Trends and Timing of Interventions in Management of Acute Gallstone Pancreatitis in the United States

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Research Article

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Abstract

**Background:** Only about 50% of acute gallstone pancreatitis admissions undergo index cholecystectomy.

**Aims:** We aimed to analyze the national trends in acute gallstone pancreatitis management: the proportion and optimal timing of cholecystectomy.

**Methods:** Adult admissions with acute gallstone pancreatitis and associated procedures were extracted from National Inpatient Sample (2005-2014yy). Patients with index cholecystectomy were identified and divided into early and delayed intervention groups. Trends, complications, mortality, and hospital resource utilization were analyzed.

**Results:** In 991,476 acute gallstone pancreatitis hospitalizations, the rate of index cholecystectomy remained low at 53-55%. Analysis of cholecystectomy complications and resource utilization demonstrated the safest and most cost-effective strategy is to perform cholecystectomy during 24-72 hours of admission. A risk difference of 12.6% in the complication rate was observed between early (<72hrs) versus delayed (>72hrs) cholecystectomy groups. Delay in cholecystectomy to day five or beyond was associated with significantly higher morbidity, mortality, and resource utilization.

**Conclusion:** The rate of index cholecystectomies to prevent recurrent acute gallstone pancreatitis remains significantly low nationally (53-55%). Our analysis demonstrates that cholecystectomy should be avoided in the first 24 hours, and optimal timing for intervention is from 24 to 72 hours of acute gallstone pancreatitis hospitalization. Careful patient selection and timing of definitive operative management are important to ensure the best clinical outcomes and avoid unnecessary healthcare expenses.

Background And Aims

The incidence of acute pancreatitis (AP) hospitalizations has been increasing in the US and worldwide (1–3). Gallstones represent a major etiologic factor in developed nations and account for approximately half of AP presentations (2, 4, 5). Most episodes of AP (80%) are mild and self-limiting with less than 1% mortality. However, 10–20% of cases develop into severe pancreatitis (4). An increase in recurrence rate, readmission, associated morbidity, and healthcare utilization has been demonstrated if cholecystectomy (CCY) is not performed on index admission for acute gallstone pancreatitis (AGP) (4, 6–8). Analysis of the Nationwide Readmissions Database (NRD) demonstrated that the 30-day readmission rate for patients undergoing index CCY (I-CCY) was 6.5% compared to 15.1% in those who did not (9). I-CCY reduces the rate of recurrent gallstone-related complications in patients with mild AGP, compared with interval CCY (7) and demonstrated to be more effective and less costly (7). Accordingly, major national and international societal practice guidelines recommend performing CCY during index hospitalization in AGP (10–14).

Despite evidence-based benefits and clear recommendations, several studies have demonstrated a lack of adherence to the guidelines in the US, with only about half of the AGP patients (50–55%) undergoing
CCY during the same admission (9, 15, 16). Similar non-adherence has been demonstrated worldwide (17–19). The most recent National Inpatient Sample (NIS) trend analysis of 10 years by Bilal et al. showed even decreasing trends of I-CCY in the US from 48.7% in 2004 to as low as 45% in 2014 (20). However, these lower rates are attributed to differences in patient selection criteria.

Considering the ongoing need for improvement in adherence to evidence-based guidelines in the United States and the lack of current data, we decided to analyze the largest national administrative database to assess trends of care for AGP. We aimed to investigate the rate of same-admission CCY, morbidity, mortality, and complication rates based on the timing of the surgery, associated resource utilization, and optimal timing for I-CCY.

**Materials And Methods**

**Data source**

We performed a retrospective, cross-sectional analysis of 10 years of the National (Nationwide) Inpatient Sample (NIS) (21, 22). The NIS is one of the databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) through a Federal-State-Industry partnership and sponsored by the Agency for Healthcare Research and Quality (AHRQ) (23). It is the largest publicly available, all-payer inpatient health care database in the United States. NIS is analyzed to make national estimates of health care utilization, access, charges, quality, and outcomes (22). HCUP databases have been extensively used for health policy issues and outcome research, including comparative studies of health care services, longitudinal trend analysis, racial and socioeconomic disparities, variation in healthcare access, medical treatment, and cost-effectiveness. NIS data are available from 1988 to 2016; it approximates a 20-percent stratified sample of all discharges from US hospitals, excluding rehabilitation and long-term acute care hospitals. Unweighted, it contains data from more than 7 million hospital stays each year. Weighted, it estimates more than 35 million hospitalizations nationally and has more than 100 clinical and nonclinical data elements for each hospital stay. This includes up to 25 primary and secondary diagnoses and 15 procedural codes, patient demographics, hospital characteristics, expected payment source, total charges, length of stay, discharge status with in-hospital mortality, severity, and comorbidity measures.

**Study design and statistical analysis**

We extracted all adult discharges (age $\geq$ 18) from NIS 2005 to 2014, who had associated previously validated International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for AGP, which was defined as AP (577.0) and a concurrent diagnosis of cholelithiasis (574. x). We excluded patients who underwent endoscopic retrograde cholangiography (ERCP) before or on the day of the admission to remove potential post-ERCP pancreatitis cases (16). ICD-9 procedure codes were used to identify laparoscopic and open CCY (51.21, 51.22, 51.23, 51.24), ERCP and endoscopic sphincterotomy/papillotomy (51.10, 51.11, 51.13, 51.85) as well as parenteral nutrition (99.15), as used and validated in previous studies (16, 24).
We used the weights provided in the database to calculate national estimates. Since the NIS was redesigned in 2012, we used the trend weights to replace discharge weights to make the adjustment. After calculating national estimates, we calculated percentage changes for diagnoses and procedures from 2005 to 2014.

Extracted hospitalizations were analyzed for all billable data provided in each discharge abstract. Trends and available patient demographics were reviewed. The primary outcome was defined as the proportion of CCY performed during the index admission. First, we identified the percentage of patients who had CCY and ERCP performed on index admission. From all AGP patients, we separately calculated the number of patients who received only CCY, only ERCP, both CCY and ERCP, and identified the group of patients who did not undergo either. Next, we used PRDAY (procedure day) variable to stratify the procedures by the number of days from the admission to the procedure. Patients who had CCY and ERCP performed during the index hospitalization were analyzed separately by the day of admission that the day the procedures were performed, starting from the day of hospitalization (day 0) to > 5 days.

Patients who underwent CCY or ERCP within the index hospitalization were then divided into two groups: early (procedure performed within 72 hours of the admission) and delayed (> 72 hours) intervention group. Subsequently, the complication rates for these groups were calculated. Secondary outcomes were defined as mortality, mean charges (MC), and length of hospital stay (LOS). Technical, surgical, and systemic postoperative complications were identified by several ICD-9 codes (Appendix 1.), and inpatient mortality was calculated from available data variables. All secondary outcomes were analyzed from the day of admission to the first procedure performed, and the outcomes of the patients who did not undergo I-CCY were reported separately.

All the discharges with missing data were excluded. Total charges were adjusted to 2014 US dollars using the inflation factors on Medical Expenditure Panel Survey (MEPS) recommendations (25). All statistical analyses were performed using SAS Enterprise Guide, Version 7.11 HF3 (SAS Institute Inc., Cary, NC, USA).

As we analyzed publicly available de-identified data, this study was not considered human subject research. Therefore, it was exempt from NYU Grossman School of Medicine and SUNY Downstate Health Sciences University institutional review board approval.

**Results**

**Trends of hospitalizations and rates of procedures**

In NIS 2005–2014, which represents the national estimate of 4,064,037 hospitalizations, we identified a total number of 840,585 adult patients with AP. The number of hospital encounters had increased from 360,472 in 2005 to 432,810 in 2014, corresponding to a 20% increase. Twenty-five percent of AP admissions were associated with cholelithiasis. By excluding patients who underwent ERCP on the same day or day before admission, we derived a cohort of 205,351 patients with AGP, estimated at 991,476
hospitalizations nationally. The total number of AGP hospitalizations had increased by 16.3% (from 87,961 in 2005 to 102,305 in 2014), with a proportionate 12% increase in I-CCY. Sub-analysis demonstrated that the number of open CCY had decreased by 35%, and laparoscopic CCY increased by 17.5%. The rate of index admission CCY for AGP remained stable throughout the analyzed ten years, with a slight decrease from 55% in 2005 to 53% in 2014. The total number of ERCP performed for AGP had increased by 7% (from 23,852 in 2005 to 25,510 in 2014). Notably, after stratification of ERCP by different codes, we found that the overall number of ERCP had decreased by 54%, endoscopic retrograde cholangiography (without pancreatography) had decreased by 44.7%, and endoscopic sphincterotomy/papillotomy had increased by 22.6%. The use of parenteral nutrition during hospitalizations had decreased by 27%. In all AGP admissions, the proportion of parenteral nutrition administration was 3.7% in 2005 and decreased to 2.3% in 2014.

Out of nationally estimated 991,476 AGP patients in the 10-year period, a total of 540,295 patients underwent CCY (54.5% of the total sample). Among all AGP patients: 154,089 (15.54%) patients had both ERCP as well as CCY, 386,206 patients underwent CCY but no ERCP (38.9% of the total sample), 102,500 (10.3%) patients had ERCP, but no CCY, and 348,681 (35.16%) patients were discharged without ERCP or CCY performed during the index hospitalization.

**Timing of procedures and analysis of complications**

A total of 540,295 CCY was performed throughout the 10-year study period. 492,216 CCY cases had time variables to stratify the procedures by days from admission. Patients who underwent CCY were divided into two groups: early (within 72 hours of admission) and delayed (>72 hours of admission) intervention group. 65% of CCY were performed within 72 hours and 35% after 72 hours of admission. Analysis of complications in the early versus delayed CCY groups demonstrated a risk difference of 12.6% [14.2% in the early (CI 13.9–14.5) versus 26.8% in the delayed group (CI 26.2–27.2)]. The complication rate was higher (18.2%) when the procedure was performed on the day of admission as opposed to 24 or 48 hours after hospitalization (12.4% and 12.9%, respectively) and highest if CCY was delayed until day five or beyond (31.8% (CI 31.0-32.6); Risk difference of 19.4% and 18.9%, respectively) (Fig. 1.).

Analysis of ERCP complications in the early versus delayed group demonstrated a risk difference of 11.1%; 17.1% in early (CI 16.7–17.6) versus 28.2% in the delayed group (CI 27.5–29). However, complication rates were not significantly different if ERCP was performed on days 1, 2, or 3 of hospitalization (16.4, 17.3%, and 17.8%, respectively) as opposed to 20.9% on day 4, and 32.5 if ERCP was delayed until day five or beyond (Fig. 2.)

Overall comparison analysis of complications including mortality in all AGP patients with or without interventions demonstrated that the CCY group had the least percent of complications in each analyzed year with a decreasing trend. In contrast, the overall percent of complications had increased from 17.74% in 2005 to 22.95% in 2014 (Fig. 3.).
Inpatient mortality has not changed significantly but demonstrated a decreasing trend from 1.6% in 2005 to 1.4% in 2014, corresponding to a 12.5% relative decrease in all-cause mortality.

**Patient and Hospital Characteristics**

Socio-demographic analysis demonstrated female predominance: 62.4% versus 37.6% in 2005 and 58% versus 42% in 2014. 64.8% of patients were white, 10.6% black, 17.2% Hispanic, 3.1% Asian/Pacific Islander, and 4.2% represented Native American and other races. Racial distribution has not significantly changed throughout the years except for a slight increase in hospitalizations of black patients (+Δ1.1%), Asian/Pacific Islanders (+Δ0.7%), Native Americans/other (+Δ0.3%). Hospitalizations of white and Hispanic patients decreased by 1.2% and 0.8%, respectively. Age distribution in 2014 was similar in the 2nd, 3rd, and 4th decades of life (11%, 10%, and 12%, respectively). There was a higher incidence in the older population: 17% in the 5th decade, 18% in the 6th decade, and 31% of hospitalizations in patients above age 70.

Almost 80% of patients have been discharged home consistently throughout the analyzed years, 6–7% discharged with home health care, and 11% were sent to short-term or other facilities. In 2014, 61.5% of patients were publicly insured (increased from 58% in 2005) and 30.5% had private insurance (decreased from 33% in 2005).

**Hospital resource utilization**

The MC for inpatient management of AGP increased by 36.4% ($43,303 in 2005 to $59,047 in 2014; Δ$15,744) and LOS decreased by 0.8 days, 6.7 in 2005 to 5.9 days in 2014. It was demonstrated to be the most cost-effective strategy, with the least hospital bed utilization, if CCY was performed during 24–72 hours of admission (MC of $46,646 - $47,177; Mean LOS of 3.8–4.4 days). Significant increases in MC and LOS were observed when CCY was delayed beyond 72 hours, reaching the highest MC ($96,856) and LOS (11.9 days) when CCY was performed on or after day five from admission (Table 1).
Table 1
Mean charges (MC) and mean length of stay (LOS) by timing of cholecystectomy (CCY).

<table>
<thead>
<tr>
<th>Number of days from admission to CCY</th>
<th>N</th>
<th>Mean</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CCY</td>
<td>9,877</td>
<td>$44,585</td>
<td>$1,423</td>
<td>$41,797 - $47,374</td>
</tr>
<tr>
<td>CCY on admission day</td>
<td>6,853</td>
<td>$47,469</td>
<td>$992</td>
<td>$45,524 - $49,413</td>
</tr>
<tr>
<td>CCY on day 1</td>
<td>14,849</td>
<td>$46,646</td>
<td>$643</td>
<td>$45,385 - $47,908</td>
</tr>
<tr>
<td>CCY on day 2</td>
<td>22,417</td>
<td>$47,177</td>
<td>$523</td>
<td>$46,152 - $48,208</td>
</tr>
<tr>
<td>CCY on day 3</td>
<td>19,846</td>
<td>$52,503</td>
<td>$583</td>
<td>$51,360 - $53,647</td>
</tr>
<tr>
<td>CCY on day 4</td>
<td>13,673</td>
<td>$59,333</td>
<td>$704</td>
<td>$57,954 - $60,713</td>
</tr>
<tr>
<td>CCY &gt; = 5 days</td>
<td>21,523</td>
<td>$96,856</td>
<td>$1,399</td>
<td>$94,114 - $99,598</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of days from admission to CCY</th>
<th>N</th>
<th>Mean</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CCY</td>
<td>9,957</td>
<td>6.3</td>
<td>0.1</td>
<td>6.1 - 6.5</td>
</tr>
<tr>
<td>CCY on admission day</td>
<td>7,133</td>
<td>4.3</td>
<td>0.1</td>
<td>4.2 - 4.5</td>
</tr>
<tr>
<td>CCY on day 1</td>
<td>15,442</td>
<td>3.8</td>
<td>0.0</td>
<td>3.7 - 3.9</td>
</tr>
<tr>
<td>CCY on day 2</td>
<td>23,150</td>
<td>4.4</td>
<td>0.0</td>
<td>4.4 - 4.5</td>
</tr>
<tr>
<td>CCY on day 3</td>
<td>20,396</td>
<td>5.5</td>
<td>0.0</td>
<td>5.5 - 5.6</td>
</tr>
<tr>
<td>CCY on day 4</td>
<td>13,984</td>
<td>6.8</td>
<td>0.0</td>
<td>6.7 - 6.8</td>
</tr>
<tr>
<td>CCY &gt; = 5 days</td>
<td>21,963</td>
<td>11.9</td>
<td>0.1</td>
<td>11.7 - 12.0</td>
</tr>
</tbody>
</table>

There has been a significant shift in AGP management to teaching hospitals (> 105% increase), and 60% of all AGP patients were treated in teaching hospitals in 2014.

Discussion

Our study demonstrates an increasing trend of hospitalization for AP from 2005 to 2014, similar to previously reported trends(3). A quarter of AP admissions were associated with gallstones, consistent with the previous reports (9). The total number of AGP hospitalizations had increased by 16.3% over a decade, with a proportionate 12% increase in the rate of I-CCY. Despite clear societal recommendations, improvement in hospital resources, standardization of treatment protocols, and enhanced health care access, our study demonstrates a persistently low adherence to guidelines to perform CCY during index hospitalization in AGP patients. Slightly over half of the patients undergo CCY during the index admission, consistent with previous analyses (9, 15).
There are other possible reasons for the low rate of I-CCY, such as lack of adequate surgical resources at the hospital, patient preferences, and severity of pancreatitis. Our data showed a significant shift of AGP management to teaching hospitals; a 105% increase in hospitalizations to teaching hospitals in 10 years corresponds to a 20% proportionate shift. Sixty percent of all AGP patients were treated in teaching hospitals in 2014 compared to 40% in 2005. Despite this significant shift of AGP care to teaching hospitals, the overall rate of CCY has not changed. Therefore, it seems less likely that either the lack of equipment or training in laparoscopic techniques are responsible for poor adherence to the evidence-based guidelines, as demonstrated by the overall unchanged, low rate of index admission cholecystectomy.

More importantly, the presentation with severe AP may be the reason for not performing I-CCY, as surgical intervention is not recommended and should be deferred in severe cases until after discharge due to the increased associated risk of complications and worse outcomes (4). Though we cannot stratify AGP admissions’ severity, considering that about 80% of pancreatitis presentations are mild (4), the I-CCY rate is expected to be higher even after accounting for disease severity. Furthermore, in the analysis of NRD 2013, Krishna et al. reported an I-CCY rate of 55%, specifically in non-severe pancreatitis patients defined by sepsis and number of comorbidities (9). Therefore, delay in CCY should not have been prompted solely by the severity of the disease presentation. NRD, in conjunction with NIS, is part of the family of HCUP databases, and results derived from its analysis, including similar rates of CCY, are interchangeable. The same analysis demonstrated that patients with severe AP, sepsis, three or more comorbidities, and admission to small or rural hospitals were less likely to undergo I-CCY (9).

Our analysis of secondary outcomes, including systemic and technical surgical complications, mortality, MC, and LOS, demonstrated that CCY should be avoided within the first 24 hours of AGP admission. The optimal timing for intervention is 24 to 72 hours from the day of admission. Further delay in surgical intervention leads to poor resource utilization and worse clinical outcomes. To our knowledge, this is the first attempt to define optimal timing of I-CCY during AGP hospitalization using a large national database and highlights the importance of adherence to best practice guideline recommendations and providing high-quality care for these patients.

Our study has limitations inherent to NIS, which is an administrative database including, but not limited to, coding errors with or without billing incentives, lack of disease severity data, inability to track complications in time, and most importantly, the deficiency of clinical variables and data to track clinical outcomes. NIS does not contain clinical variables, and we used MC, LOS, complications, and inpatient mortality as surrogate endpoints for outcomes.

A specific limitation that may affect the results of our study is the inability to stratify the severity of AGP, considering that about 80% of AP presentations are mild and self-limited, and 55% CCY rate reported by Krishna et al. in non-AP, the severity of disease could not have solely been the reason for delaying or not performing I-CCY. Unfortunately, due to a lack of clinical data, we cannot comment about the patient or physician-related reasons for lack of adherence to guidelines. Additionally, considering the improvement
in mortality rates and other favorable changes throughout the analyzed years as well as improved access
to healthcare resources and increasing rates of hospitalizations, the majority of hospitalizations should
be representative of mild, rather than severe acute gallstone pancreatitis episodes, and there is an
opportunity to improve I-CCY rates by 20–25%. Additionally, considering the inpatient nature of the NIS
database solely, it is impossible to track readmissions, and several different admissions of the same
patients might be represented in our sample.

Despite the above limitations, the main strength of NIS is its ability to produce a large sample size of
validated national estimates across multiple years, to identify certain disease/procedure trends, and to
demonstrate patterns of care nationwide without selection bias, encompassing more patients with
disease of interest than a single or multi-institutional study can provide. To strengthen our data, we
designed the study by carefully choosing previously validated ICD-9 codes. Our codes have been
consistent with previous study methods (15), and procedural literature has demonstrated that major
operative procedures are generally reasonably coded in administrative databases (24). We compared our
results with previous NIS analysis, excluded hospitalizations with missing variables, and only reported
conclusions strongly supported by our data analysis.

To our knowledge, this is the second study performed with NIS years from 2005 to 2014 assessing
national trends in AGP and management patterns, including rates of I-CCY. Our data is consistent and
continuous with those of Nguyen et al., who reported 50% and 51% of I-CCY from NIS 2003 (15, 16), and
we reported 55% in 2005 and 53% in 2014. Krishna et al. demonstrate a 55% I-CCY rate analyzing NRD
2013 (9). Bilal et al. reported a decrease of I-CCY from 49% in 2004 to 45% in 2014 in the analysis of
2004, 2009, and 2014 of NIS (20). This slightly lower percentage and decreasing trend of I-CCY may be
attributed to differences in study methodology and patient selection criteria. Similar to Nguyen et al., our
methods excluded patients with AGP who had ERCP performed on the same day or day before the
admission, as these might represent post-ERCP pancreatitis cases (16). Additionally, while Bilal et al.
excluded elective admissions, we have not implemented this method in our study to keep a continuous
trend with NIS analysis from 1998 to 2003 by Nguyen et al. Despite cited differences, all reported data are
consistent with significant non-adherence to societal guidelines, which besides affecting clinical
outcomes, significantly impacts the cost of care and increases unnecessary healthcare resource
utilization, increasing financial burden associated with recurrent gallstone pancreatitis if CCY is not
performed in eligible cases on index hospitalization. Interventions such as increasing the awareness of
guidelines among physicians, improved operation room and surgical personnel availability, and attention
to prompt optimization of any medical comorbidities that may contribute to delays in admission
cholecystectomy can potentially improve the low I-CCY rates.

In conclusion, our study demonstrated that I-CCY was only performed in 53–55% of hospitalized patients
with AGP in the United States over the decade of 2005 to 2014. A significantly low rate of I-CCY for the
prevention of recurrent AGP remains to be addressed. Our analysis of complication rate, MC, and LOS
demonstrated that CCY should be avoided in the first 24 hours of AGP admission. The optimal timing for
intervention is 24 to 72 hours from admission to achieve the best clinical outcomes and optimize
resource utilization. Delaying CCY until day 5 of admission or beyond is associated with significantly increased morbidity and mortality and an unfavorable increase in hospital resource utilization. The overall analysis of complications in all AGP hospitalizations with or without interventions compared to procedure groups demonstrated that the CCY group had the lowest complication rate in each analyzed year with decreasing trend. Careful patient selection and timing of definitive operative management following the major societal guidelines and recommendations is of utmost importance to provide high-quality care, ensure the best clinical outcomes, and avoid unnecessary healthcare expenses.

Declarations

Ethics approval and consent to participate

As we analyzed publicly available de-identified data, this study was not considered human subject research. Therefore, it was exempt from NYU Grossman School of Medicine and SUNY Downstate Health Sciences University institutional review board approval. All methods were performed in accordance with relevant guidelines and regulations.

Consent for publication

-Not applicable

Availability of data and materials


Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions
Acknowledgments

Not applicable

References


Figures

Figure 1: Complication rate by timing of cholecystectomy (CCY)

Please See image above for figure legend.
Figure 2

Please See image above for figure legend.
Figure 3

Please See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1ICD9codes.docx