

Temporal Trends in Incidence and Outcomes of Acute Pancreatitis in Hospitalized Patients in the United States From 2002 to 2013

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Objectives: We sought to examine temporal trends in incidence and outcomes of acute pancreatitis (AP) in hospitalized adult patients in the United States.

Methods: Subjects were obtained from the Healthcare Cost and Utilization Project–Nationwide Inpatient Sample database using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for the years 2002–2013. Incidence of AP, all-cause mortality, cost, and duration of hospitalization were assessed.

Results: We identified 4,791,802 cases of AP. A significant increase in the incidence of AP was observed from 9.48 cases per 1000 hospitalizations in 2002 to 12.19 per 1000 hospitalizations in 2013 ($P < 0.001$). In-hospital mortality decreased from 2.99 cases per 100 cases in 2002 to 2.04 cases per 100 cases in 2013 ($P < 0.001$). Mean length of stay decreased from 6.99 (standard deviation [SD], 9.37) days in 2002 to 5.74 (SD, 7.94) days in 2013 ($P < 0.001$). Cost of hospitalization increased from \$27,827 (SD, \$54,556) in 2002 to \$49,772 (SD, \$106,205) in 2013 ($P < 0.001$).

Conclusions: Hospital admissions for AP in adults increased significantly in the United States from 2002 to 2013. In-hospital all-cause mortality and mean length of stay significantly decreased. In contrast, total cost of hospitalization rose.

Key Words: acute pancreatitis, epidemiology, in-hospital mortality, temporal trends

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Acute pancreatitis (AP) is the most common gastrointestinal condition requiring hospitalization in the United States.^{1,2} The American College of Gastroenterology defines AP as the presence of 2 of the following 3 criteria: (i) epigastric abdominal pain, (ii) serum amylase or lipase at least 3 times the upper limit of normal, and/or (iii) findings suggestive of AP on abdominal imaging.³ Acute pancreatitis in the United States accounts for health care costs of \$2.5 billion and 275,000 admissions each year.⁴ Acute pancreatitis can be caused by numerous pathologies including gallstones (most common), alcohol, hypertriglyceridemia, autoimmune, drug induced, pancreatic malignancy, and idiopathic.^{3–5} Severity ranges from mild to severe, which may include multiple organ failures and/or death,^{3,4} but most cases of AP are self-limiting and mild, requiring only minimal hospitalization.⁴ Mortality ranges from approximately 1% to 2%, with mortality increasing toward 30% in severe cases with persistent organ failure.^{1,4,6} There are numerous studies demonstrating increasing incidence

of AP throughout Europe and the United Kingdom^{5,7–11} and within the pediatric population in the United States.¹² In a US study, Fagenholz et al⁶ concluded hospital admissions for AP increased from 101,000 cases in 1988 to 210,000 cases in 2002. However, there is minimal evidence on the incidence of AP in adult patients within the United States over the last decade. This knowledge gap inhibits concrete conclusions as to the cause and progression of AP from being made. In this work, we sought to evaluate the current temporal trends in incidence of AP within the United States. We also evaluated temporal trends in in-hospital mortality, cost of hospitalization, and mean length of stay (LOS). Such analyses may facilitate accurate evaluation of prognosis and determinants of treatment successes for a common disease.

MATERIALS AND METHODS

Subjects were obtained from the Healthcare Cost and Utilization Project–Nationwide Inpatient Sample (HCUP-NIS) database for the years 2002–2013.¹³ The HCUP-NIS database is an all-payer inpatient health care database within the United States. It represents a 20% stratified sample of all discharges within the United States, including community and academic hospitals. Rehabilitation facilities and long-term acute-care hospitals are excluded. Hospital discharges are organized by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes providing information on diagnoses and resources used; *ICD-9-CM* codes were used to identify patients hospitalized with AP. Inclusion criteria encompassed adults older than 18 years. No individuals were excluded from our research. Acute pancreatitis was the dependent variable. Additional variables obtained included patient demographics, comorbid conditions, in-hospital mortality, LOS, and cost of hospitalization. Cases were considered “moderate or severe” if the subject’s record contained diagnostic or procedural codes related to organ failure, intra-abdominal infection, sepsis, or operative debridement or drainage. Respiratory failure was defined by the presence of codes 518.5, 518.81, 518.82, 96.04, 31.1, 31.2, or 96.7; renal failure by the presence of codes 39.95 or 584; sepsis by the presence of 785.52, 038, or 995.9; and intra-abdominal infection by the presence of codes 567.2, 567.1, 567.29, 567.22, 567.38, or 567.39. Abdominal surgery for complications of pancreatitis was defined by codes 54.91, 54.0, 54.11, 54.19, 54.99, and 52.22. Cases in which subjects were administered vasopressors (00.17) or activated drotrecogin alfa (00.11) were also considered moderate or severe. Differentiation between moderate and severe was not feasible as data on the duration of organ dysfunction were not available. Our primary analysis was to determine incidence of AP in the United States and its trend from 2002 to 2013. Our secondary analysis reviewed severity, in-hospital mortality, gender differences, mean LOS, and cost of hospitalization. The HCUP-NIS database is anonymous, and *ICD-9-CM* codes do not account for recurrent admissions. Advocate Christ Medical Center institutional review board

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deemed this study exempt because the HCUP-NIS is a publicly available database containing deidentified patient information.

Statistical Analysis

For descriptive analysis, we compared baseline patient characteristics. All continuous data are presented as means with standard deviation (SD), whereas categorical data are presented as percentages. We assumed the incidence and mortality rates followed a Gaussian distribution. Categorical variables were analyzed with Pearson χ^2 test and continuous variables with Student *t* tests for means with normal distribution. Significance level for this study was set at 0.05, and all tests were 2-tailed. All statistics were computed with the SPSS software (version 24.0; IBM Corp, Armonk, NY).

RESULTS

During the study period, we identified 4,791,802 admissions for AP. Baseline characteristics of the study population are shown

in Table 1. More than half of the subjects were white. Males had a significantly higher prevalence of diabetes, dyslipidemia, current tobacco use, and alcohol-related disorders. Females were older with a significantly higher prevalence of obesity, cholelithiasis, enteritis and ulcerative colitis, systemic lupus erythematosus, and liver and biliary disorders.

Incidence of AP

From 2002 to 2013, admissions for AP increased from 346,092 to 433,805. We observed a significant increase in the overall incidence of AP from 9.48 admissions per 1000 hospitalizations in 2002 to 12.19 admissions per 1000 hospitalizations in 2013 ($P < 0.001$). In the sex analysis, a significant increase in incidence of AP was noted in both the male and female populations. In males, incidence of AP increased from 11.42 admissions per 1000 hospitalizations in 2002 to 14.54 admissions per 1000 hospitalizations in 2013 ($P < 0.001$). In the female cohort, incidence of AP increased from 8.13 admissions per

TABLE 1. Baseline Characteristics

	Male (n = 2,383,762)	Female (n = 2,401,828)	<i>P</i>
Age, mean (SD), y	52.1 (17.1)	53.8 (20.2)	<0.001
Race			
White	1,258,223 (64.3)	1,266,484 (64.2)	<0.001
African American	334,653 (17.1)	314,286 (15.9)	
Hispanic	248,188 (12.7)	276,070 (14.0)	
Asian	40,697 (2.1)	44,602 (2.3)	
Native American	15,256 (0.8)	15,113 (0.8)	
Other	59,409 (3.0)	55,211 (2.8)	
Current tobacco use	573,675 (24.1)	371,026 (15.4)	<0.001
History of tobacco use	142,106 (6.0)	99,927 (4.2)	<0.001
Obesity	168,938 (7.1)	245,097 (10.2)	<0.001
Hypertension	1,145,977 (48.1)	1,076,559 (44.8)	<0.001
Diabetes mellitus	675,843 (28.4)	570,385 (23.7)	<0.001
Dyslipidemia	579,153 (24.3)	486,728 (20.3)	<0.001
Chronic renal failure	172,955 (7.3)	159,872 (6.7)	<0.001
Congestive heart failure	149,734 (6.3)	175,319 (7.3)	<0.001
Chronic obstructive pulmonary disease	226,252 (9.5)	191,332 (8.0)	<0.001
Asthma	92,545 (3.9)	169,194 (7.0)	<0.001
Peripheral vascular disease	65,689 (2.8)	60,333 (2.5)	<0.001
Coronary artery disease	352,435 (14.8)	252,268 (10.5)	<0.001
Pulmonary hypertension	24,883 (1.0)	32,388 (1.3)	<0.001
Thyroid disorders	89,157 (3.7)	283,674 (11.8)	<0.001
Coagulation and hemorrhagic disorders	193,574 (8.1)	124,558 (5.2)	<0.001
Cholelithiasis	458,142 (19.2)	739,227 (30.8)	<0.001
Hepatitis	144,546 (6.1)	95,887 (4.0)	<0.001
Enteritis and ulcerative colitis	26,940 (1.1)	32,305 (1.3)	<0.001
Esophageal disorders	404,193 (17.0)	437,817 (18.2)	<0.001
Gastroduodenal ulcer	78,136 (3.3)	78,035 (3.2)	0.076
Gastritis/duodenitis	158,123 (6.6)	156,765 (6.5)	<0.001
Diverticulosis/diverticulitis	81,332 (3.4)	94,406 (3.9)	<0.001
Liver and biliary disease	832,925 (34.9)	1,076,536 (44.8)	<0.001
Malignancy	200,112 (8.4)	204,589 (8.5)	<0.001
Gastrointestinal malignancy	66,695 (2.8)	58,399 (2.4)	<0.001
Systemic lupus erythematosus and connective tissue disorder	5624 (0.2)	38,622 (1.6)	<0.001
Human immunodeficiency virus	46,540 (2.0)	22,370 (0.9)	<0.001
Alcohol-related disorder	520,541 (21.8)	196,745 (8.2)	<0.001

Data expressed as number (%) unless otherwise indicated.

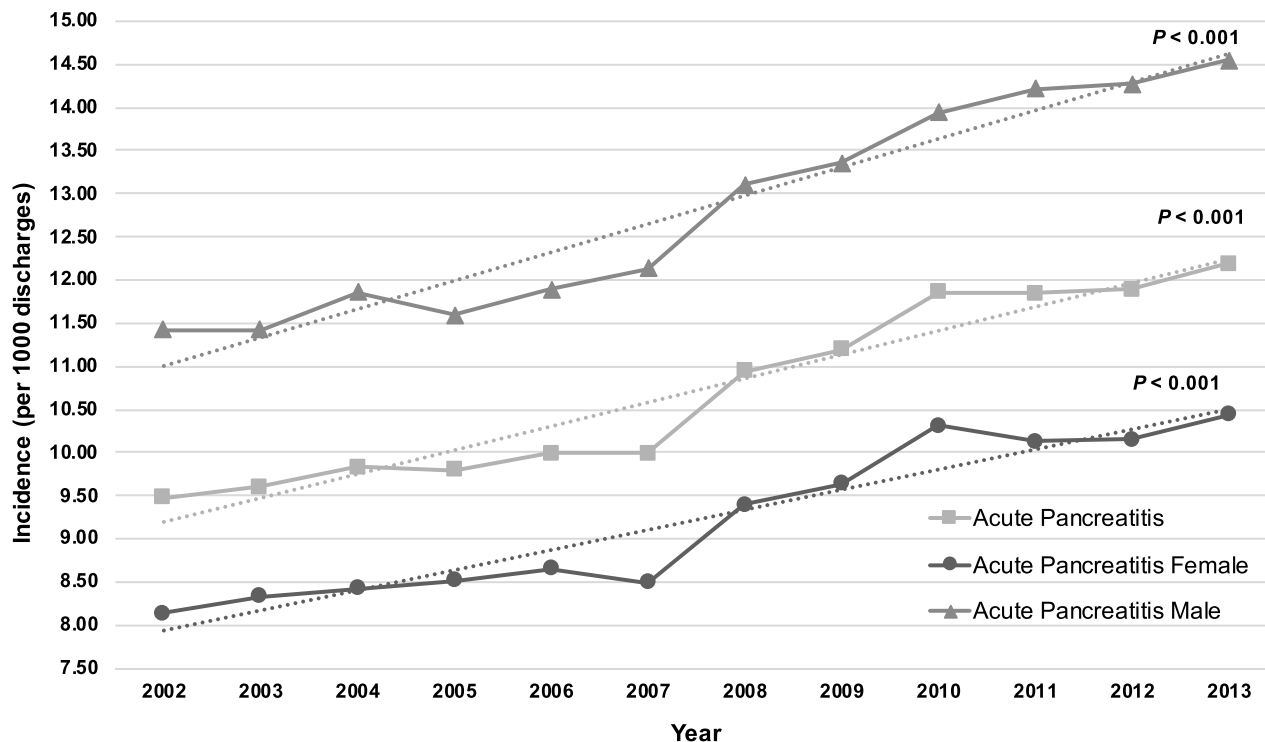


FIGURE 1. Incidence of AP.

1000 hospitalizations in 2002 to 10.44 admissions per 1000 hospitalizations in 2013 ($P < 0.001$) (Fig. 1). Acute pancreatitis was more common in the male population for every year of study compared with the female population.

Severity and Incidence of Mortality in AP

The prevalence of moderate or severe AP significantly increased from 9.79 in 2002 to 21.63 in 2012 per 100 discharges ($P < 0.001$). This increase in prevalence remained true during sex analysis, with females having an increase from 8.63 cases to 19.17 cases per 100 discharges ($P < 0.001$) and males having a rise from 11.0 cases to 24.0 cases per 100 discharges ($P < 0.001$) (Fig. 2). The overall incidence of in-hospital mortality for patients with a diagnosis of AP was 2.99 per 100 admissions in 2002, decreasing to 2.04 per 100 admissions in 2013 ($P < 0.001$). Although males presented with a higher in-hospital mortality (2.6% vs 2.2%, $P < 0.001$), a significant decrease in the incidence of in-hospital mortality during the study period was observed for both sexes. In 2002, in-hospital mortality incidence was 3.13 per 100 admissions for males and 2.85 per 100 admissions for females; this down trended to 2.25 deaths per 100 admissions in 2013 for males and 1.83 deaths per 100 admissions in 2013 for females ($P < 0.001$) (Fig. 3).

Mean LOS and Mean Cost of Hospitalization

Mean LOS and mean cost of hospitalization were also analyzed. Over our study period, mean LOS significantly decreased for the total cohort from 6.99 (SD, 9.37) days in 2002 to 5.74 (SD, 7.94) days in 2013 ($P < 0.001$). This trend remained during analysis of sexes (7.03 days in 2002 to 5.86 days in 2013 [$P < 0.001$] for males and 6.95 days in 2002 to 5.60 days in 2013 [$P < 0.001$] for females). Males had a prolonged mean

LOS compared with females (6.5 [SD, 9.2] days vs 6.3 [SD, 8.1] days; $P < 0.001$) (Fig. 4).

However, this decrease in LOS did not translate to lowering mean cost of hospitalization. In our study population, mean cost of hospitalization rose from \$27,827 (SD, \$54,556) in 2002 to \$49,772 (SD, \$106,205) in 2013 ($P < 0.001$). The same trend was confirmed in the sex-specific analysis. Mean cost of hospitalization increased from \$28,533 in 2002 to \$51,645 in 2013 for males and from \$27,147 in 2002 to \$47,848 in 2013 for females ($P < 0.001$) (Fig. 5). Again, male sex was associated with higher mean cost of hospitalization (\$41,423 [SD, \$87,598] vs \$38,710 [SD, \$73,016]; $P < 0.001$) (Table 2).

DISCUSSION

In our study, we sought to evaluate temporal trends in incidence and outcomes of hospitalized adult patients in the United States diagnosed with AP. Our data demonstrate a significant increase in hospital admissions for AP during the last 12 years from 9.48 cases per 1000 hospitalizations in 2002 to 12.19 cases per 1000 hospitalizations in 2013 ($P < 0.001$). This finding is in accordance with the reported increase in the incidence of AP in the European and UK population.^{5,7-11} Male patients had a higher incidence of AP and in-hospital all-cause mortality compared with the female patients, precipitated by underlying differences in baseline risk factors associated with disease development and progression. The observed increase in incidence for the entire study population can be partially attributed to the growing prevalence of known environmental risk factors, such as obesity,^{14,15} tobacco,¹⁶ and alcohol use.¹⁶

Obesity can lead to AP by increase in gallstone formation.^{1,14} Novel studies have also demonstrated an inherent risk of AP associated with obesity, although the exact causative mechanism of

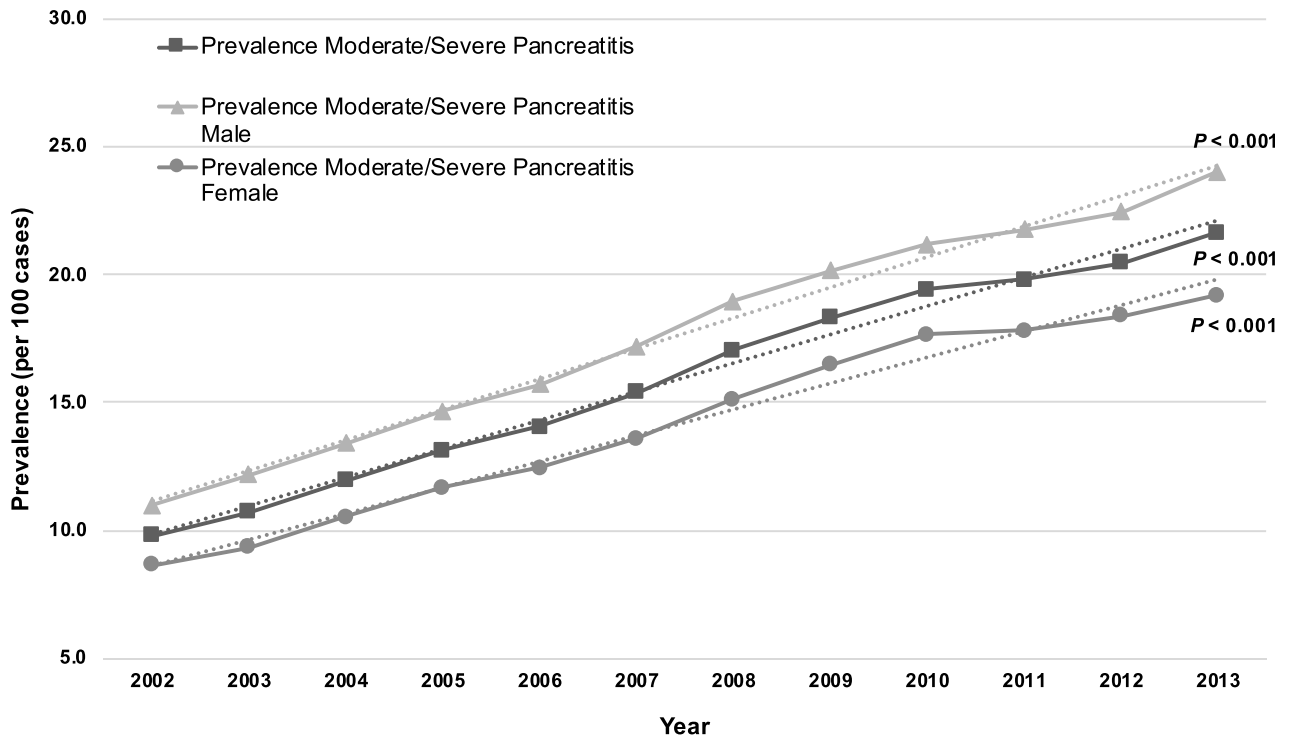


FIGURE 2. Prevalence of moderate and severe pancreatitis.

this has not been determined.¹⁴ Additionally, obesity has been demonstrated to increase the risk of developing more significant systemic and local complications.^{1,14,15} During the study period, the Centers for Disease Control and Prevention reported an increase in the prevalence of obesity within the United States from 30.5% in 1999 to 37.7% in 2014.¹⁷ In our study population, 7.1% of the male population and 10.2% of the female population had obesity ($P < 0.001$). Although the prevalence of obesity we report is lower than the one described by the Centers for Disease Control and Prevention, we believe this is secondary to an underreporting limitation of the database and does not depict the true prevalence in our population.

Gallstone formation is considered the most common cause of AP.^{1,4,5} Lindkvist et al¹¹ reported a positive correlation for gallstone AP incidence with an increase in the incidence of gallstone diseases in Sweden between 1985 and 1999. In the US adult population, the prevalence of gallstones is 7%,^{1,18} significantly lower than the observed prevalence in our large national registry population, 19.2% for males and 30.8% for females ($P < 0.001$). Although the exact prevalence of gallstone pancreatitis in our population cannot be calculated utilizing the HCUP-NIS database, one can hypothesize that the higher prevalence of cholelithiasis described in our population can explain the observed increase in the incidence of AP.

Recently, type 2 diabetes mellitus (DM) and use of antidiabetic medications have been linked to increased risk of development of AP. In large retrospective cohort studies, type 2 DM was shown to increase the risk of AP by 1.5- to 3-fold, after controlling for demographic and other risk factors.^{1,19-21} Additionally, a recent study evaluating reports to the US Food and Drug Administration found a greater than 6-fold increase in the risk of AP among users of medications for type 2 DM, such as sitagliptin (a dipeptidyl peptidase-4 inhibitor) and exenatide (a glucagon-like peptide-1 analog).²² During our study period, the prevalence of diabetes increased from 13.49 million Americans (4.84%) in 2002

to 22.30 million Americans (7.18%) in 2013.²³ The increasing prevalence of diabetes may be contributing to the increasing incidence of AP. In our study population, 28.4% of men and 23.7% of women had comorbid DM, underlying the higher prevalence of diabetes in the AP population. Furthermore, it might contribute to the observed gender-specific differences in incidence of AP.

With a higher prevalence of known risk factors for AP (obesity, cholelithiasis, systemic lupus erythematosus, inflammatory bowel disease) in the female population, a parallel or higher incidence of AP in the females would have been expected. Previously, equal proportions of men and women were described to develop AP.¹ In our nationwide database analysis, incidence of hospitalizations for AP was significantly higher in the male population compared with the female population. We believe this difference underlines the multifactorial nature of AP development. Apart from the previously described difference in diabetes prevalence, males in our study presented with a higher prevalence of smoking and alcohol use. Smoking is a known risk factor for AP with numerous studies confirming this association.^{1,4} More recently, smoking has also been associated with the development of chronic pancreatitis.^{4,16} In the United States, smoking has declined from 20.9% in 2005 to 15.1% in 2015; however, the percentage of men currently smoking remains higher than women.²⁴ Our study data reinforce this point, with 24.1% of men currently smoking compared with 15.4% of women ($P < 0.001$). Moreover, according to the World Health Organization report published in 2010, 23.3% of males and 10.9% of females participate in heavy episodic drinking, defined as at least 60 grams of pure alcohol at least once in the past 30 days.²⁵ Although AP does not only present in patient's consuming alcohol, the sensitivity of the pancreas to injury from other factors (genetic or environmental) and the risk of AP is most likely increased by alcohol consumption.²⁶ Once again, our study data are in accordance with the World Health Organization published data with 21.8% of men having an alcohol-related disorder compared with 8.2% of women ($P < 0.001$). Finally, race

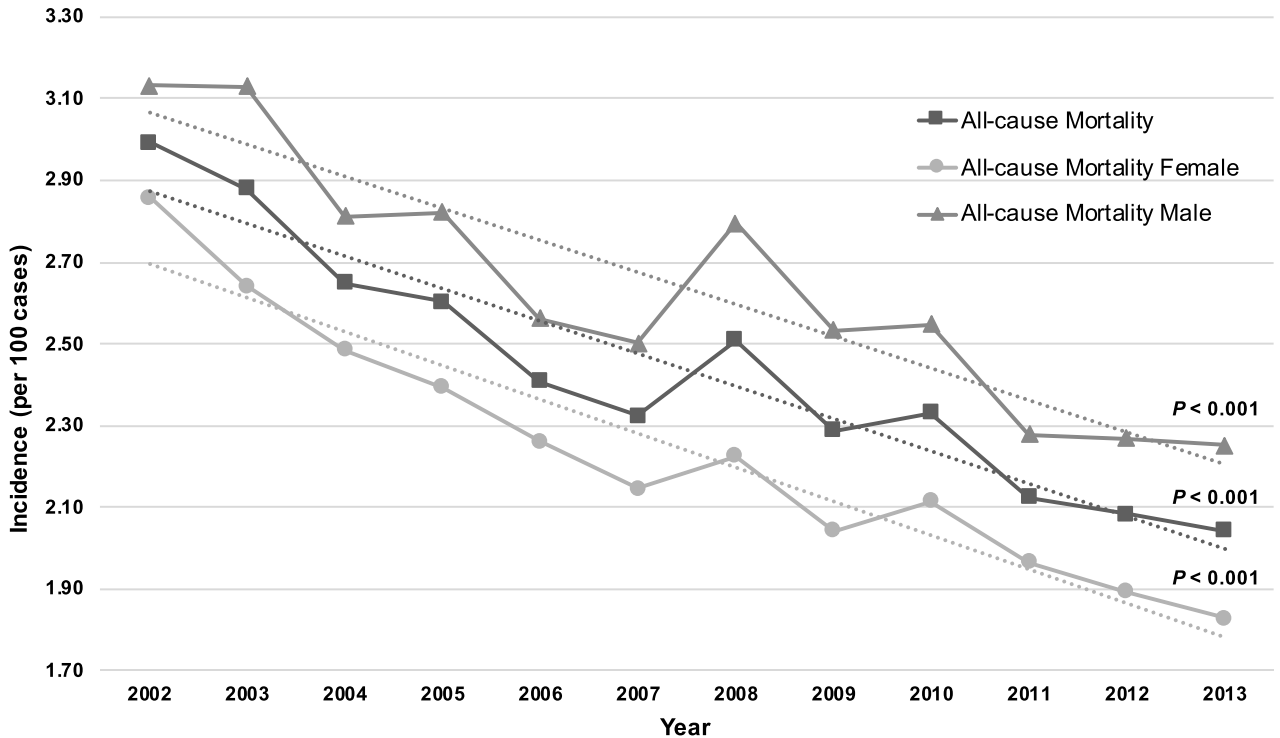


FIGURE 3. Incidence of mortality in AP.

alone has been previously reported to contribute to increased risk of AP. Compared with their white counterparts, African Americans have 2- to 3-fold higher risk of AP.^{1,27} Our study population included statistically significantly more African American males compared with females (17.1 vs 15.9, $P < 0.001$).

Despite the persistent increase in the incidence and severity of AP in our study, there was a statistically significant decrease in the incidence of in-hospital mortality from 2.99 cases per 100 cases of AP in 2002 to 2.04 per 100 cases in 2013 ($P < 0.001$). We hypothesize this decline in mortality to be the result of

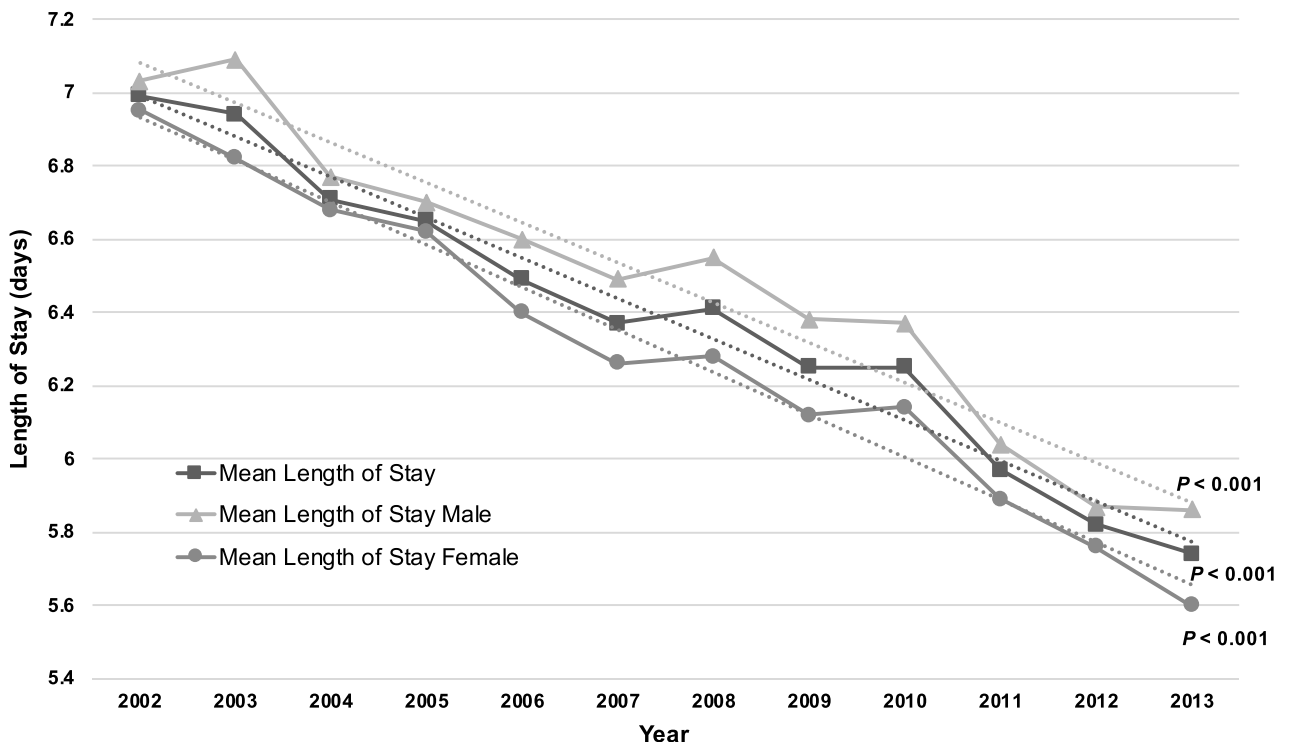


FIGURE 4. Mean LOS.

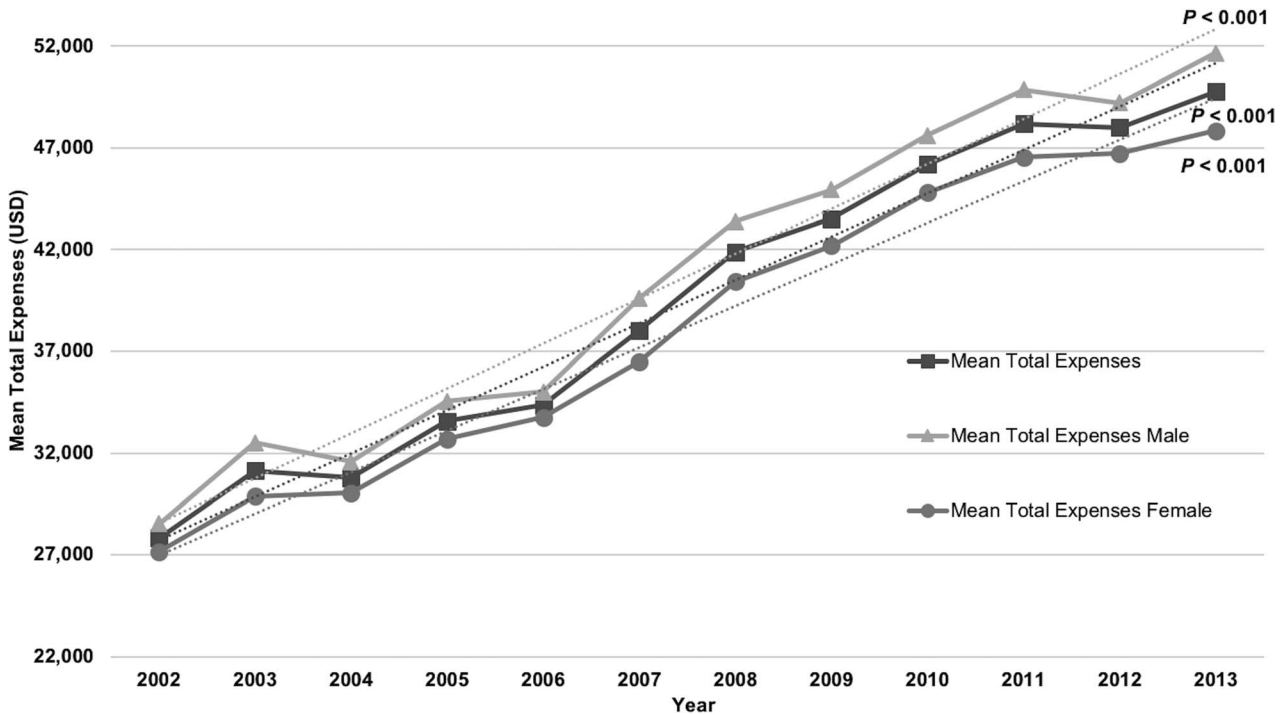


FIGURE 5. Mean total expenses per year.

changes in clinical and procedural management of AP over the past decade.

Substantial fluid resuscitation to reverse third space and intravascular volume depletion is the cornerstone of AP management.^{3,4} Multiple studies have demonstrated early and vigorous fluid administration within the first 24 hours to be associated with decreased morbidity and mortality.^{28,29} A better understanding of feeding patterns has changed the applied methods in current practice. Traditionally, AP was treated with prolonged bowel rest, nasogastric tube feeding, or total parenteral nutrition.^{3,4} Recent studies have demonstrated early feeding, prior to resolution of abdominal pain, to be a safe alternative in patients with mild pancreatitis, as long as the patient can tolerate it.^{4,30} For more severe cases, initiating nasogastric tube feeding within 24 hours was not shown to be superior to a strategy of attempting oral diet at 72 hours and starting tube feedings 2 to 3 days later, if unsuccessful.³¹ Nowadays, placement of a nasojejunal tube is required for only selected patients as feeding through a nasogastric or nasoduodenal tube has been shown to be clinically equivalent to nasojejunal tube feeding.³² Utilization of endoscopic retrograde cholangiopancreatography in AP is primarily indicated for patients with AP and concurrent acute cholangitis within 24 hours of admission. Magnetic resonance cholangiopancreatography and endoscopic ultrasound can assist in the evaluation for choledocholithiasis in the absence of cholangitis and/or jaundice.

More conservative management of acute pancreatic fluid collections has also evolved over the past several years, which may affect morbidity and survival.^{4,33} Although there are currently no studies evaluating the impact of these therapeutic modalities in the management of AP and the trends in their utilization, we believe their use may also be contributing to the witnessed decrease in mortality, considering the increasing severity. Further research in this area is required.

The previously described advances in management might have also contributed to the observed decrease in mean LOS from 6.99 (SD, 9.37) days in 2002 to 5.74 (SD, 7.94) days in 2013 ($P < 0.001$). However, this decline in mean LOS did not translate into a reduction in the total cost of hospitalization. In a study by Saligram et al,³⁴ the researchers hypothesized that decreasing LOS will reduce the total cost of hospitalization. In our analysis, the total cost of hospitalization increased from \$27,827 (SD, \$54,556) in 2002 to \$49,772 (SD, \$106,205) in 2013 ($P < 0.001$); males had significantly higher total cost of hospitalization compared with females (\$41,423 [SD, \$87,598] vs \$38,710 [SD, \$73,016], $P < 0.001$), possibly affected by increasing utilization of imaging studies, diagnostic tests, and procedural modalities in AP management, although further studies need to be performed.

Our study has limitations that originate from the nature of the database. The HCUP-NIS is a comprehensive, real-world

TABLE 2. In-Hospital Outcomes

	Male (n = 2,383,762)	Female (n = 2,401,828)	P
All-cause mortality, n (%)	62,442 (2.6)	53,291 (2.2)	<0.001
LOS, mean (SD), d	6.5 (9.2)	6.3 (8.1)	<0.001
Total cost related to hospitalization, mean (SD), \$	41,423 (87,598)	38,710 (73,016)	<0.001

all-comers registry of a large sample of US hospitalizations, utilizing ICD-9-CM codes to record primary hospital diagnoses. Events in the HCUP-NIS database are physician and institution reported. There is no way to validate the accuracy of diagnoses coded within the database. A study analyzed the use of diagnosis codes to estimate incidence of AP and found the positive predictive value to be 80% to 85%.³⁴ Relevant data about medication utilization, laboratory values, imaging findings, and management patterns were not available. Additionally, identification and description of incidence of AP subtypes were not possible. Finally, no long-term clinical outcomes data were available.

In conclusion, our study found a significant increase in incidence of AP within the United States from 2002 to 2013. During the same period, AP-related in-hospital mortality declined, although moderate and severe cases were observed more frequently. Additionally, mean LOS decreased, whereas mean cost of hospitalization increased. Male patients had a higher incidence of AP and in-hospital all-cause mortality compared with the female patient. The reported trends might be the result of changes in environmental and lifestyle risk factors as well as advancements in clinical management. With AP being the leading gastrointestinal condition causing hospitalization, it is imperative to further evaluate the cause of the increasing incidence of AP and decreasing in-hospital mortality.

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