MAYO CLINIC

Acute Pancreatitis in Advanced Chronic Kidney Disease and Kidney Transplant Recipients: Results of a US Nationwide Analysis

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Abstract

Objective: To study the prevalence, etiology, and outcome of acute pancreatitis (AP) in kidney transplant and stage 5 chronic kidney disease (CKD) populations in comparison to a non-CKD cohort.

Patients and Methods: Using the Nationwide Inpatient Sample database, we identified patients with acute pancreatitis as the primary discharge diagnosis, after which propensity scores were used to create 2 cohorts of patients: 1 with CKD (n=13,425) and 1 without CKD (n=13,425). The CKD group was subsequently subdivided into dialysis-independent stage 5 CKD (n=690), dialysis-dependent stage 5 CKD (n=11,415), and kidney transplant recipients (n=1320). Patients younger than 18 years old, those who received a kidney transplant during the incident admission, and pancreas transplant recipients were excluded.

Results: The adjusted odds ratios (ORs) of AP were comparable between the no CKD, stage 5 CKD, and kidney transplant populations. Adjusted inpatient mortality was highest in patients with dialysis-dependent stage 5 CKD (OR, 2.72; 95% CI, 2.2-3.3; $P<.01$), followed by kidney transplant recipients (OR, 2.29; 95% CI, 1.12-4.51; $P=.02$), compared to the non-CKD group. Patients with stage 5 CKD experienced higher rates of shock and intensive care unit admission and had more prolonged and costly hospitalizations than the non-CKD group ($P<.01$ for all). Hypercalcemia was the most common cause of AP in both dialysis-dependent and dialysis-independent patients with stage 5 CKD, while viral and drug-induced pancreatitis were more prevalent in the transplant recipients.

Conclusion: Despite comparable adjusted prevalence of AP among the stage 5 CKD, transplant, and non-CKD populations, mortality, morbidity, and resource utilization were higher in the patients with stage 5 CKD and transplant recipients. Hypercalcemia is the most common cause of AP in the stage 5 CKD population irrespective of dialysis requirement.

 ■ Mayo Clin Proc Inn Qual Out 2019;3(2):160-168

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Acute pancreatitis (AP) is complex inflammatory process of the pancreas and the leading cause of hospitalization among gastrointestinal disorders within the United States, accounting for more than 270,000 admissions annually.[1] Although most cases of AP are managed conservatively, severe disease has a mortality rate approaching 50%.[2] In patients with advanced chronic kidney disease (CKD), management of AP is complicated because of limitations in fluid resuscitation, a cornerstone of treatment known to decrease mortality associated with AP, as well as baseline abnormalities in biomarkers of adequate resuscitation such as serum urea nitrogen.[3,4] Serum amylase level is chronically elevated in patients with advanced CKD, which might lead to overdiagnosis of AP in this population. Additionally, advanced CKD is associated with electrolyte abnormalities including hypercalcemia, which is a relatively uncommon cause of pancreatitis in the general population but may be a larger contributor of AP within the CKD population.[5]

Mayo Clin Proc Inn Qual Out ■ June 2019;3(2):160-168 ■ https://doi.org/10.1016/j.mayocpiqo.2019.03.006
www.mcpiqojournal.org

Although advanced CKD has a considerable impact on treatment and prognostication of AP, it is unclear whether AP is more prevalent in patients with advanced CKD compared to the general population. Autopsy data from patients with end-stage renal disease (ESRD) suggest that 28% of the ESRD populations had pancreatitis at the time of death, a prevalence that far exceeds the AP rates in the general populations.[6] Mortality and morbidity of AP in patients with stage 5 CKD (CKD5) and kidney transplant recipients have not been systematically studied. Therefore, the aims of this study were to evaluate the prevalence of AP within the advanced CKD population, including kidney transplant recipients, and compare outcomes of AP in these patients to outcomes in a matched cohort of non-CKD patients with AP using a large national database of inpatient hospitalizations within the United States.

PATIENTS AND METHODS

Study Design and Data Source

Patients were selected from the Nationwide Inpatient Sample (NIS), which is the largest publically available, inpatient, all-payer database in the United States. The data set for the year 2014 contains more than 7 million hospital stays, which are a 20% stratified sample of more than 4000 nonfederal acute care hospitals in more than 40 states of the United States, and is representative of 95% of hospital discharges nationwide. A principal diagnosis, defined as the primary discharge diagnosis, as well as 24 other secondary diagnoses are included in the data set. The data set also includes codes for up to 15 procedures performed during the hospital stay. It also allows determining length of hospital stay and total hospitalization charges, as well as desired outcome measures such as calculations of inpatient disease prevalence. All analyzed data were extracted from the database for the year 2014 to design this retrospective cohort study.

Study Population

All patients in the NIS data set for 2014 with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) principal diagnostic code for AP (577.0) were identified. Patients with *ICD-9-CM* codes for kidney transplant (V42.0), dialysis-dependent CKD5 (585.6) and dialysis-independent CKD5 (585.5) were included in the study (CKD cohort). Patients younger than18 years of age, elective admissions, pancreas transplant recipients, and patients undergoing kidney transplant on that same admission were excluded. Propensity scores were used to match the CKD cohort to patients admitted with AP and no *ICD-9-CM* CKD diagnostic codes (no CKD group) as described in the statistical section. The etiology of AP was also stratified using the associated additional *ICD-9-CM* codes.

Variable Definition

Patient general characteristics included demographic characteristics such as age, sex, race/ethnicity, median income in zip code, and insurance type. Hospital characteristics included hospital region, teaching status, number of hospital beds, and hospital location. The Hospitalization Cost and Utilization Project divides the United States into 4 geographic locations and census regions. Each patient's vital status at the conclusion of hospital stay, total days of hospitalization, and total hospitalization charges were also abstracted from the database. To account for patient comorbidities, the Deyo adaptation of the Charlson Comorbidity Index (CCI) was used, which is a validated tool for large database analyses.[7]

Aims

The primary aim of the study was to determine the relative frequency of AP as a discharge diagnosis in patients with CKD5 and kidney transplant recipients when compared to patients without CKD. Secondary outcomes were divided into etiologies of AP, inpatient mortality, morbidity, resource utilization, and expenditures. Examined indicators of morbidity included the occurrence of shock and intensive care unit (ICU) admission. Resource utilization was measured by abdominal ultrasonography (US), abdominal computed tomography, and endoscopic retrograde cholangiopancreatography (ERCP) use and duration of hospital stay. Finally, expenditures were subdivided into total hospitalization charges and hospital costs.

Statistical Analyses

Discharge-level weights published by the Hospitalization Cost and Utilization Project were used to estimate the number of patients with AP and advanced CKD. Propensity scores were used to match patients with advanced CKD and AP to patients who had AP without CKD. A nonparsimonious multivariate logistic regression model was developed to estimate the propensity scores for development of AP using age, sex, race/ethnicity, median income in patients' zip code, CCI, and hospital region, location, teaching status, and number of beds as covariates, with a caliper distance of 0.01. The double robust method was then used to generate treatment weights, and the inverse probability of treatment weighting was used to match cases with controls using generalized linear equation models. Logistic regression was used to estimate the adjusted odds ratios (ORs) of mortality, morbidity, and resource utilization in each of the studied groups. Fisher exact test was used to compare proportions, and analysis of variance test was utilized to compare means. All statistical analyses were conducted using Stata statistical software, version 14 (StataCorp).

RESULTS

Of 442,340 AP admissions that were documented in the study period, 433,805 met the inclusion criteria, and of these, 13,425 patients had advanced CKD. After obtaining propensity scores, the advanced CKD cohort was subdivided into dialysis-independent CKD5 (n=690), dialysis-dependent CKD5 (n=11,415), and kidney transplant recipients (n=1320).

Table 1 summarizes unadjusted patients' and hospital characteristics. Overall, non-transplant CKD5 patients with AP were older, were more likely to be African American, included a higher proportion of low- to medium-income patients, and had higher CCI compared to the non-CKD patients and kidney transplant recipients with AP ($P<.01$ for all). The cohorts did not differ in terms of day of the week of the incident hospital admission. All cohorts were primarily composed of patients from the Southern region, although proportionately more patients with dialysis-dependent CKD5 corresponded to this geographic location compared to the other cohorts with AP. In general, although most patients in all cohorts were seen at urban teaching centers with large numbers of beds, a greater proportion of kidney transplant recipients were admitted to a large bed size teaching hospital.

Outcomes

After adjusting for age, sex, race/ethnicity, median income in patients' zip code, CCI score, and hospital region, location, teaching status, and number of beds, the adjusted ORs of AP in the dialysis-independent CKD (OR,1.15; 95% CI, 0.85-1.56; $P=.4$), dialysis-dependent CKD (OR, 1.01; 95% CI, 0.89-1.13; $P=.4$), and kidney transplant (OR, 0.90; 95% CI, 0.72-1.13; $P=.3$) populations were comparable to those without CKD.

Etiology of AP

The potential different etiologies of AP were subdivided using the respective *ICD-9-CM* codes. The adjusted odds of AP substratified by etiologies are presented in Table 2. Hypercalcemia had the strongest association with AP in the dialysis-independent (OR, 4.59; 95% CI, 2.02-10.48; $P<.01$) and dialysis-dependent (OR, 1.65; 95% CI, 1.14-2.38; $P<.01$) CKD5 cohorts compared to the non-CKD population. Kidney transplant recipients also had higher odds of hypercalcemia-associated AP, but this association did not reach statistical significance (OR, 1.77; 95% CI, 0.73-4.29; $P=.21$). The miscellaneous category (which included drug-associated, viral infections, hereditary, and autoimmune causes, among others) was the main cause of AP in the kidney transplant population and was the second most common cause of AP in dialysis-dependent CKD5 patients (OR, 1.75; 95% CI, 1.41-2.18; $P<.01$ and adjusted OR,1.58; 95% CI, 1.41-1.78; $P<.01$, respectively).

In contrast, all cohorts displayed a negative association with alcohol-associated AP when compared to patients without CKD. For gallstone-associated AP, only the kidney transplant recipient cohort displayed significantly lesser odds of AP (OR, 0.59; 95% CI, 0.42-0.85; $P<.01$). There were no noted differences in the odds of occurrence of post-ERCP pancreatitis among cohorts.

Mayo Clin Proc Inn Qual Out ■ June 2019;3(2):160-168 ■ https://doi.org/10.1016/j.mayocpiqo.2019.03.006
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TABLE 1. Baseline Unadjusted Patient and Hospital Characteristics[a,b]

Variable	No CKD (n=13,425)	CKD 5 without dialysis (n=690)	CKD 5 with dialysis (n=11,415)	Kidney transplant (n=1320)	*P* value
Mean age (y)	52	61	56	49	<.01
Female	6579 (49%)	325 (47%)	5480 (48%)	634 (48%)	.89
Race/ethnicity					
White	66%	43%	33%	58%	
African American	15%	31%	41%	20%	<.01
Hispanic	13%	15%	17%	17%	
Other	6%	11%	10%	5%	
Weekend admission	26%	26%	25%	26%	.73
Income in zip code					
$1-$37,999	31%	40%	41%	28%	
$38,000-$47,999	29%	25%	27%	24%	<.01
$48,000-$63,999	22%	24%	19%	23%	
≥$64,000	18%	11%	13%	25%	
Charlson score					
0	50%	0%	0%	21%	
1-2	38%	25%	19%	38%	<.01
≥3	12%	75%	81%	41%	
Hospital region					
Northeast	17%	17%	13%	12%	
Midwest	22%	26%	20%	27%	<.01
South	40%	35%	45%	41%	
West	22%	22%	22%	20%	
Urban location	89%	92%	95%	91%	<.01
Hospital size (beds)					
Small	21%	19%	15%	12%	
Medium	30%	33%	27%	23%	<.01
Large	49%	48%	57%	65%	
Hospital teaching status					
Teaching	59%	64%	66%	67%	
Nonteaching	41%	36%	34%	33%	<.01

[a]CKD = chronic kidney disease.
[b]Data are presented as No. (percentage).

Mortality and Morbidity

Table 3 demonstrates that the adjusted mortality was higher in the dialysis-dependent CKD5 (OR, 2.72; 95% CI, 2.22-3.33; *P*<.01) and in the kidney transplant population (OR, 2.29; 95% CI, 1.12-4.51; *P*=.02) compared to patients without CKD but not in the dialysis-independent CKD5 patients (OR, 2.13; 95% CI, 0.91-4.94; *P*=.08). Patients with AP and dialysis-dependent CKD5 displayed significantly higher odds of shock (OR, 1.53; 95% CI, 1.38-1.73; *P*<.01) and ICU stay (OR, 1.32; 95% CI, 1.13-1.52; *P*<.01) compared to non-CKD patients. Kidney transplant recipients and the dialysis-independent CKD5 patients had comparable odds of shock and ICU stay to the general non-CKD population.

Resource Utilization

Patients with AP and dialysis-independent CKD5 had lesser odds of undergoing ERCP, while patients with dialysis-dependent CKD5 displayed lesser odds of both abdominal US and ERCP use when compared to patients without CKD. Similarly, patients with kidney transplant did not display statistically significant differences in terms of computed tomography (*P*=.83), US (*P*=.75), or ERCP (*P*=.28) when compared to patients with no CKD (Table 4).

TABLE 2. Adjusted Odds Ratios for Occurrence of Acute Pancreatitis in Patients With Stage 5 CKD and Kidney Transplant Cohorts Compared to Patients Without CKD (Reference Group, n=13,425)[a]

Potential cause of acute pancreatitis	Adjusted OR (95% CI), *P* value		
	CKD5 without dialysis (n=690)	CKD5 with dialysis (n=11,415)	Kidney transplant (n=1320)
Alcoholic	0.49 (0.28-0.85), *P*=.01	0.22 (0.18-0.27), *P*<.01	0.10 (0.05-0.19), *P*<.01
Gallstone	1.18 (0.79-1.76), *P*=.41	0.90 (0.79-1.02), *P*=.11	0.59 (0.42-0.85), *P*<.01
Hypertriglyceridemia	0.78 (0.24-2.46), *P*=.66	0.32 (0.20-0.51), *P*<.01	0.55 (0.27-1.13), *P*=.10
Hypercalcemia	4.59 (2.02-10.48), *P*<.01	1.65 (1.14-2.38), *P*<.01	1.77 (0.73-4.29), *P*=.21
Post-ERCP	0.99 (0.74-1.34), *P*=.98	1.02 (0.91-1.13), *P*=.79	1.02 (0.83-1.26), *P*=.84
Miscellaneous[b]	1.28 (0.95-1.73), *P*=.11	1.58 (1.41-1.78), *P*<.01	1.75 (1.41-2.18), *P*<.01

[a]CKD = chronic kidney disease; CKD5 = stage 5 CKD; ERCP = endoscopic retrograde cholangiopancreatography; OR = odds ratio.
[b]Miscellaneous causes of acute pancreatitis included drug-associated, viral infections, hereditary, and autoimmune causes, among others.

Economic Burden

The average total duration of hospital stay, total costs, and total hospitalization charges for patients with AP and the different CKD cohorts are presented in Table 5. Total hospital costs, total hospitalization charges, and duration of hospital stay were higher in patients with CKD5 and kidney transplant recipients compared to the non-CKD population.

DISCUSSION

The current study examined the prevalence, etiology, and outcomes of AP in a large cohort of patients with CKD5 and kidney transplant recipients and compared these end points to a propensity-matched non-CKD cohort. Results indicated that adjusting for other covariates, the prevalence of AP was comparable between patients with advanced CKD, kidney transplant recipients, and non-CKD patients. The adjusted mortality, morbidity, and hospital-associated costs were higher in the advanced-stage CKD group, especially in the dialysis-dependent CKD5 populations. Etiology of AP also varied, with hypercalcemia being the most prevalent cause of AP in both dialysis-dependent and dialysis-independent patients with CKD5 and viral, medication-induced, and AP from miscellaneous causes was most prevalent in kidney transplant recipients. The current study also demonstrated that AP in the CKD5 and kidney transplant populations had significant economic impact and higher rates of resource utilization compared to AP in the general population.

Single-center experience and population studies suggest that the prevalence of AP is higher in patients with ESRD. In an uncontrolled study, Rutsky et al[8] determined that the 10-year risk of AP is 2.3% in the ESRD population, with the highest risk being in patients undergoing peritoneal dialysis . In a study similar to ours, Hou et al[9] found a 3.4-fold increased risk of AP in 2603 patients with ESRD compared to a cohort of more than 770,000 propensity-matched individuals

TABLE 3. Adjusted ORs for Inpatient Mortality and Morbidity of Acute Pancreatitis in Patients With CKD5 and Kidney Transplant Recipients Compared to Patients Without CKD (Reference Group, n=13,425)

Variable	Adjusted OR (95% CI), *P* value		
	CKD5 without dialysis (n=690)	CKD5 with dialysis (n=11,415)	Kidney transplant (n=1320)
Adjusted OR for in-hospital mortality	2.13 (0.91-4.94), *P*=.08	2.72 (2.22-3.33), *P*<.01	2.29 (1.12-4.51), *P*=.02
Adjusted OR for shock	0.78 (0.35-1.70), *P*=.52	1.53 (1.38-1.73), *P*<.01	1.10 (0.61-1.89), *P*=071
Adjusted OR for ICU stay	0.63 (0.29-1.35), *P*=.23	1.32 (1.13-1.52), *P*<.01	0.82 (0.50-1.37), *P*=.45

CKD = chronic kidney disease; CKD5 = stage 5 CKD; OR = odds ratio.

Mayo Clin Proc Inn Qual Out ■ June 2019;3(2):160-168 ■ https://doi.org/10.1016/j.mayocpiqo.2019.03.006
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TABLE 4. Resource Utilization in Patients With Acute Pancreatitis and CKD5 and Patients With Kidney Transplant Compared to Patients With Acute Pancreatitis Without CKD (Reference Group, n=13,425)

Variable	Adjusted OR (95% CI), *P* value		
	CKD5 without dialysis (n=690)	CKD5 with dialysis (n=11,415)	Kidney transplant (n=1320)
Abdominal CT	0.66 (0.17-2.64), *P*=.56	0.86 (0.62-1.21), *P*=.40	0.91 (0.38-2.19), *P*=.83
Abdominal US	0.25 (0.04-1.72), *P*=.59	0.63 (0.45-0.88), *P*<.01	0.89 (0.41-1.89), *P*=.75
ERCP	0.17 (0.04-0.66), *P*=.01	0.68 (0.56-0.82), *P*<.01	0.78 (0.50-1.22), *P*=.28

CKD = chronic kidney disease; CKD5 = stage 5 CKD; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; OR = odds ratio; US = ultrasonography.

without dialysis over a 4-year period using a large administrative database in Taiwan. Although our findings differed from those of Hou et al,[9] the variabilities in medical practice including definition and coding for AP, criteria for hospitalization, and administrative databases between Taiwan and the United States could have accounted for some of this discrepancy. Also, Hou at al[9] did not exclude dialysis-independent CKD5 and pancreas transplant or kidney recipients from their control group. We used the NIS data, which has been validated in previous studies, to identify our cohort of patients from a total of 433,805 AP admissions in 2014. We believe that the results of the current study demonstrated that the prevalence of AP in the United States is comparable between advanced CKD and non-CKD and that advanced CKD per se is not a risk factor for AP.

The current study showed higher inpatient mortality in dialysis-dependent CKD5 patients. The reason for this higher mortality could be related to higher severity of AP in the ESRD population, especially since we demonstrated that dialysis-dependent CKD5 patients were more likely to have development of shock and require ICU admission. Another potential explanation is the difficulty in assessing AP disease severity and that difficulty in managing AP in dialysis-dependent CKD5 patients could have led to higher mortality. Various scoring systems used for early identification of patients at risk for severe disease are hampered in ESRD patients because of their reliance on surrogate markers for adequate hydration such as serum urea nitrogen and hematocrit level, which are frequently abnormal in the ESRD population.[4] Failure to identify patients at risk for severe disease may result in delayed or inadequate escalation of care. Early and aggressive fluid resuscitation with lactated Ringer solution, an early intervention that has proven to decrease mortality in AP, is limited in the ESRD patient population given the potential risk of volume overload and hyperkalemia.[3,10,11] Also, hypercalcemia, which was a more prevalent cause of AP in dialysis patients, may contribute to the higher all-cause mortality among the ESRD population.[12,13] Irrespective of the etiology, our results indicated that AP in the CKD5 population is a serious complication that needs to be managed aggressively. Future studies should examine strategies for adequate fluid resuscitation in the ESRD population and their effect on AP mortality and associated outcomes.

One interesting finding of the current study is the variability of AP etiology among the CKD and non-CKD populations. Understandably, the strongest association of AP in

TABLE 5. Economic Burden of Acute Pancreatitis in Patients With CKD5 With and Without Dialysis and Patients With Kidney Transplant Compared to Patients Without CKD

Variable	No CKD (n=13,425)	CKD5 without dialysis (n=690)	CKD5 with dialysis (n=11,415)	Kidney transplant (n=1320)	*P* value
Total hospital costs	$13,357	$16,140	$29,208	$16,078	<.01
Hospitalization charges	$51,452	$65,723	$122,235	$66,792	<.01
Duration of stay (d)	5.6	7.4	10.3	6.1	<.01

CKD5 patients was with hypercalcemia. Hypercalcemia in animal models has been shown to induce a sustained increase in intracellular calcium inducing a functional secretory blockade within acinar cells and leading to increased intracellular activation of trypsinogen that predisposes to pancreatitis.[14] It is worth noting, however, that the role of hypercalcemia in AP is incompletely understood and that the link between AP and secondary hyperparathyroidism remains poorly explained.[15] However, the specific serum calcium levels were not known in this study, which would have proven to be important because it is possible that certain levels of serum calcium could have displayed stronger association to AP than other less severe hypercalcemia. Similarly, the database does not include the specific cause of hypercalcemia in these patients. Therefore, further care in understanding hypercalcemia and its management is warranted. Similarly, optimal strategies for monitoring and maintaining normal serum calcium levels in patients with advanced kidney disease may impact the occurrence of AP.

The current study is the first to examine the prevalence, etiology, and outcome of AP in dialysis-independent CKD5 patients. Our results indicated that AP in this group of patients is still associated with twice (adjusted OR, 2.13) the mortality risk of AP in the non-CKD population. Although this increased mortality did not reach statistical significance (P=.08), which could be due to the small number of patients in this cohort, these results are clinically meaningful. Intensive care unit admission in the dialysis-independent CKD5 cohort was comparable to that in the non-CKD population and much lower than their dialysis-dependent CKD5 counterparts. Although it is difficult to speculate whether early care in the ICU would have altered the mortality risk in these patients, our results suggest that AP might be equally lethal in CKD5 patients irrespective of dialysis need.

Acute pancreatitis in kidney transplant recipients has not been systematically studied. Case reports and limited single-center experience have estimated the risk AP in this population to be between 2% and 8%.[16-19] In the current study, the association with miscellaneous/unspecified etiologies of AP was noted to be positive in patients with kidney transplant. This category includes, but is not limited to, medication-associated AP and infectious causes, especially viral infections. These results confirm the findings from previous studies that showed that both immunosuppressive medications and cytomegalovirus infection are important causes of AP in this population.[17,20] We demonstrated that there was a 68% increased risk of hypercalcemia associated AP in the kidney transplant population compared to the non-CKD cohort. Although this association did not reach statistical significance, these results still might be clinically meaningful. Hypercalcemia after kidney transplant occurs in almost one-third of patients and can persist for many years after transplant.[21] Persistent hyperparathyroidism is the most common cause of hypercalcemia after kidney transplant, and the risk of hypercalcemia can be modified with calcimimetic agents.[22] The results of our study should alert clinicians caring for these patients to be vigilant in detecting and treating hypercalcemia to reduce the posttransplant risk of AP.

Previous reports suggested that the mortality from AP in the kidney transplant population approaches 40% and that mortality risk parallels AP disease severity and is highest with the occurrence of superimposed infections.[19] Our results confirmed these previous observations and demonstrated that adjusted mortality of post—kidney transplant AP is more than double the mortality risk in the non-CKD population. Reasons for the increased mortality are difficult to determine because of the lack of granularity in the NIS regarding cause of patients' deaths, but we can postulate that dissociation between AP disease severity and clinical presentation, which has been previously described in the kidney transplant population,[17,19] could have delayed early intensive care management in these patients. Our results suggest that AP in kidney transplant recipients is a serious and potentially fatal complication that warrants intensive care management even without the presence of hemodynamic instability.

The current study shed light on the economic impact of AP in the advanced CKD population. Expectedly, patients with AP and dialysis-dependent CKD5 faced longer and more costly hospitalizations when compared to those patients without CKD. This difference

Mayo Clin Proc Inn Qual Out ■ June 2019;3(2):160-168 ■ https://doi.org/10.1016/j.mayocpiqo.2019.03.006
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may represent inherent expenses in patients with ESRD (ie, inpatient dialysis, nephrology consultations), which is further backed up by the fact that patients with dialysis-independent CKD5 had significantly less crude total costs, hospitalization charges, and durations of hospital stay compared to patients undergoing dialysis. Intensive care unit stay, which was more common in the patients with ESRD, could have also translated into higher hospitalization cost in these patients.

There are multiple limitations to this study. By being a retrospective, observational study, there is potential for selection bias. This factor was reduced by the utilization of the NIS database, which provides information on patients hospitalized with AP as the main diagnosis. This allowed us to exclude patients with clinically insignificant cases of AP who have mild elevation in serum amylase levels without other manifestations of AP. The large sample size representative of the vast majority of hospital discharges within the United States allowed us to extract a large and heterogeneous population that was further reduced by utilization of propensity matching and multivariate analysis to establish comparable populations for analysis. Nevertheless, the associations highlighted in this study that involve the kidney transplant and dialysis-independent CKD5 cohorts could be affected by relatively smaller numbers compared to non-CKD patients with AP. Understandably, patients with advanced CKD have higher rates of hospitalization than patients without CKD, which could have affected our results. The administrative nature of the database may lead to another potential source of selection bias in the identification of study populations with AP, CKD5, and kidney transplant by using *ICD-9-CM* codes, which depends on proper diagnosis, codification, and maintenance of the database, and cannot be easily verified. We are contended, however, that the inpatient *ICD-9-CM* codes for AP were previously validated.[23] In addition, the etiology of AP was based on code combination, which does not necessarily reflect that the patient's pancreatitis etiology was the one mentioned. Kidney transplant recipients are a heterogeneous group of patients with wide range in kidney function. Unfortunately, there is no *ICD-9-CM* code that can stratify these patients according to the degree of their kidney function, which could have affected our results. The large, heterogeneous population is representative of the US inpatient population and lends itself to broad generalizability, for which the observed association between variables is thought to be real. Other limitations inherent to the NIS include the inability to assess for medication use and that the financial burden measurement is limited to inpatient costs and charges. Another limitation is the inability to stratify dialysis into peritoneal dialysis vs hemodialysis. Several previous reports have demonstrated a higher risk of AP in ESRD patients undergoing peritoneal dialysis when compared to those undergoing hemodialysis.[8,24] The underlying mechanisms involved are thought to involve exposure of the pancreas to nonphysiologic dialysate at supraphysiologic intra-abdominal pressures leading to premature proteolytic enzyme activation.[8,24-26]

CONCLUSION

This study highlights that despite overall comparable risk of AP between the general and the advanced CKD populations, patients with ESRD have high mortality and morbidity and add substantial burden to the health care system after AP development.

Abbreviations and Acronyms: **AP** = acute pancreatitis; **CKD** = chronic kidney disease; **CKD5** = stage 5 CKD; **CCI** = Charlson Comorbidity Index; **ERCP** = endoscopic retrograde cholangiopancreatography; **ESRD** = end-stage renal disease; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **ICU** = intensive care unit; **NIS** = Nationwide Inpatient Sample; **OR** = odds ratio; **US** = ultrasonography

Potential Competing Interests: The authors report no competing interests.

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