Extrapancreatic Complications in Hospitalized Patients With Mild Acute Pancreatitis Are Associated With Poorer Outcomes

Results From a Single-Center Study

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Objective: Patients with acute pancreatitis (AP) are at risk for extrapancreatic complications (EPCs) when admitted to the intensive care unit (ICU). We assessed the prevalence of EPCs in non-ICU AP patients and their outcomes.

Methods: We retrospectively studied EPCs in non-ICU AP patients between 2008 and 2018. Outcomes such as length of stay (LOS), inpatient mortality, and 30-day readmission rates were compared between those with and without EPC.

Results: Of the 830 AP patients, 151 (18.1%) had at least 1 EPC. These included urinary tract infection (15.9%), *Clostridium difficile* infection (17.2%), pneumonia (7.3%), bacteremia (17.2%), acute kidney injury requiring dialysis (3.3%), gastrointestinal bleeding (12.5%), alcohol withdrawal (24.5%), delirium (14.5%), and falls (1.32%). Patients with EPC had increased mean LOS (6.98 vs 4.42 days; $P < 0.001$) and 30-day readmissions (32.5% vs 19%; $P < 0.001$). On multivariate regression, EPCs were independently associated with higher LOS (odds ratio, 1.45 [95% confidence interval, 1.36–1.56]; $P < 0.001$) and 30-day readmissions (odds ratio, 1.94 [95% confidence interval 1.28–2.95]; $P < 0.001$).

Conclusions: The EPCs are common among noncritical AP patients and contribute to poor outcomes like increased LOS and 30-day readmissions.

Key Words: acute pancreatitis, alcohol withdrawal, delirium, bacteremia, *Clostridium difficile* infection, gastrointestinal bleeding

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Acute pancreatitis (AP) is the most common gastrointestinal (GI) condition necessitating hospitalization and has an annual incidence of 34 per 100,000 person-years with the annual cost exceeding $2 billion.[1–3] Although most patients with AP have a mild course, about 20% to 30% patients develop moderate to severe pancreatitis with associated local complications and multisystem organ failure, which contributes to the overall morbidity and mortality associated with AP.[4,5] To reduce these complications, several societies provide guidance for both early management of AP and management of local pancreatic complications.[6–11]

In addition to local and systemic complications associated with AP, extrapancreatic complications (EPCs) are highly prevalent in patients admitted with AP and are associated with longer lengths of stay (LOS) especially in patients admitted to intensive care units (ICUs).[12,13] However, little is known regarding the prevalence of EPCs in AP patients who are admitted to a non-ICU setting.

We thus sought to quantify the prevalence and determine the impact of EPCs on patient-related outcomes such as LOS, inpatient mortality, and 30-day readmission among non-ICU patients admitted with AP.

MATERIALS AND METHODS

Data Source and Study Design

We retrospectively evaluated patients with AP who were admitted to our tertiary care center between January 1, 2008, and December 31, 2018. We included adult patients who met the diagnosis of AP based on the revised Atlanta criteria (ie, 2 of the following 3 criteria: epigastric pain, elevation of serum lipase level >3 times upper limit of normal, and/or evidence of pancreatitis on cross-sectional imaging).[4] Patients younger than 18 years, those with chronic pancreatitis, or those with known pancreaticobiliary malignancy were excluded from the study. In addition, patients who were discharged from the emergency department without being admitted to the inpatient unit were also excluded from our study. Those patients who were admitted to the ICU at any point of their hospital stay were also excluded from the study.

Data Collection, Study Groups, Outcomes, and Subgroup Analyses

Demographic, clinical, laboratory, and radiological data were collected. In addition, patients were categorized as mild (AP without any local or systemic complications), moderate (AP with transient [<48 hours] end-organ failure, with or without local complications), or severe (AP with persistent [>48 hours] end-organ damage, with or without local complications).[4] Local pancreatic complications included pancreatic necrosis, pancreatic fluid collection, and pancreatic abscess. We then recorded EPCs as defined by Table 1 and further categorized them as either infectious or noninfectious. Infectious EPCs consisted of bacteremia, pneumonia, urinary tract infection (UTI), and *Clostridium difficile* infection, and noninfectious EPCs included acute kidney injury

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TABLE 1. Definitions of EPC

EPC	Definition
AKI requiring hemodialysis	Renal failure unrelated to AP requiring initiation of renal replacement therapy
Bacteremia	Positive blood culture data in more than 1 culture bottle (excluded patients with bacteremia from infected pancreatic necrosis)
Pneumonia	Positive culture data in a respiratory sample obtained from expectorated or induced sputum
UTI	Positive culture data in urine obtained from either a clean catch sample or from indwelling catheter
C. difficile infection	Toxin assay or PCR-positive stool assay for *C. difficile*
GI bleeding	GI bleed from any part of the GI tract either detected on endoscopy or based on documentation of clinical course
Delirium	Acute state of confusion associated with fluctuating mental status changes in the absence of an underlying neurological disorder
Alcohol withdrawal	Documented evidence of symptoms of alcohol withdrawal such as tremulousness, anxiety, hyperreflexia, tachycardia, palpitations, headache, mental status changes, delirium tremens requiring pharmacologic treatment
Fall with injury	Fall resulting in physical harm to the patient

PCR, polymerase chain reaction.

(AKI) requiring hemodialysis, GI bleeding, alcohol withdrawal, delirium, and fall associated with injury. Of note, only those EPCs that were not direct sequelae of the AP episode, but rather unrelated to the AP, were included.

We separated our patients into 2 groups: those without EPCs and those at least 1 EPC. We then compared demographic characteristics, severity, local complications, and outcomes between the 2 groups. Our primary outcomes were inpatient mortality, LOS, and 30-day readmissions. We then performed a subgroup analysis studying these outcomes based on severity of AP in patients with mild AP and in those with moderate to severe AP.

Statistical Analysis

All data analyses were performed using the R software (version 3.6.1; R Core Team 2018a, Vienna, Austria) within RStudio (version 1.1463; RStudio, Inc, Boston, Mass) via the Tidyverse package.[14] Continuous variables were presented as means with range and standard deviation (SD). These were analyzed using the *t* test or Wilcoxon rank sum test as deemed appropriate. Categorical variables were presented as frequencies (%) and analyzed using the Pearson χ^2 test. Univariate analyses comparing demographic characteristics and outcomes between the EPC and non-EPC groups were performed. Furthermore, we performed a multivariate regression analysis of the significant findings from univariate analysis after adjusting for demographic characteristics, Charlson Comorbidity Index (CCI), severity of AP, and local pancreatic complications. A logistic regression model was used for 30-day readmissions, whereas a negative binomial model was used for LOS. A P value of less than 0.05 was considered statistically significant.

Ethical Considerations

The institutional review board at our hospital approved this study.

RESULTS

Patient Characteristics and EPCs

In our study period, 830 patients met the inclusion criteria for analysis. The mean age of our study cohort was 52.3 years. A majority of patients were male (50.7%), White (74.2%), and admitted with mild AP (77.6%). The most common etiology of AP was gallstone related (32.2%), and approximately 22% of patients developed local complications of AP. The overall in-hospital mortality rate in our group was 0.7% (6 of 830).

In our study cohort, 151 patients (18.1%) developed at least 1 EPC during the course of their hospital stay for a total of 172 EPCs (85 noninfectious and 87 infectious) occurring during the study period (1.13 events/patient; Fig. 1). Alcohol withdrawal (24.5%) was the most common noninfectious EPC followed by delirium (17.8%), GI bleed (12.5%), AKI requiring dialysis (3.3%), and fall with injury (1.3%). Among infectious EPCs, bacteremia and *C. difficile* infection (17.2% each) were the most common EPC, followed by UTI (15.8%) and pneumonia (7.3%).

Univariate and Outcome Analysis

Univariate analysis is summarized in Table 2. Compared with the non-EPC group, patients in the EPC group were significantly older (55.9 vs 51.5 years, $P = 0.005$), had significantly greater comorbidity (1.03 vs 0.79, $P = 0.008$), and had a greater proportion of active alcohol use (49% vs 33.6%, $P = 0.001$). A significantly greater proportion of patients with EPC had alcoholic AP (37.1% vs 21.5%, $P < 0.001$), higher BISAP score (1.38 vs 0.89, $P < 0.001$), moderately severe or severe AP (31.1% vs 20.3%, $P < 0.01$), and local complications (42.7% vs 19.9%, $P < 0.001$).

Table 3 outlines outcomes in the 2 groups. Mean LOS was significantly longer for patients in the EPC group (6.98 vs 4.42 days, $P < 0.001$), and the rate of 30-day readmissions was significantly higher in the EPC group (32.5% vs 19%, $P < 0.001$). No significant differences were noted in inpatient mortality between the 2 groups ($P > 0.05$).

We also separately analyzed outcomes in patients with infectious and noninfectious EPC. Patients with 1 or more infectious EPC had longer mean hospital stays (8.40 vs 4.551 days, $P < 0.001$) and higher 30-day readmissions (35.5% vs 19.9%, $P = 0.002$) compared with patients without any EPC. Similarly, patients with noninfectious EPC also had longer mean hospital stays (6.26 vs 4.73 days, $P = 0.013$) as compared with patients without any EPC; however, no significant difference was seen in 30-day readmissions (29.3% vs 20.6%, $P = 0.093$).

Multivariate Analyses

Table 4 summarizes EPCs as independent predictors of LOS and 30-day readmissions after adjusting for age, severity of AP, etiology, CCI, and local pancreatic complications. In this group,

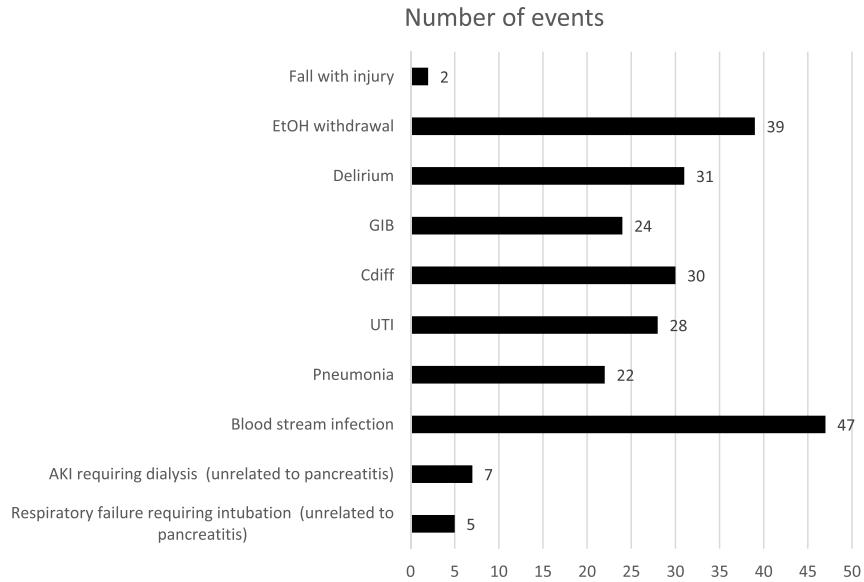

FIGURE 1. Histogram describing the number of events for each EPC. Cdiff, *C. difficile*; EtOH, alcohol; GIB, GI bleeding.

EPC was independently associated with increased LOS and 30-day readmissions ($P < 0.001$). Infectious EPCs were independent predictors for longer hospital stays and higher 30-day readmissions, whereas noninfectious EPCs were independent predictors of only longer hospital stays. Individually, bacteremia, *C. difficile* infection, GI bleeding, and delirium were significant predictors for LOS, whereas bacteremia and *C. difficile* infection were predictors for 30-day readmissions.

TABLE 2. Univariate Descriptive Analysis of AP Patients With and Without EPC

	EPC Not Present (n = 679)	EPC Present (n = 151)	*P*
Demographics			
Age, mean (SD), y	51.5 (15.7)	55.9 (17.4)	0.005
Sex, female, n (%)	344 (50.7)	65 (43)	0.109
Race, n (%)			0.371
African American	137 (20.2)	38 (25.3)	
White	510 (75.1)	105 (70)	
Body mass index, mean (SD), kg/m^2	27.4 (6.93)	26.5 (6.48)	0.113
Comorbidities, n (%)			
Active alcohol use	228 (33.6)	74 (49)	0.001
Active tobacco use	180 (26.6)	47 (31.1)	0.308
History of AP	354 (52.1)	69 (45.7)	0.18
CCI, mean (SD)	0.79 (1.02)	1.03 (1.03)	0.008
Etiology, n (%)			<0.001
Alcohol	146 (21.5)	56 (37.1)	
Gallstone	235 (34.6)	33 (21.9)	
Idiopathic	193 (28.4)	46 (30.5)	
BISAP score, mean (SD)	0.89 (1.02)	1.38 (1.04)	<0.001
Modified Atlanta criteria, n (%)			0.009
Mild	538 (79.6)	104 (68.9)	
Moderate	125 (18.5)	40 (26.5)	
Severe	13 (1.92)	7 (4.64)	
Local complications of AP (fluid collection/necrosis/abscess), n (%)	134 (19.9)	64 (42.7)	<0.001

Subgroup Analyses

A subgroup analysis was completed based on severity as defined by the revised Atlanta criteria, and the results of the analysis are listed in Tables 5 and 6. In patients admitted with mild AP, 16.2% of patients experienced at least 1 EPC, whereas 25.4% of patients in the moderately severe and severe groups had at least 1 EPC. In both groups, LOS was significantly longer ($P < 0.05$); however, 30-day readmission was only significantly higher in patients with mild AP ($P = 0.004$).

DISCUSSION

Acute pancreatitis is a common diagnosis for hospitalization and is associated with a significant economic burden on the healthcare system.[15] Although there can be several factors responsible for poorer outcomes in AP, we have previously reported the prevalence of EPCs in patients admitted to the ICU with AP and their impact on hospital-related outcomes.[13] In the current study, we sought to characterize the impact of such similar EPCs on outcomes in non-ICU patients admitted with AP.

TABLE 3. Univariate Analysis of Outcomes and Resource Utilization Between AP Patients With and Without EPC

	EPC Not Present (n = 679)	EPC Present (n = 151)	*P*
LOS, mean (SD), d	4.42 (3.23)	6.98 (5.19)	<0.001
LOS, median (IQR), d	5.0 (3.0–9.0)	3.8 (2.0–5.3)	<0.001
30-d readmission, n (%)	128 (19)	49 (32.5)	<0.001
Inpatient mortality, n (%)	4 (0.59)	2 (1.32)	0.301

IQR, interquartile range.

TABLE 4. Multivariate Analysis for EPC as Independent Predictors of LOS and 30-Day Readmissions

	Length of Stay		30-d Readmissions	
	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Any EPC	1.45 (1.36–1.56)	<0.001	1.94 (1.28–2.95)	<0.001
Any infectious EPC	1.66 (1.52–1.81)	<0.001	2.17 (1.27–3.65)	0.003
Bacteremia	1.89 (1.61–1.97)	<0.001	1.25 (1.11–1.98)	0.003
Pneumonia	1.01 (0.87–1.11)	0.57	0.98 (0.67–1.10)	0.83
UTI	1.41 (1.21–1.64)	<0.001	2.86 (2.28–6.87)	0.016
C. difficile infection	1.26 (1.08–1.47)	0.002	3.34 (1.45–7.55)	0.003
Any noninfectious EPC	1.26 (1.14–1.38)	<0.001	1.45 (0.84–2.43)	0.15
GI bleeding	1.68 (1.42–1.97)	<0.001	2.02 (0.72–5.22)	0.15
Delirium	1.30 (1.11–1.52)	<0.001	1.09 (0.37–2.81)	0.85
Alcohol withdrawal	0.89 (0.75–1.05)	0.18	1.18 (0.51–2.52)	0.66
AKI requiring dialysis	1.40 (1.01–1.88)	0.03	0.65 (0.03–5.09)	0.71
Fall with injury	1.13 (0.57–1.98)	0.68	5.49 (0.21–13.9)	0.23

In our cohort, an EPC occurred in nearly 1 in every 5 patients and contributed to an increase in both LOS and 30-day readmissions. Because the mortality rate was overall very low (<1%), in-hospital mortality was not significantly higher in patients with EPC. After controlling for age, etiology, comorbidity, severity of AP, and presence of local pancreatic complications, EPC was associated with longer LOS and high rates of 30-day readmissions and remained significant in our subgroup analysis of patients with mild AP.

Our study follows our previous report on all EPCs in patients admitted to the ICU with AP.[13] Furthermore, it corroborates the results of previous studies demonstrating the impact of infectious EPCs, which reported bacteremia, UTIs, and respiratory infections being the most common infections.[12,16–18] In addition to infectious EPC, our cohort demonstrated a nearly 10% incidence of noninfectious EPCs in non-ICU patients. Some of these noninfectious EPCs, particularly delirium, were a significant predictor of LOS, whereas others, such as fall with injury, were not. It is well documented that in-hospital complications such as falls prolong hospitalization.[19,20] Thus, it is common practice that hospitals devise care pathways to minimize the risks of these complications, which is particularly true at our institution. For these reasons, the incidence of falls with injury was possibly low in our patients with AP. We suspect that, given the global interest to reduce fall-associated

TABLE 5. Comparison of Patients With Mild AP With and Without EPC

	EPC Not Present (n = 538)	EPC Present (n = 104)	*P*
Demographics			
Age, mean (SD), y	51.1 (15.6)	54.6 (16.2)	0.045
Sex, female, n (%)	276 (51.3)	70 (68)	0.99
Race, n (%)			0.257
African American	119 (22.1)	30 (29.1)	
White	393 (73)	105 (70)	
Body mass index, mean (SD), kg/m^2	27.4 (7.05)	27.0 (7.17)	0.584
Comorbidities, n (%)			
Active alcohol use	187 (34.8)	54 (51.9)	0.001
Active tobacco use	144 (26.9)	33 (31.7)	0.377
History of AP	271 (50.4)	46 (44.2)	0.299
CCI, mean (SD)	0.78 (1.00)	1.08 (1.09)	0.012
Etiology, n (%)			<0.001
Alcohol	124 (23)	40 (38.4)	
Gallstone	229 (42.5)	28 (26.9)	
Idiopathic	185 (34.3)	36 (34.6)	
Outcomes			
LOS, mean (SD), d	4.01 (2.78)	6.08 (4.94)	<0.001
30-d readmission, n (%)	91 (17)	31 (29.8)	0.004
Inpatient mortality, n (%)	4 (0.74)	1 (0.96)	0.589

TABLE 6. Comparison of Patients With Moderate to Severe AP With and Without EPC

	EPC Not Present (n = 138)	EPC Present (n = 47)	*P*
Demographics			
Age, mean (SD), y	52.6 (15.9)	58.7 (19.8)	0.061
Sex, female, n (%)	67 (48.6)	12 (25.5)	0.01
Race, n (%)			0.279
African American	18 (13)	8 (17)	
White	115 (83.3)	35 (74.5)	
Body mass index, mean (SD), kg/m^2	27.5 (6.52)	25.3 (4.46)	0.012
Comorbidities, n (%)			
Active alcohol use	41 (29.7)	20 (42.6)	0.15
Active tobacco use	36 (26.1)	14 (29.8)	0.762
History of AP	81 (58.7)	23 (48.9)	0.320
CCI, mean (SD)	0.81 (1.08)	0.94 (0.87)	0.429
Etiology, n (%)			<0.001
Alcohol	22 (16)	16 (34)	
Gallstone	6 (4.34)	5 (10.6)	
Idiopathic	8 (5.79)	10 (21.2)	
Outcomes			
LOS, mean (SD), d	6.01 (4.23)	8.95 (5.23)	0.001
30-d readmission, n (%)	37 (26.8)	18 (38.3)	0.192
Inpatient mortality, n (%)	0	1 (2.13)	0.254

injury in hospitalized patients, this incidence may be generalizable to other institutions.

Furthermore, in our study, alcohol-related comorbidity was highly prevalent with nearly one-quarter of all EPCs being alcohol withdrawal. Not surprisingly, there were a significantly higher proportion of patients with EPCs who either had AP due to alcohol use and/or had active alcohol use of some degree. Alcohol withdrawal, however, was not found to have an independent association with our outcomes of interest. The reason for this could have been use of a comprehensive alcohol withdrawal pathway at our institution, which involves frequent assessment and treatment of symptoms of alcohol withdrawal among patients with alcohol use disorder. Use of such alcohol withdrawal pathways at other institutions has in fact shown a decrease in the hospital LOS.[21] Whether these results would be applicable to patients with AP or not has not been studied yet and therefore needs further research.

Lastly, GI bleeding in AP has been previously described in several studies.[22–24] These studies suggest several causes such as bleeding from stress ulcers, visceral artery pseudoaneurysms, varices, duodenal necrosis, bleeding from erosion of adjacent pancreatic necrosis into the duodenal wall, and traumatic injury from nasogastric tube, as plausible reasons for GI bleeding in the AP population. Less than 3% (19 of 830) of our patients developed GI bleeding, which is lower than an incidence rate of 3.7% to 17.8% in these previous studies. We hypothesize that the reason for such lower rate could be due to the regular use of stress ulcer prophylaxis and early feeding strategies at our institution. Furthermore, given the wide use of acid suppression in the general population, it is possible that the overall incidence is lower because of the high use of these medications at baseline in our study. Not surprisingly, GI bleeding was an independent predictor of LOS as seen in previous studies.[13]

In our study, we demonstrate that 1 in 5 patients with mild AP will have an EPC, which contributes to the LOS. Patients with mild AP typically have minimal symptoms and, in many cases, can improve within 24 hours. However, the reported LOS in patients with mild AP ranges from 3 to 7 days, suggesting significant in-hospital delays to discharge. Recent studies created innovative management pathways to streamline the care for patients with mild AP with the intention to reduce LOS and improve care delivery.[25,26] By implementing efficient care, these pathways have the potential to reduce in-hospital complications. Given how most of these EPCs are unrelated to the natural history of AP, these can essentially be preventable if close attention is paid toward improvised quality control measures such as judicious antibiotic use, avoidance of urinary catheters, stress ulcer prophylaxis, fall risk assessments, implementation of alcohol withdrawal pathways, and minimizing opioid use in individuals at risk for delirium. Further work should focus on the impact of innovative care design on EPCs especially in patients with mild AP.

Our study is naturally limited by its retrospective design and the potential inability to have complete data on all patients. Furthermore, we did not study the impact of institutional changes on the incidence of EPCs (ie, institutional efforts to reduce delirium, UTI, and falls), and thus, overall incidence is likely affected by the temporal trends in healthcare improvement. Lastly, we did not have data on the impact of interventions for local complications and thus is not clear how these interventions would impact LOS independently and the incidence of EPCs.

In conclusion, we report the prevalence of several infectious and noninfectious EPCs in non-ICU patients hospitalized with AP. Our study highlights that, even within the noncritically ill cohort, EPCs are frequently present in patients with mild AP. We demonstrate the significance of these EPCs by illustrating longer LOS in patients with both infectious and noninfectious EPCs and higher readmissions in patients with infectious EPCs. Further research is needed to establish predictors and risk factors of developing such EPCs, and strategies to curb their occurrence.

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