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Admissions for acute biliary pancreatitis without necrosis and infection complicated by severe sepsis and septic shock: a national study

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Abstract

Background Severe sepsis with septic shock (SSWSS) is a potential and severe complication that can arise among patients hospitalized for acute biliary pancreatitis.

Methods We queried the 2018-2021 National Inpatient Sample for adults with a primary diagnosis code of acute biliary pancreatitis without necrosis or infection. Baseline characteristics of the patients were studied and multivariate regression models were used to appraise the roles of different factors for events of SSWSS.

Results We evaluated 136,140 adults who had acute biliary pancreatitis without necrosis or infection on admission; their median age was 57.0 years, and the majority were female (60.6%). Of these, 435 patients developed SSWSS. Higher odds were seen in cases with coexisting chronic kidney disease (P<0.001), liver cirrhosis (P<0.001), and human immunodeficiency virus infection (P<0.001). Races other than White/Black/Hispanics had higher odds (P<0.001) than Whites. Females were less likely to report SSWSS (P<0.001) than males. Moreover, patients from the 26th-50th median household quartiles had lower odds of SSWSS than those in the 0-25th quartiles. Medium (P<0.001) and large (P<0.001) hospitals reported more cases than small hospitals. Admissions in the southern areas of the United States also exhibited higher odds (P=0.026), than Northeast regions. Lower odds were noted in smokers (P<0.001) and cases with dyslipidemia (P=0.048). SSWSS led to higher mortality rates (65.5% vs. 0.4%).

Conclusions In our nationwide analysis, we found that episodes of SSWSS among patients with acute biliary pancreatitis were influenced by several factors. SSWSS patients also had higher mortality.

Keywords Acute biliary pancreatitis, severe sepsis, critical care, United States of America

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Introduction

Acute pancreatitis (AP) is a major healthcare burden in the USA, accounting for over 200,000 admissions and hospital visits each year [1] with a rising trend [2,3]. Obstruction due to gallstone (acute biliary pancreatitis, ABP) is the most common cause of AP, representing 38% of all cases, while alcohol is a close second with 36% [4-6]. Other less common pathologies can involve medications, autoimmune diseases, recent endoscopic retrograde cholangiopancreatography/abdominal surgery, trauma, and infections, among others [7].

Although most patients with ABP experience an event-free recovery, there is a risk of local and systemic complications [8]. One such complication involves severe sepsis with septic shock (SSWSS), which has high mortality and risk of morbidity. In fact, in rare cases, even ABP patients with no necrosis or

infection on admission can develop SSWSS. Acute pancreatitis can increase the expression of various proinflammatory factors, such as tumor necrosis factor and interleukin-6, that can cause damage to the intestinal mucosal membranes. The impaired intestinal barrier allows bacterial spread, which plays an important role in the development of pancreatic infection, necrosis, and eventual sepsis [9-12]. Moreover, the leakage of pancreatic enzymes into the pancreatic and neighboring tissues can trigger a direct insult that may complicate with obstruction, inflammation and necrosis, and become a nidus of infection [13]. However, at present, there is a lack of recent data concerning the presence of ABP and complications such as SSWSS. Therefore, we designed a designed a retrospective analysis that would help identify the incidence of SSWSS among ABP cases initially admitted with no necrosis or infections, and the factors that led to SSWSS. We also aimed to estimate the mortality risk associated with SSWSS in ABP patients.

Materials and methods

Design and data source

We performed a retrospective analysis of hospital records from the National Inpatient Sample (NIS). The NIS contains billing data from hospitals across the USA and is produced annually as part of the Healthcare Cost and Utilization Project (HCUP). The publicly-accessible database is a 20% stratified sample, which can be used to estimate over 98% of the national hospitalization records, via proper adjustments, as per HCUP's recommendations [14].

The NIS contains no identifying patient information, only patient data such as age, sex, race and primary payer form, as well as hospital demographics. Users can further input additional diagnoses and procedures using International Classification of Diseases version 10 - Clinical Modification (ICD-10-CM) and Procedural (ICD-10-PR) codes [14,15].

Study population

For our study, we focused on patients admitted with a primary diagnosis of biliary acute pancreatitis without necrosis or infection, using the ICD-10 code K85.10. Data between 2018 and 2021 were analyzed, restricted to patients aged 18 years and over. Patients with COVID-19 were also excluded [16]. To avoid duplication of data, we did not include cases that were transferred in or out. Finally, cases with missing data for our variables of interest were also removed from our analysis. Our study conformed with the reporting standards of the STROBE guidelines [17].

Study variables and outcomes

First, we evaluated the baseline patient variables including sex, race, age, weekend (vs. weekday) admission, median household income quartiles, and primary payer forms. The presence of multiple comorbidities was also assessed: hypertension, dyslipidemia, diabetes, liver cirrhosis, smoking, chronic kidney disease, peripheral vascular disease, alcohol abuse, obesity, human immunodeficiency virus (HIV), cachexia, drug abuse, and chronic obstructive pulmonary disease (COPD). Hospital demographics, such as rural vs. urban (teaching vs. non-teaching), size (no. of beds) and region, were also evaluated.

The main outcome of the study involved the occurrence of SSWSS (ICD-10 code R65.21). Other outcomes of interest compared the median ages, length of stay (LOS), and hospital charges between patients with and without SSWSS.

Statistical analysis

We performed our statistical analyses using STATA version 18.0 and SPSS version 29.0. Adhering to HCUP's guidelines, our study used the variable "DISCWT" to produce a national estimate. Variables ≤10 were not reported to protect the patients' identity. To estimate the impact of variables that contributed to SSWSS events, a multivariate logistic regression model was constructed, containing variables found to have significance ($P<0.05$) on univariate screening, or were deemed relevant (race, income quartile, hospital region, size, and insurance type). The differences in ages, LOS, and hospital charges were compared via Mann-Whitney *U* tests, and reported as median value and interquartile range. Statistical significance was maintained at $P<0.05$ for our study.

Ethical clearance and user agreement

As our study relied solely on the NIS, which is released with no patient identifiers, it was exempt from ethics board approval or institutional Review Board review. This complies with the guidelines issued by HCUP on the use of the NIS. Authors handling the raw data from HCUP took the mandated training and signed their user agreement.

Results

Baseline patient and hospital characteristics

We evaluated a total of 136,140 adults who were hospitalized for biliary acute pancreatitis without necrosis or infection between 2018 and 2021 (Fig. 1). The median age was 57.00 years, with an interquartile range of 41.00-71.00. Most patients were females (60.6% vs. 39.4% males), who were also younger (females: median 55.00 years, IQR 36.00-69.00, vs. males: median 61.00 years, IQR 47.00-72.00). Most patients (62.0%) were racially White, followed by Hispanics (20.0%), and Blacks (10.4%). Medicare covered 36.4% of cases, while

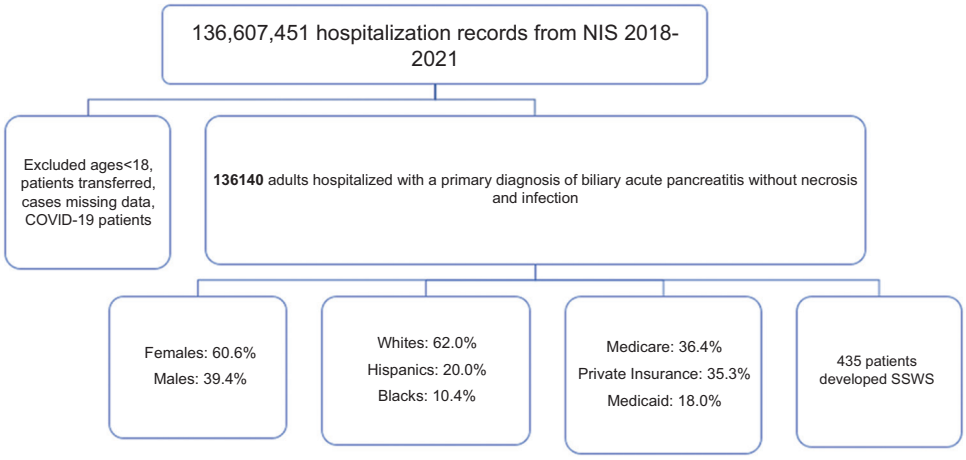

Figure 1 Selection of patients from the NIS
NIS, National Inpatient Sample; SSWS, severe sepsis with septic shock

private insurances and Medicaid covered 35.3% and 18.0%, respectively.

Most patients (27.7%) were from the lower (0-25th) median household income quartiles. We further found that 28.1% of all hospitalizations took place during the weekend. The majority of patients were treated in hospitals classified as large (45.3%), urban teaching centers (70.0%), and in southern regions of the USA (39.4%).

Most commonly observed comorbidities included hypertension (39.7%), dyslipidemia (33.6%), smoking (31.7%), obesity (30.1%) and diabetes (22.5%), with fewer cases exhibiting chronic kidney disease (9.0%), peripheral vascular disease (2.1%), liver cirrhosis (5.3%), alcohol abuse (5.2%), HIV (0.4%), cachexia (0.2%), drug abuse (3.1%), or COPD (6.7%) (Table 1).

SSWSS, predictors, and overall impact on mortality

There were 435 cases that developed SSWSS (320 cases per 100,000 ABP admissions); these patients were older: median age 70.00 years (IQR 60.00-78.00) vs. median 57.00 years, (IQR 41.00-71.00) in patients without SSWSS.

Univariate regression analyses

Patient demographics and comorbidities in our univariable analyses that reported a P-value less than 0.05 included sex (odds ratio [OR] 0.377, 95% confidence interval [CI] 0.310-0.459, P<0.001), hypertension (OR 0.577, 95%CI 0.467-0.712; P<0.001), dyslipidemia (OR 1.532, 95%CI 1.267-1.852; P<0.001), smoking (OR 0.485, 95%CI 0.381-0.618; P<0.001), diabetes (OR 2.114, 95%CI 1.741-2.567; P<0.001), liver cirrhosis (OR 10.539, 95%CI 8.660-12.825; P<0.001), obesity (OR 0.786, 95%CI 0.633-0.975; P=0.029), HIV status (OR 12.651, 95%CI 8.011-19.979; P<0.001), COPD (OR 1.813, 95%CI 1.349-2.436; P<0.001) (Table 2).

Multivariate regression analyses

Following the previously described multivariate regression model, factors associated with higher odds of SSWSS included chronic kidney disease (adjusted odds ratio [aOR] 4.766, 95%CI 3.685-6.163, P<0.001), liver cirrhosis (aOR 7.942, 95%CI 6.477-9.739, P<0.001) and HIV (aOR 15.308, 95%CI 8.976-26.107, P<0.001). Moreover, patients admitted to medium-sized (aOR 1.877, 95%CI 1.383-2.549, P<0.001) or large hospitals (aOR 2.095, 95%CI 1.568-2.799, P<0.001) were more likely to report SSWSS than those in small hospitals. While no racial differences were seen for Blacks (aOR 0.755, 95%CI 0.526-1.085, P=0.128) and Hispanics (aOR 0.941, 95%CI 0.700-1.264, P=0.684) as compared to Whites, those classified as non-White/Black/Hispanic (aOR 2.128, 95%CI 1.600-2.830, P<0.001) had higher odds of SSWSS. Sex-based differences were also noted, with lower odds among females (aOR 0.456, 95%CI 0.372-0.559, P<0.001). Finally, we also saw socioeconomic disparities, with lower odds among those in the 26th-50th percentile (aOR 0.578, 95%CI 0.432-0.775, P<0.001) (vs. 0-25th), while patients in the 51st-75th (aOR 0.761, 95%CI 0.580-1.000, P=0.050) and 76th-100th (aOR 0.930, 95%CI 0.708-1.222, P=0.601) percentiles were all comparable (Table 3).

Patients with dyslipidemia (aOR 0.808, 95%CI 0.671-1.120, P=0.048) and smoking (aOR 0.374, 95%CI 0.290-0.483, P<0.001) recorded lower odds of SSWSS. No statistically significant differences were seen for other variables, including hypertension (aOR 0.867, 95%CI 0.671-1.120, P=0.274), diabetes (aOR 1.127, 95%CI 0.910-13.96, P=0.272), obesity (aOR 1.134, 95%CI 0.900-1.428, P=0.286), COPD (aOR 1.202, 95%CI 0.878-1.647, P=0.251) and primary payer insurance type (Table 3). SSWSS events were associated with a longer LOS (median 9.00 days, IQR 5.00-19.00 vs. 4.00, IQR 2.00-5.00; P<0.001) and higher hospital charges (median $178,926 IQR $90,054-318,288 vs. median $47,147, IQR $28,806-73,493; P<0.001). An estimated 65.5% of patients with SSWSS died (vs. 0.4% in the non-SSWSS cohort).

Table 1 Baseline characteristics of patients admitted with acute biliary pancreatitis

Characteristics	% of cases (out of 136140)
Age (median, IQR)	57.00 (41.00-71.00)
Sex	
Male	39.4
Female	60.6
Race	
White	62.0
Black	10.4
Hispanic	20.0
Rest	7.5
Primary payer form	
Medicare	36.4
Medicaid	18.0
Private	35.3
Rest	10.3
Weekend hospitalization	28.1%
Median household income quartiles	
0-25th percentile	27.7
26th to 50th percentile (median)	25.8
51st to 75th percentile	25.2
76th to 100th percentile	21.3
Size (no. of beds)	
Small	24.6
Medium	30.1
Large	45.3
Location/teaching status	
Rural	8.0
Urban nonteaching	22.0
Urban teaching	70.0
Region of hospital	
Northeast	18.5
Midwest	18.4
South	39.4
West	23.6
Hypertension	39.7
Dyslipidemia	33.6
Smoking	31.7
Diabetes	22.5
Chronic kidney disease	9.0
Peripheral vascular disease	2.1
Liver cirrhosis	5.3
Alcohol abuse	5.2
Obesity	30.1
HIV	0.4
Cachexia	0.2
Drug abuse	3.1
COPD	6.7

IQR, interquartile range; HIV, human immunodeficiency virus; COPD chronic obstructive pulmonary disease

Discussion

To our knowledge, our study is the first extended, national analysis to evaluate the baseline characteristics of patients with biliary acute pancreatitis without necrosis or infection, as well as the factors that influence the occurrence of SSWSS. In total, we evaluated 136,140 adult cases and found that a higher proportion were females, a finding that is comparable with the higher odds of gallstones in women as compared to men, as previously reported [18,19]. We also found that majority of the patients were White, which reflects the US census distribution. In addition, the second most involved racial group were Hispanics, with almost twice the percentage of Blacks. In the core NIS file of all hospitalizations between 2018-2021, Hispanics usually cover 12-13% of sample sizes, while Blacks cover 15-16%. The higher percentage of Hispanic patients with acute biliary pancreatitis compared to Blacks correlates with a study by Figueiredo *et al*, where Hispanics in the USA were linked with higher odds of reporting gall bladder-related disease; this could be connected to genetic as well as environmental factors, including diet [20].

Our study further found that 27.7% of cases were from people with the lowest household income quartile in the United States. Li *et al*, in their analysis, found that this group also represented the highest proportion of patients admitted for symptomatic cholelithiasis (32.5%) and cholecystitis (29.1%) [21]. It is vital to understand whether the socioeconomic disparities impacted their access to care and follow up, which in turn led to complications, including acute biliary pancreatitis. Our study also showed similar geographic distributions, with more cases being treated in the southern regions of the USA [21] and in urban hospitals [22], as with other gallbladder and biliary diseases.

A significant portion of patients were also obese (30.1%), which is a major risk factor for gallbladder and biliary complications [23]. We also found a higher prevalence of smoking, which can slow down gallbladder emptying, thus predisposing to gallstone formation [24] and eventual biliary pancreatitis. While the NIS does not include precise coding details for medications, 39.7% of patients had a history of hypertension and 33.6% of them had dyslipidemia. The direct impact of cholesterol and the influence of lipid-lowering medications, such as fibrates, and antihypertensive medications, such as thiazides, on the development of gallstones could predispose such patients to biliary pancreatitis [25-27]. A more thorough comparison, using retrospective records from different centers, could help clarify such issues.

In the second part of our analysis, we found that, among the 136,140 cases who were admitted with no necrosis and infection, there were 435 patients (320 cases per 100,000) who developed SSWSS, potentially attributable to a variety of factors. Higher odds were seen with age, as SSWSS patients were older. Such a finding might be related to the waning immune response seen with aging, as well as the potential

Table 2 Univariate regression models and the odds ratios of severe sepsis with septic shock among adults with acute biliary pancreatitis

Variable	P-value	OR	Lower 95%CI	Upper 95%CI
Weekend admission	0.065	0.813	0.653	1.013
Female sex	<0.001	0.377	0.310	0.459
Median household income national quartile (0-25th as reference)				
26th to 50th percentile	<0.001	0.597	0.450	0.792
51st to 75th percentile	0.234	0.856	0.663	1.106
76th to 100th percentile	0.242	1.158	0.905	1.482
Bed size of hospital (small as reference)				
Medium	<0.001	1.976	1.462	2.670
Large	<0.001	2.087	1.570	2.774
Region of hospital (Northeast as reference)				
Midwest	0.102	0.756	0.541	1.057
South	0.303	1.147	0.884	1.488
West	0.897	0.981	0.731	1.317
Comorbidities				
Hypertension	<0.001	0.577	0.467	0.712
Dyslipidemia	<0.001	1.532	1.267	1.852
Smoking	<0.001	0.485	0.381	0.618
Diabetes	<0.001	2.114	1.741	2.567
CKD	<0.001	9.138	7.563	11.041
Peripheral vascular disease	0.172	0.541	0.224	1.308
Liver cirrhosis	<0.001	10.539	8.660	12.825
Alcohol abuse	0.120	1.343	0.926	1.947
Obesity	0.029	0.786	0.633	0.975
HIV	<0.001	12.651	8.011	19.979
Drug abuse	0.352	0.742	0.396	1.390
COPD	<0.001	1.813	1.349	2.436
Race (White as reference)				
Black	0.654	1.075	0.783	1.478
Hispanic	0.293	0.867	0.665	1.131
Other race	<0.001	2.311	1.771	3.014
Insurance form (Medicare as reference)				
Medicaid	<0.001	0.381	0.281	0.515
Private	<0.001	0.369	0.292	0.466
Other forms	<0.001	0.333	0.221	0.502

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; HIV, human immunodeficiency virus; COPD chronic obstructive pulmonary disease

presence of multiple comorbidities and age-related changes in pathophysiology [28-30]. In addition, although 60.6% of all admitted patients were female, SSWSS was more likely to involve males than females—possibly because the male patients in our study were older than the female patients.

While events of SSWSS were comparable between Whites, Blacks and Hispanics, other races exhibited higher odds of such events. We also found that those in the 26th-50th income quartile had lower odds of SSWSS than those in the lower quartile, with no differences between the top two quartiles. To reduce such disparities, studies at various community levels should be encouraged, to help openly address any issues these patients had in seeking medical care, as well as at hospital level, to identify other factors that contributed to such racial and socioeconomic discrepancies.

Our study further identified that patients in large centers, as compared to small centers, were more prone to experience SSWSS, as were patients in Southern as compared to Northeastern regions. While the center size differences might be linked with the more complex cases being treated, underdiagnosis and underreporting of SSWSS in small centers cannot be ruled out. A center-based retrospective analysis of cases should be encouraged, which could help map the distribution of centers and elucidate any link with a hospital's region.

In addition, we also noted that some factors, such as chronic kidney disease, liver cirrhosis and HIV, predisposed patients to SSWSS. The liver is a key organ involved in a balanced immune response to trauma and exposure to potential infectious agents; it is therefore vital for physicians to properly assess patients' liver function and, if necessary, quantify them as high-risk for complications [31]. Similarly, patients with impaired kidney function will have a buildup of toxic materials that can impair healing [32], impact appetite [33] and weaken their immune system [34]. Patients with HIV have a blunted immune system, with a potentially lower T-cell count. The NIS data, however, did not allow us to identify and adjust for T-cell levels or any ongoing antiretroviral therapy. Nevertheless, our finding

Table 3 Adjusted odds ratio (aOR) of severe sepsis with septic shock among adults with acute biliary pancreatitis

Variable	P-value	aOR	Lower 95%CI	Upper 95%CI
Age	<0.001	1.031	1.022	1.04
Female sex (vs. male)	<0.001	0.456	0.372	0.559
Median household income national quartile (0-25th as reference)				
26th to 50th percentile	<0.001	0.578	0.432	0.775
51st to 75th percentile	0.05	0.761	0.58	1
76th to 100th percentile	0.601	0.93	0.708	1.222
Size of hospital (no. of beds; small as reference)				
Medium	<0.001	1.877	1.383	2.549
Large	<0.001	2.095	1.568	2.799
Region of hospital (Northeast as reference)				
Midwest	0.626	0.917	0.646	1.3
South	0.026	1.371	1.038	1.81
West	0.645	0.93	0.683	1.266
Comorbidities				
Hypertension	0.274	0.867	0.671	1.12
Dyslipidemia	0.048	0.808	0.654	0.998
Smoking	<0.001	0.374	0.29	0.483
Diabetes	0.272	1.127	0.91	1.396
CKD	<0.001	4.766	3.685	6.163
Cirrhosis	<0.001	7.942	6.477	9.739
Obesity	0.286	1.134	0.9	1.428
HIV	<0.001	15.308	8.976	26.107
COPD	0.251	1.202	0.878	1.647
Race (White as reference)				
Black	0.128	0.755	0.526	1.085
Hispanic	0.684	0.941	0.7	1.264
Other race	<0.001	2.128	1.6	2.83
Insurance form (Medicare as reference)				
Medicaid	0.256	1.236	0.857	1.782
Private	0.682	0.94	0.701	1.262
Other forms	0.949	0.985	0.629	1.544

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; HIV, human immunodeficiency virus; COPD chronic obstructive pulmonary disease

of a high adjusted odds ratio raises serious concerns about these patients' outcomes. It is important to understand the key reasons that caused such risks, other than their immune system, and promote adequate changes. We noted that patients who were smokers or had dyslipidemia had lower odds of reporting SSWSS. Prior studies have confirmed that smokers have a downregulated immune response [35-37]. Since part of the pathophysiology of sepsis in acute pancreatitis relies on the immune response and damage caused by cytokines [12], smokers may be experiencing a suppressed immune reaction, which could explain the lower odds seen in our study. Patients with dyslipidemia may be on drugs such as statins. The ASEPSIS trial by Rachoin *et al* found that statins impaired the progression of sepsis [38]. As the NIS does not include data for the current drugs taken by patients, we were unable to take such potential confounders into account. As the pathophysiology of sepsis in pancreatitis involves a complex interplay of multiple factors, it is imperative to advocate for further research. Such future studies, carried out at multiple centers, should also include a range of medications that might impact the variables of our study.

Finally, we confirmed that SSWSS was a major factor that contributed to death among patients admitted with acute biliary pancreatitis, with a higher hospital charge and a longer stay. To help reduce the burden of healthcare, it is important that physicians are able to identify patients who are at risk for SSWSS. Changes in protocols should be implemented, including a more thorough check of vitals and appropriate identification of the early signs of sepsis.

Our evaluation of data from the biggest inpatient database provided very important findings. However, there were several limitations that need to be addressed. First, the database relies on hospital codes for various procedures and conditions. Mistakes in coding and differences in coding for SSWSS or similar comorbidities might have influenced our results. Moreover, our data did not contain information on the severity at time of admission, the time from symptom to admission, the medications being used, and patients' laboratory values. With such limitations, we were unable to categorize the ABP patients based on severity, or to adopt various scoring systems, such as the Ranson criteria, APACHE II (Acute Physiology and Chronic Health Evaluation II), BISAP (Bedside Index for Severity in Acute Pancreatitis), or Glasgow scores. A retrospective review of hospital cases in future studies can overcome such limitations and help consolidate our results.

In addition to several retrospective studies, it is important to promote future research to improve our understanding of the various pathways that are involved in the pathogenesis of sepsis in ABP patients. Moreover, additional studies targeting the management of ABP with SSWSS, and factors impacting the patients' short and long-term outcomes, mortality and healthcare burden, should also be considered.

To conclude, our study confirmed that, while SSWSS is a rare occurrence among patients with acute biliary pancreatitis with no necrosis or infection on admission, it is associated with a range of factors, including sex, race, age, hospital demographics and comorbidities. Moreover, SSWSS is a major predictor of mortality among such patients, and there is an urgent need to conduct more studies so that other factors can be identified and disparities remedied.

Acknowledgment

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Summary Box

What is already known:

- More than 200,000 cases of acute pancreatitis hospitalizations are encountered annually
- Acute biliary pancreatitis (ABP) due to gallstones is the leading cause of pancreatitis, followed by alcohol
- Severe sepsis can develop in some cases of acute biliary pancreatitis, with a high mortality rate

What the new findings are:

- The incidence of severe sepsis with septic shock was 320 cases per 100,000 ABP admissions
- Higher odds of septic shock were seen in older patients, males, races other than White/Black/Hispanic, those in the lowest income quartiles, in medium and large hospitals, in admissions within the southern region, among patients with chronic kidney disease, liver cirrhosis or human immunodeficiency virus infection
- The overall mortality rate in patients with septic shock was 65.5%

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