Importance  Current guidelines recommend that patients with an initial episode of gallstone pancreatitis receive cholecystectomy. However, for various reasons, many patients do not.

Objective  To determine the risk of developing recurrent gallstone pancreatitis in patients who never receive a cholecystectomy.

Design  Retrospective cohort study using electronic medical records.

Setting  Inpatient and outpatient.

Patients  All patients in Kaiser Permanente Southern California with a primary diagnosis of acute gallstone pancreatitis hospitalized from January 1, 1995, through December 31, 2010, with no previous diagnosis of gallstone pancreatitis documented in the medical record.

Interventions  Endoscopic retrograde cholangiopancreatography (ERCP) with or without sphincterotomy and/or stent placement, or no intervention.

Main Outcomes and Measures  Recurrent acute pancreatitis.

Results  A total of 1119 patients were identified. The median age at diagnosis was 63 years. Among the patients, 802 received no intervention and 317 received ERCP. After a median follow-up of 2.3 years, the overall risk of recurrent pancreatitis was 14.6%; it was 8.2% and 17.1% in patients who had ERCP and no intervention, respectively ($P < .001$). The median time to recurrence was 11.3 and 10.1 months in the patients who had ERCP and no intervention, respectively. Kaplan-Meier estimates of recurrence for 1, 2, and 5 years in the ERCP group were 5.2%, 7.4%, and 11.1%, compared with 11.3%, 16.1%, and 22.7% in the no-intervention group (hazard ratio = 0.45; 95% CI, 0.30-0.69; $P < .001$). Charlson Comorbidity Index and intensive care unit stay were independently associated with recurrence, whereas age, sex, and admission Ranson score were not associated.

Conclusions and Relevance  In patients who did not undergo cholecystectomy, the risk of recurrent pancreatitis is significant. Endoscopic retrograde cholangiopancreatography mitigates this risk and should be considered during initial hospitalization if cholecystectomy is not done.
The current recommendation for patients who present with mild gallstone pancreatitis is to undergo cholecystectomy during the initial hospitalization to prevent recurrent episodes of pancreatitis.1,2 The Society of American Gastrointestinal and Endoscopic Surgeons recommends (level II grade B recommendation) cholecystectomy for mild and self-limited gallstone pancreatitis after symptoms have subsided and laboratory values have normalized, usually during the same hospital admission.3 Similarly, the American Gastrointestinal Association Institute recommends cholecystectomy as soon as possible, and in no case beyond 2 to 4 weeks after discharge.4 However, cholecystectomy during initial hospitalization may not be feasible because of clinical factors, patient preference, or operating room resources that may be fully used. Many patients return for elective interval cholecystectomy after their initial hospitalization, but some patients may never undergo cholecystectomy.

Studies during the last decade have shown a wide range of recurrent acute gallstone pancreatitis, between 2.5% and 21.1% in patients who did not have cholecystectomy.5-13 Recurrent pancreatitis is a significant problem with associated morbidity and potentially mortality. Although many of the studies are small with short follow-up, several are large population-based studies in the United States, Sweden, and England that all show significant numbers of patients who do not have definitive treatment during or after hospital discharge.5-13 Patients who undergo cholecystectomy have a significantly decreased risk of recurrent gallstone pancreatitis, ranging between 1% and 1.7%11,14; therefore, it is currently recommended that patients undergo cholecystectomy soon after their initial episode of gallstone pancreatitis.

The purpose of our study is to evaluate the risk of recurrent gallstone pancreatitis in patients who have never had a cholecystectomy either at initial hospitalization or during follow-up within a large population in an integrated health care system in California.

Methods

Data Sources and Study Subjects
Kaiser Permanente Southern California is a managed care organization that serves approximately 3 million members in its 14 hospitals in southern California. Electronic medical records from all 14 Kaiser Permanente Southern California hospitals were used to identify patients with acute gallstone pancreatitis between January 1, 1995, and December 31, 2010, who had Kaiser Permanente memberships for at least 6 months. Acute gallstone pancreatitis was identified using International Classification of Diseases, Ninth Revision (ICD-9) code 577.0X, with concurrent ICD-9 codes for cholelithiasis, cholecystitis, or biliary colic (576.1X, 574, 574.0, 574.1, 574.2, 574.21, 574.3, 574.31, 574.4, 574.41, 574.5, 574.51, and 575.1) during the same hospitalization.

Patients were excluded if they had previous episodes of pancreatitis or if they had prior cholecystectomy (using ICD-9 codes 51.2, 51.21, 51.22, 51.23, and 51.24 or Current Procedural Terminology codes 47562, 47563, 47564, 47600, 47605, 47610, 47612, and 47620). We also excluded patients with less than 8 weeks’ follow-up after index diagnosis of acute gallstone pancreatitis.

Treatment at Initial Hospitalization
The patients were divided into treatment groups during initial hospitalization, which included patients who received endoscopic retrograde cholangiopancreatography (ERCP) with or without sphincterotomy and/or stent placement (ICD-9 codes 51.10, 51.85; CPT: 43260, 43261, 43262, 43264, 43265, and 43268) or patients who received no intervention.

Main Outcome
Recurrent gallstone pancreatitis was defined as patients who were readmitted with acute pancreatitis during follow-up (ICD-9 code 577.0X). Only first recurrences were evaluated. Secondary outcome was mortality, which was evaluated as all-cause mortality.

Statistical Analysis
We used χ² test (or Fisher exact test when large sample assumption for χ² test failed) to detect the difference in proportions of categorical predictors, described using frequencies and percentages, between treatment groups. Wilcoxon rank sum test was used to detect the difference in medians of continuous predictors, described using medians and interquartile ranges, between treatment groups. In addition to predictors, we also described follow-up time, time to recurrent acute gallstone pancreatitis, length of hospital stay, and percentages of recurrence among treatment groups.

We plotted cumulative incidence using Kaplan-Meier survival function estimations, checked proportional hazard assumption by testing time-dependent variables, did log-rank tests, and performed univariable- and multivariable-adjusted Cox regression with adjustment on age (continuous variable), sex, Charlson Comorbidity Index (0 or ≥1), admission Ranson score (<3 or ≥3), and whether patients were treated in an intensive care unit (ICU) during the index hospitalization. We used hazard ratios and 95% confidence intervals to measure the relative risk of recurrent acute pancreatitis among treatment groups, P < .05 indicated statistical significance. All tests were 2-tailed.

All statistical analyses were performed using SAS Enterprise Guide version 4.3 statistical software (SAS Institute, Inc.).

Results
There were 7970 patients who had an initial diagnosis of acute gallstone pancreatitis; 5754 remained after applying the exclusion criteria. The main focus of our study was on a cohort of 1119 patients, including 802 (71.7%) who had no intervention and 317 (28.3%) who had ERCP only during the initial hospitalization (Table 1). Most patients were in their 60s, and the majority were women. In most cases, the severity of pancreatitis was mild, as seen by a usually low admission Ranson score and infrequent ICU stay. Follow-up in these 2 groups ranged from 1.9 months to 16 years, with a median of 2.3 years. There
were 163 patients who developed recurrent gallstone pancreatitis; in addition, 21 patients developed cholangitis, 71 developed choledocholithiasis, and 31 developed acute cholecystitis. In the patients who underwent ERCP only, 26 (8.2%) developed recurrent gallstone pancreatitis, compared with 137 (17.1%) among those who had no intervention (Table 1). In the 802 patients who received no intervention, 31 (3.9%) died during follow-up. In the 317 patients who received ERCP during the initial hospitalization, 15 (4.7%) died during follow-up (Table 2).

According to the Kaplan-Meier curve, both groups continued to be at risk for recurrent gallstone pancreatitis many years after their initial episode, with relative protection after ERCP (Figure). The median time from the initial episode to onset of recurrence was 11.3 months for patients who underwent ERCP and 10.1 months for patients who had no intervention. Kaplan-Meier estimates of recurrence for 1, 2, and 5 years in the ERCP group were 5.2%, 7.4%, and 11.1%, compared with 11.3%, 16.1%, and 22.7% in the no-intervention group (P < .001). In the Cox proportional hazards model, treatment with ERCP was independently associated with a reduction in the risk of recurrent pancreatitis compared with no intervention (hazard ratio = 0.45; 95% CI, 0.30-0.69) (Table 3). Charlson Comorbidity Index and ICU stay were independently associated with recurrence, whereas age, sex, and admission Ranson score were not associated.

Patients who underwent ERCP had a longer initial length of hospitalization, 4 days, compared with 3 days for patients who had no intervention (P < .001).

Three remaining groups of patients underwent limited analysis. The first group included 3447 patients who had a cholecystectomy during the initial hospitalization; of these, 187 (5.4%) had recurrent pancreatitis before their delayed cholecystectomy, with a median time to recurrence of 9.7 months. The all-cause mortality rate in this initial cholecystectomy group was 2.1%. The second group included 1135 patients who had an elective cholecystectomy during follow-up; of these, 82 (7.2%) had recurrent gallstone pancreatitis before their delayed cholecystectomy, with a median time to recurrence of 7 months. All-cause mortality in this group was 2.6%. The third group included 53 patients who had an elective ERCP only after discharge; of these, 26 (49.1%) had recurrent pancreatitis before their delayed ERCP, with a median time to recurrence of 9.6 months. All-cause mortality in this third group was 3.8%.

Table 2 summarizes the overall risk of recurrent pancreatitis and all-cause mortality in the different groups.
Kaiser Permanente Southern California is unique in that it maintains both a long-standing electronic database system and a large number of members with long-term continuity of care. Thus, we were able to accumulate a large number of patients with follow-up as long as 16 years after discharge. As expected, most patients received a cholecystectomy during the initial hospitalization or after hospital discharge on an elective basis, but a large number of patients received no intervention after discharge.

Other population studies have shown that a large number of patients may never undergo cholecystectomy either during initial hospitalization or electively. A recent study from England included a cohort of 5454 patients with initial gallstone pancreatitis with a median follow-up of 18 months. Inter- estingly, 3824 patients (70.1%) were discharged without definitive treatment (either cholecystectomy or endoscopic sphincterotomy), and about 32% still did not have any definitive treatment 1 year after discharge. Similarly, a population study in Sweden revealed that 5804 of 8419 patients (68.9%) do not have either cholecystectomy or endoscopic sphincterotomy within 30 days of discharge. Finally, in a study of 5% of US Medicare beneficiaries, 2084 of 8452 patients (24.7%) during a 10-year period had not received a cholecystectomy 2 years after initial hospitalization for acute gallstone pancreatitis.

In an aging US population, we will encounter these patients more frequently. An interesting question is whether cholecystectomy is indicated for these patients who seem to be doing well after an ERCP and have no recurrences of pancreatitis years after discharge. From our study, the risk lessens after several years, so perhaps watchful waiting is reasonable for these patients; patients with no intervention, on the other hand, may still be better off undergoing a much-delayed cholecystectomy, as the risk does not lessen until a decade or so after initial hospitalization.

Patients who have no intervention have a high rate of recurrent gallstone pancreatitis, and initial ERCP more than halved the risk of recurrence in our study. Other studies have also shown ERCP to be superior to no intervention. Our Kaplan-Meier curves show that patients are at risk for recurrence early after discharge. The risk continues for years afterward, and it continues about a decade in those with no intervention. Those who had initial ERCP have a recurrence rate that is reduced and truncated over time. In addition, in our study, ICU stay and Charlson Comorbidity Index were independent risk factors for recurrence of gallstone pancreatitis, and cholecystectomy during index admission may not have been done in these patients with these risk factors. From this, patients who cannot have cholecystectomy during their index admission or are predicted to be unable to undergo elective cholecystectomy, whether because of severe illness and deconditioning or personal preference, should be considered for initial ERCP to reduce the risk of recurrence.

Patients who undergo cholecystectomy are still at risk for recurrent gallstone pancreatitis, but the risk is significantly less than that in patients who do not undergo cholecystectomy. The rate of recurrence is slightly higher in our study than in previous studies; however, this risk is still smaller than in patients who undergo ERCP only or no intervention. Furthermore, all-cause mortality was lowest in the group who underwent cholecystectomy during initial hospitalization. This may be explained by selection of healthier patients for surgery, but laparoscopic cholecystectomy is considered a safe operation in most patients and should be considered the gold standard in preventing recurrent gallstone pancreatitis.
Our study focused on recurrent pancreatitis, but we also found that patients had other complications during follow-up, including acute cholecystitis, choledocholithiasis, and cholangitis. Other studies have also shown that in patients who do not receive cholecystectomy during the initial hospitalization for gallstone pancreatitis, biliary colic may occur in 5.2% to 11.8% of patients, acute cholecystitis may occur in 1% to 5.6%, and cholangitis may occur in 0.8% to 7%. Although these risks of other events are small, they can be life threatening. Thus, these are more reasons patients should be urged to undergo cholecystectomy as definitive treatment after an initial episode of gallstone pancreatitis.

We acknowledge that our study has several limitations. Selection bias will be a factor in this retrospective study. Clear reasons for why patients did not have a cholecystectomy are unknown, as are the indications for ERCP in this nonsurgical group. Furthermore, we tried to measure severity of pancreatitis by using admission Ranson criteria as all 5 parameters are accessible in our database, but some of the 48-hour criteria were not obtainable from the laboratory data. This may have underestimated the severity of pancreatitis. In an effort to further identify more severe cases, ICU stay was used as a measure of organ function, assuming there was dysfunction if admitted to the ICU. Other unmeasured factors may certainly be at play for treatment group assignment, and coding issues may affect assessment of outcome.

Most societies currently recommend cholecystectomy during index hospitalization for gallstone pancreatitis as a preventive measure against recurrence. We also support cholecystectomy early if feasible, but as in other countries, cholecystectomy is not done for a fairly large proportion of patients. Patients who have had an initial episode of gallstone pancreatitis have a significant risk of recurrence if no intervention is performed. In patients who undergo ERCP, however, this risk is significantly decreased. Therefore, our recommendation is that patients who do not have cholecystectomy during initial hospitalization or during follow-up should undergo ERCP to decrease their risk of recurrence. These patients need ongoing monitoring as they may be at risk for recurrent pancreatitis for many years.

### Table 3. Cox Proportional Hazards Modeling of Variables and the Prediction of Recurrent Pancreatitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recurrent Pancreatitis, Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.98-1.00)</td>
<td>.08</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (Reference)</td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Female</td>
<td>1.03 (0.73-1.37)</td>
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<tr>
<td>Charlson Comorbidity Index</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (Reference)</td>
<td>.005</td>
</tr>
<tr>
<td>≥1</td>
<td>1.67 (1.17-2.40)</td>
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</tr>
<tr>
<td>Admission Ranson score</td>
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<td></td>
</tr>
<tr>
<td>&lt;3 (Reference)</td>
<td></td>
<td>.56</td>
</tr>
<tr>
<td>≥3</td>
<td>1.24 (0.60-2.56)</td>
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<tr>
<td>ICU stay</td>
<td></td>
<td></td>
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<tr>
<td>No (Reference)</td>
<td></td>
<td>.008</td>
</tr>
<tr>
<td>Yes</td>
<td>2.55 (1.28-5.07)</td>
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<tr>
<td>Treatment</td>
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<td></td>
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<tr>
<td>No intervention (Reference)</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ERCP</td>
<td>0.45 (0.30-0.69)</td>
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</tr>
</tbody>
</table>

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; ICU, intensive care unit.

### REFERENCES

Gallstone Pancreatitis
Why Not Cholecystectomy?

David J. Worhunsky, MD, Brendan C. Visser, MD

Hwang and colleagues offer an interesting look into the management of gallstone pancreatitis through the lens of an integrated health care system, Kaiser Permanente Southern California. The Kaiser system (compared with other insurance plans or hospitals) offers a unique opportunity to study this issue. They have a largely closed system offering synchronized care among various health care providers, and fewer patients move in and out of their umbrella of care. Thus, the article by Hwang et al. is an important addition to the current literature suggesting that the recurrence of gallstone pancreatitis is all too common.

Their data also suggest that endoscopic retrograde cholangiopancreatography (ERCP) during the index admission in patients who do not undergo cholecystectomy may be beneficial in preventing recurrent disease. In their cohort of 1119 patients who did not undergo cholecystectomy, 14.6% developed recurrent gallstone pancreatitis and 11.0% developed other issues related to gallstone disease. In patients who underwent ERCP, there was a 50% reduction in recurrent gallstone pancreatitis. Nonetheless, the risk of recurrence after ERCP remains elevated when compared with patients who underwent cholecystectomy (8.2% vs 5.4%, respectively). Accordingly, we agree with the authors that ERCP for the “definitive” management of gallstone pancreatitis should still be reserved for patients with a strong contraindication to surgery.

This article also highlights what we view as an even bigger problem: the significant proportion of patients (nearly 40% in this study) who still do not undergo cholecystectomy during the index hospitalization, including 20% who never go on to cholecystectomy. This problem is surely not unique to the Kaiser Permanente system, but rather is pervasive (and may be worse) throughout most hospitals. We fear that although some patients do not proceed to cholecystectomy owing to clinical factors or personal preference, in too many cases the obstacle may simply be convenience or the packed operating room schedule. Even interval cholecystectomy following mild gallstone pancreatitis is associated with higher rates of recurrence and thus readmission. In an increasingly cost-conscious and outcomes-driven health care environment, the importance of these management decisions cannot be overlooked.

Moreover, recent literature has suggested that even the hospital “cooling-off” period is unnecessary. Patients with mild gallstone pancreatitis can, in fact, safely undergo laparoscopic cholecystectomy within 24 to 48 hours regardless of the resolution of abdominal pain or abnormal laboratory findings. Endoscopic retrograde cholangiopancreatography should infrequently enter the algorithm for the management of mild gallstone pancreatitis: in patients with concomitant cholangitis, the uncommon retained stone, or extensive comorbidities precluding surgery. Evidence-based practice for the management of mild gallstone pancreatitis must include early involvement of the surgeon leading to timely cholecystectomy.

References