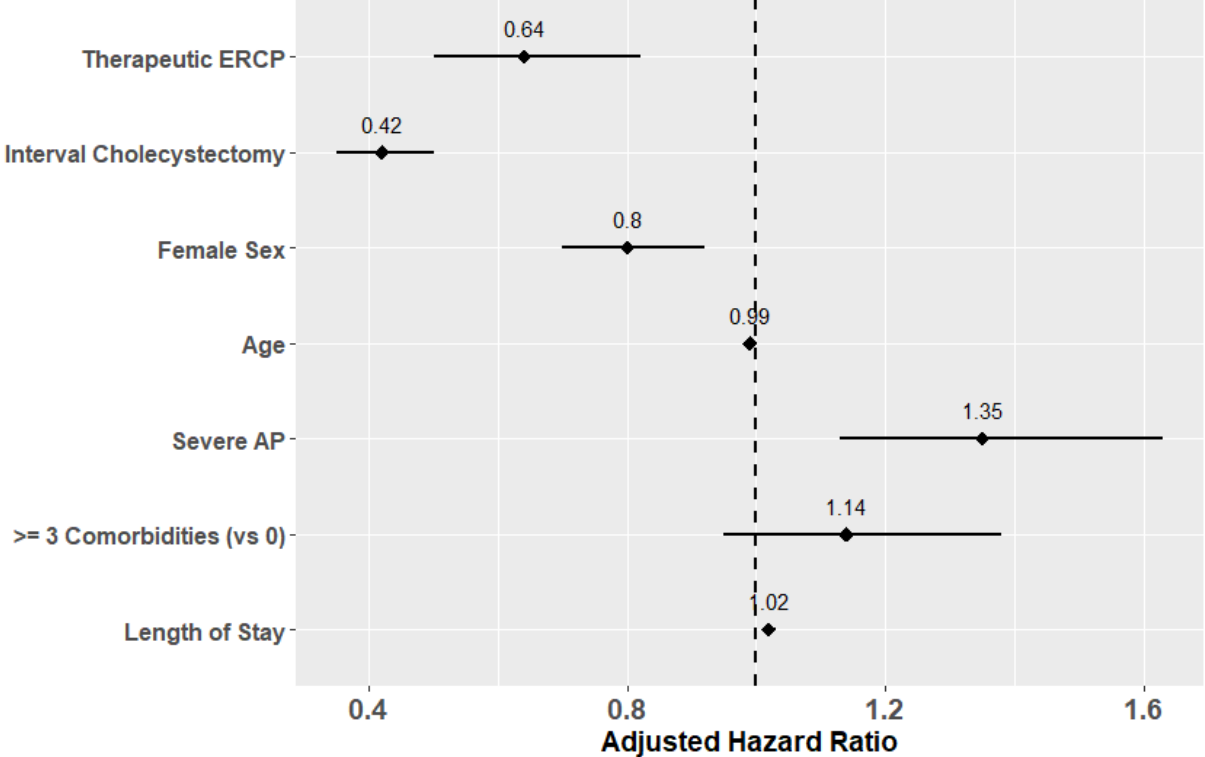
Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 2D: Odds ratios for selected covariates from the logistic regression model for the secondary outcome of all-cause emergent readmission within 30 days of discharge. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



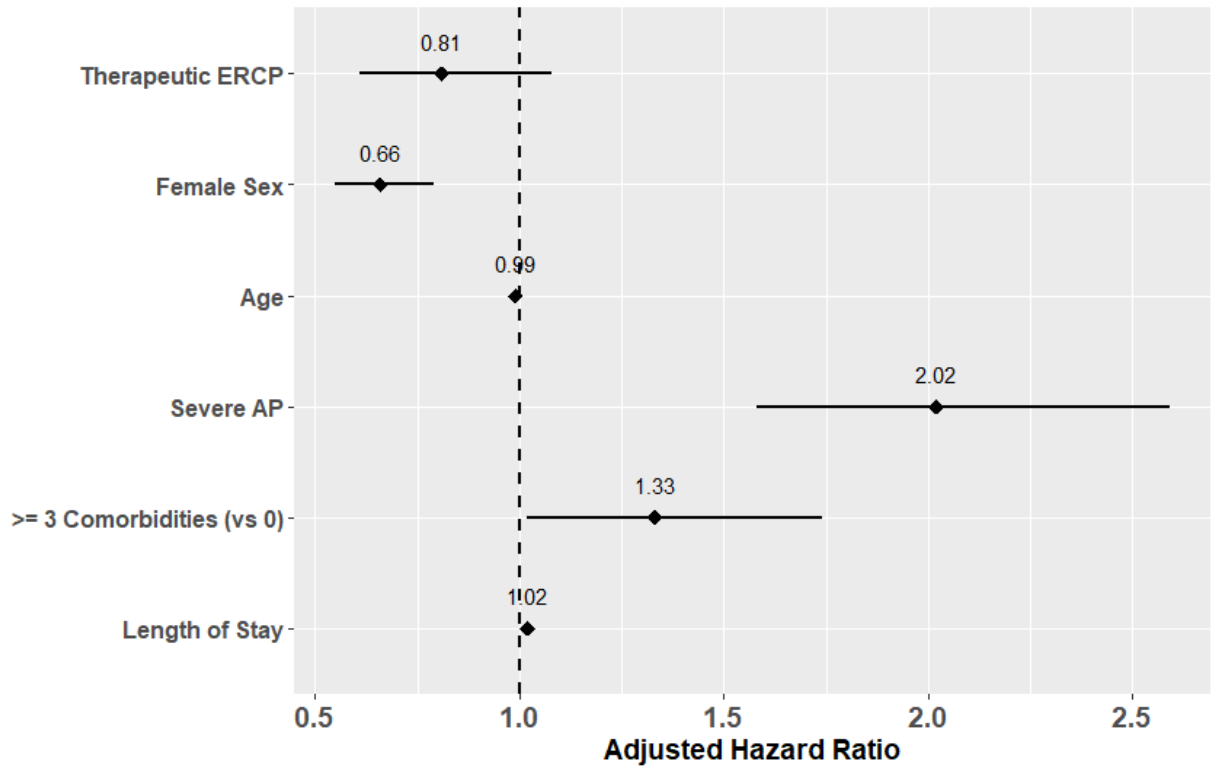
Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 3A: Hazard ratios for selected covariates from the Cox proportional hazards model for the primary outcome of recurrent pancreatitis in the subgroup of patients with gall-bladder *in situ* at time of discharge. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 3B: Hazard ratios for selected covariates from the Cox proportional hazards model for the primary outcome of recurrent pancreatitis in the subgroup of patients who had undergone a cholecystectomy during the index admission. Additional variables adjusted for included insurance plan type, region of country, presence of common bile duct stones or obstruction, cholangitis, and jaundice.



Abbreviations: AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography

Figure 4A: Kaplan-Meier survival curve of recurrent pancreatitis by therapeutic ERCP status for patients who were pre-cholecystectomy at any point in time following discharge. This is adjusted for patient demographics, comorbidities, and severity of pancreatitis by inverse probability-weighting of therapeutic ERCP via propensity scores.

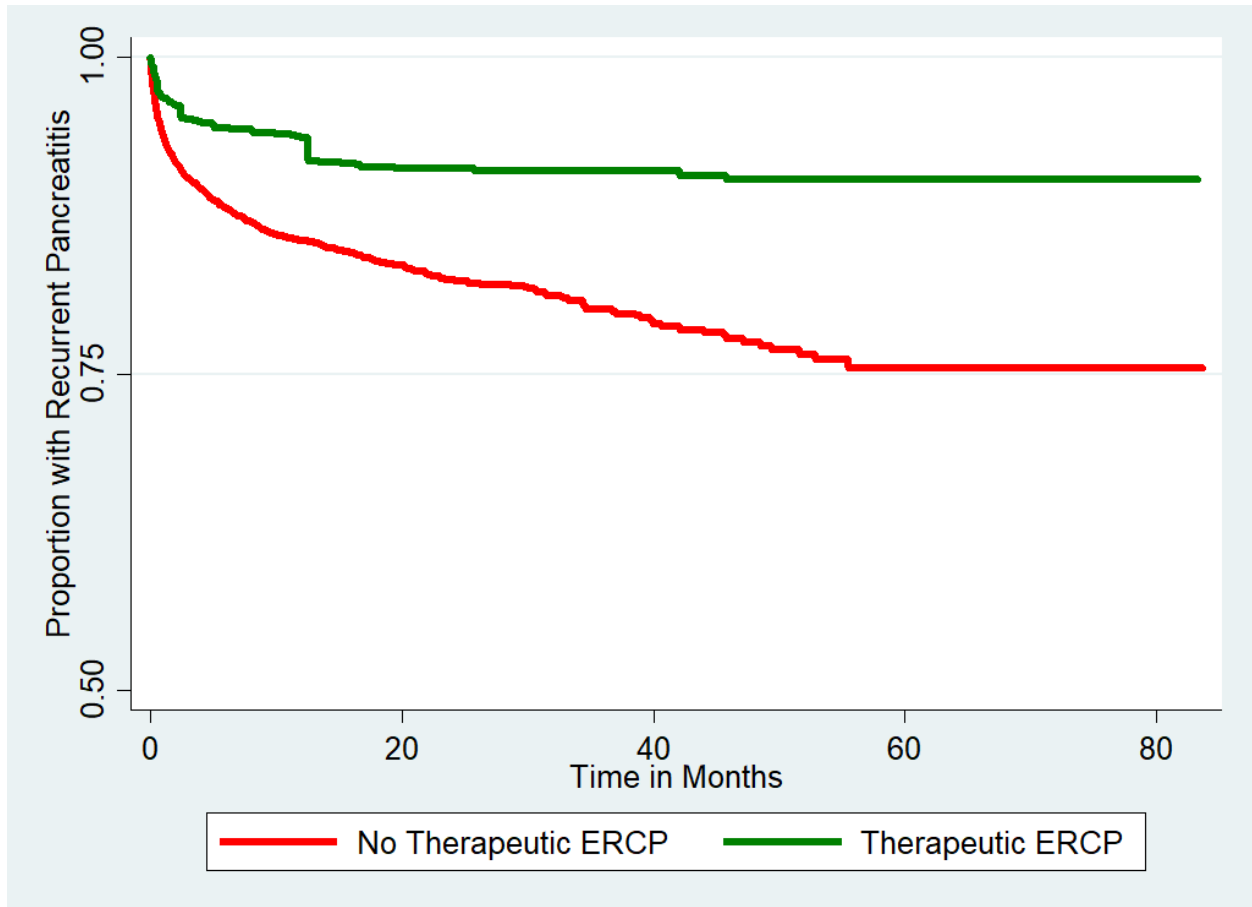


Figure 4B: Kaplan-Meier survival curve of recurrent pancreatitis by therapeutic ERCP status for patients who were post-cholecystectomy at any point in time following discharge. This is adjusted for patient demographics, comorbidities, and severity of pancreatitis by inverse probability-weighting of therapeutic ERCP via propensity scores.

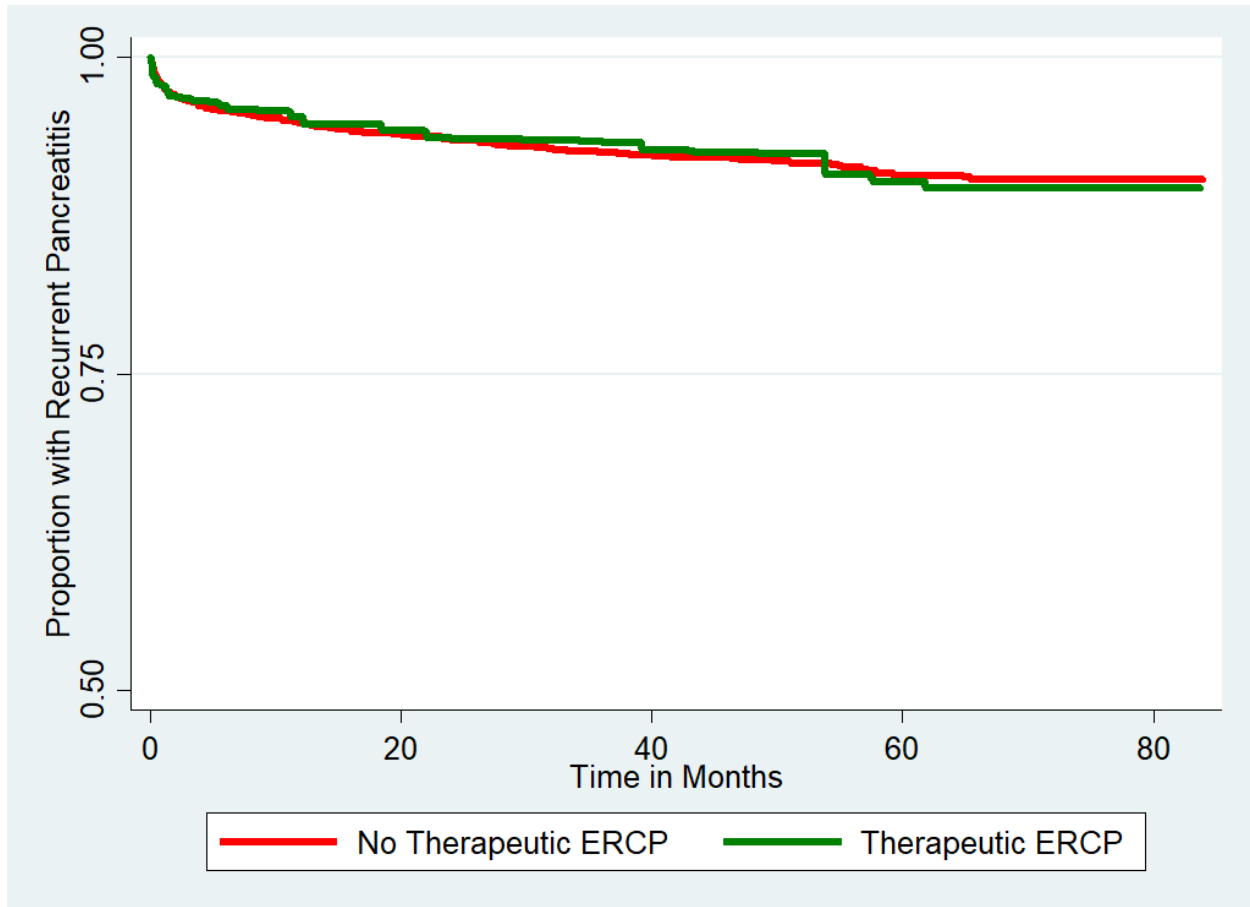


Table 1: Distribution of demographic and clinical variables for patients in the study with respect to whether they received a therapeutic ERCP.

	No therapeutic ERCP	Therapeutic ERCP	p-value
N	13,973 (80.6%)	3,375 (19.4%)	
Age (mean)	48.8 years	47.8 years	0.52
Female sex	8,255 (59.1%)	2,103 (62.3%)	< 0.001
Insurance plan			0.58
HMO Capitated	2,332 (17.5%)	541 (16.8%)	
Low OOP	10,407 (78.0%)	2,526 (78.4%)	
High OOP	605 (4.5%)	154 (4.8%)	
Region			0.002
Northeast	2,141 (15.9%)	489 (15.0%)	
North Central	3,296 (24.5%)	837 (25.7%)	
South	5,467 (40.6%)	1,238 (38.0%)	
West	2,576 (19.1%)	698 (21.4%)	
Severe Acute Pancreatitis	1,510 (10.8%)	364 (10.8%)	0.97
Elixhauser Comorbidity Index			< 0.001
0	5,396 (38.6%)	1,436 (42.5%)	
1	3,474 (24.9%)	855 (25.3%)	
2	2,256 (16.1%)	478 (14.2%)	
≥ 3	2,847 (20.4%)	606 (18.0%)	
Year Admitted			0.11
2008	1,671 (12.0%)	358 (10.6%)	
2009	2,210 (15.8%)	498 (14.8%)	
2010	2,042 (14.6%)	526 (15.6%)	
2011	2,141 (15.3%)	549 (16.3%)	
2012	2,320 (16.6%)	584 (17.3%)	
2013	1,764 (12.6%)	423 (12.5%)	
2014	1,825 (13.1%)	437 (12.9%)	
Mean length of stay	4.7 days	5.4 days	< 0.001
Cholangitis	234 (1.7%)	259 (7.7%)	< 0.001
Any CBD obstruction	1,079 (7.7%)	1,554 (46.0%)	< 0.001
CBD stone without obstruction	3,683 (26.4%)	2,538 (75.2%)	< 0.001
Jaundice	359 (2.6%)	331 (9.8%)	< 0.001
Cholecystectomy			< 0.001
None	2,224 (15.9%)	517 (15.3%)	
Prior to admission	333 (2.4%)	334 (9.9%)	
During admission	8,100 (58.0%)	2,006 (59.4%)	
≤ 30 days after discharge	2,020 (14.5%)	324 (9.6%)	

> 30 days after discharge	1,296 (9.3%)	194 (5.7%)	
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Abbreviations: CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; OOP, out-of-pocket;

Table 2: Univariate analysis of primary and secondary outcomes with respect to whether they received a therapeutic ERCP

	No therapeutic ERCP	Therapeutic ERCP	p-value
N	13,973	3,375	
Recurrent pancreatitis	1,386 (9.9%)	209 (6.2%)	< 0.001
Emergent encounter	6,388 (45.7%)	1,356 (40.2%)	< 0.001
Emergent readmission	2,445 (17.5%)	465 (13.8%)	< 0.001
Readmission within 30 days of discharge	713 (5.1%)	149 (4.4%)	0.099

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography

Appendix:

Table of Codes:

Acute pancreatitis	ICD9 577.0
Gallstone disease	ICD9 574.x
Chronic pancreatitis	ICD9 577.1
Other pancreatitis	ICD9 577.8
Cyst or pseudocyst of pancreas	ICD9 577.2
Pancreaticobiliary malignancy	ICD9 155.x, 156.x, 157.x
Therapeutic ERCP	
ERCP with sphincterotomy	ICD9 51.85; CPT 43262, 43277
ERCP with stone extraction	ICD9 51.88, 52.94; CPT 43265
Severe acute pancreatitis	
Shock	ICD9 785.x
Sepsis with organ failure	ICD9 995.92
SIRS with organ failure	ICD9 995.94
Acute renal failure	ICD9 584.x
Acute myocardial infarction	ICD9 410.x
Acute respiratory failure	ICD9 518.8x
Mechanical ventilation	ICD9 96.04, 96.7x; CPT 31500
Neurological failure	ICD9 348.x
Cholangitis	ICD9 576.1
Any CBD obstruction	ICD9 574.31, 574.41, 574.51, 574.61, 574.71, 574.81, 574.91, 576.2, 576.3
CBD stone without obstruction	ICD9 574.30, 574.40, 574.50, 574.60, 574.70, 574.80, 574.90
Jaundice	ICD9 782.4
Cholecystectomy	ICD9 51.22, 51.23; CPT 47562, 47563, 47564, 47600, 47605

Abbreviations: CBD (common bile duct), CPT (Current Procedural Terminology), ICD9 (International Classification of Disease, 9th Edition, Clinical Modification)