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Acute venous thromboembolism in acute pancreatitis based on the severity: a retrospective cohort study

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Abstract

Objective: Acute pancreatitis (AP) results in systemic inflammatory responses and activates coagulation pathways. We intend to investigate the risk and hospital outcomes of acute venous thromboembolisms (VTE) in patients with AP.

Methods: We retrospectively analyzed patients with AP from 2016 to 2019 using the National Inpatient Sample database. Primary outcome was the effect of VTE on the length of stay, inpatient costs, and mortality. Hierarchical multivariate logistic regression models were built using univariate screens.

Results: The study included 909,354 weighted discharges with AP. 2.1% of cases had an acute VTE. The length of stay was 5.9 days longer in the hospital of AP patients with VTE compared to AP with no VTE ($P < 0.001$). Total hospital charge per patient was $71,914 in patients with VTE compared to AP with no VTE ($P < 0.001$). Mortality was higher in AP patients with VTE compared to AP with no VTE (adjusted odds ratio [AOR] 4.2, 95% confidence interval [CI]: 3.4–5.3, $P < 0.001$). AP was associated with an increased VTE risk during inpatient stay (AOR 1.06, 95% CI 1.04–1.1, $P < 0.001$) There was an increased association of lower and upper extremity deep venous thrombosis with AP without necrosis (AOR 6.9, 95% CI 6.4–7.4, $P < 0.001$) and AP with infected necrosis (AOR 12.2, 95% CI 10.6–14.1, $P < 0.001$) but not in AP without necrosis (AOR 0.77, 95% CI 0.74–0.81, $P < 0.001$).

Conclusion: VTE in AP increases length of stay and inpatient costs. The prognosis is poor in such patients, with increased inpatient mortality compared to no VTE. AP with necrosis can increase chances of all VTE subtypes; however, AP without necrosis does not increase upper and lower extremity VTE risk.

Keywords: Acute pancreatitis, Deep venous thrombosis, Necrosis, Severity, Venous thromboembolism

Introduction

In recent years, the incidence of acute pancreatitis (AP) has been increasing.[1] AP results from acute inflammation of the pancreas, usually caused by gallstones and alcohol abuse.[2] The majority of patients with AP present with mild disease, but some may have moderate to severe disease with peripancreatic fluid collection, pancreatic pseudocysts, pancreatic necrosis, and systemic complications (respiratory, cardiovascular, or renal failure).[3,4] AP is associated with several complications, including acute respiratory distress syndrome, volume imbalance, and acute renal failure[3,4]; however, few studies have been conducted on the risk of venous thromboembolism (VTE) in patients with AP.[5] To date, studies have not been conducted on categorizing acute VTE according to the severity of AP. Acute pancreatic inflammation can lead to systemic inflammatory response syndrome, thus initiating the coagulation cascade.[6] Additionally, impaired fibrinolysis and intrinsic anticoagulant dysfunction in pancreatitis can contribute to the pro-inflammatory environment conducive to acute VTE formation.[6] Patients with VTE and AP have increased healthcare resource utilization resulting in increased costs, readmission rates, and emergency department visits.[7,8] VTE can delay recovery and affect inpatient outcomes in AP patients. AP is one of the most commonly occurring gastroenterology-related causes of hospitalizations in the United States.[9] We sought to estimate the trends, incidence, associations, and inpatient outcomes of acute VTE in the AP population without necrosis, with noninfected necrosis and with infected necrosis.

Materials and methods

Study design

This retrospective cohort study utilized a commercially available United States healthcare database (National Inpatient Sample (NIS) database) to investigate the effect of acute VTE on AP.[10] The NIS has been used previously to explore health-related outcomes of patients with AP.[11] Results were compared among AP hospitalizations that got VTE to AP hospitalizations without VTE. Additionally, AP was categorized into those without necrosis, with noninfected necrosis, and infected necrosis. Detailed information on the NIS design and sampling methods can be obtained at https://www.hcup-us.ahrq.gov.

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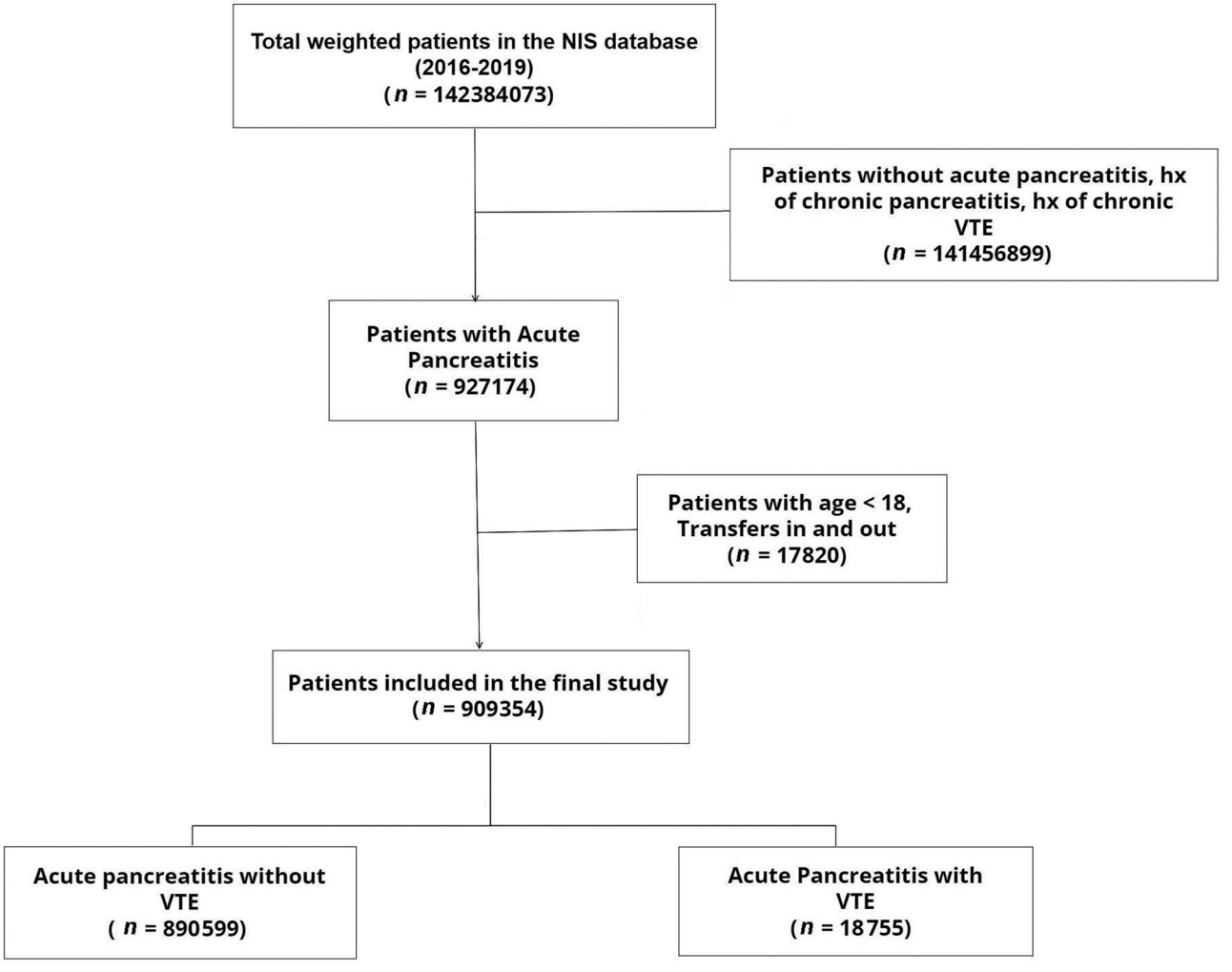

Figure 1. Flowchart of patient selection using weighted counts in the national inpatient database 2016 to 2019.

The study consisted of a 4-year period from January 1, 2016, to December 31, 2019. The data is coded using the International Classification of Diseases, tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes system in the NIS. The ICD-10-CM diagnosis codes system does not have a unified code for AP or acute VTE. Inclusion criteria included: (1) adults of age more than 18 years with diagnosis of acute pancreatitis and (2) patients with principal ICD-10-CM diagnoses specific to AP and acute VTE, listed in the Additional file 1, http://links.lww.com/JP9/A16. Acute VTE includes pulmonary embolisms and portal venous thrombosis (PVT), lower extremity DVTs, upper extremity DVTs, and other DVTs (internal jugular vein, renal vein, subclavian veins, and axillary veins). Exclusion criteria include the history of chronic VTE and chronic pancreatitis transfers in or out of the hospital (to limit confounding regarding the length of stay). This study was conducted following the 1964 *Declaration of Helsinki*, revised in 2013. As NIS contains deidentified patient data, it was deemed exempt from review by East Carolina University in Greenville, North Carolina. Patient consent was waived due to the public availability of data. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report the outcomes of this study.[12] The flowchart for weighted patient selection is shown in Figure 1.

Data collection

The data is coded using the ICD-10-CM diagnosis codes system in the NIS. The ICD-10-CM diagnosis codes system does not have a unified code for AP or acute VTE. Demographic data include age, gender, race, health insurance, hospital location, teaching status, hospital size, and patient annual income. Additionally, data was extracted regarding patient comorbidities using the Elixhauser list of 31 comorbidities (Additional file 2, http://links.lww.com/JP9/A17) for case-mix adjustment, a well-validated algorithm for predicting in-hospital mortality caused by various conditions, and utilizing ICD diagnosis codes.[13] Since only ICD codes for acute VTE were used in the analysis, it was concluded that reported cases are presumable newly diagnosed VTE. Therefore, the incidence was used instead of prevalence when reporting results.

Study variables

The primary outcome was the length of stay, total inpatient cost, and in-hospital mortality in AP patients with VTE versus those without VTE. Secondary outcomes included the incidence of categorized VTE and their associations with AP based on severity. Other covariates of interest included patient age, gender, race, health insurance, hospital location, teaching status, hospital size, and patient annual income.

Statistical analysis

Analyses were performed by using Stata Statistical Software: Release 16, College Station, TX (StataCorp LLC, STATA version 16.0). We built a hierarchical multivariate linear and logistic regression model to adjust for the confounding variables by using only variables associated with the outcome of interest on univariable regression analysis at $P < 0.2$ or known potential confounders despite *P*-value indicating no significance. Continuous variables were compared using the Student *t*-test and categorical variables were compared using the chi-square test. Our analysis has 0.05 as the threshold for statistical significance, and all *P* values were two-sided. All outcomes were adjusted for patient, and hospital-level characteristics, including age, race, sex, insurance type, residential region, Elixhauser Comorbidity Index score, hospital teaching status, hospital bed size, surgical intervention, anticoagulation use in outcomes like length of stay (LOS), inpatient hospital costs, as previous studies have utilized them as well.[11,14] Dichotomous variables were consolidated to report adjusted odds ratios (AOR) with 95% confidence interval (CI) and *P*-value. Continuous data were reported as adjusted mean differences with *P*-values. Standard errors were reported as ±standard error in linear regression outcomes.

Results

Patient characteristics

Nine hundred nine thousand three hundred fifty-four weighted discharges with AP in US hospitals from 2016 to 2019 met the study inclusion criteria using the NIS database. Acute VTE was more prevalent in males with AP than females with AP (62% vs 38%, $P < 0.001$). Among VTEs, 42.2% were PVT, 24.8% were other DVTs, 9.1% were lower extremity DVTs, 9.2% were upper extremity DVTs, and 14.7% were pulmonary embolisms. VTE had a higher incidence in patients with AP with infected and noninfected necrosis compared to AP without necrosis, as shown in Table 1 ($P < 0.001$). Approximately 70% of AP patients with VTE are white, while 15% belong to the black population ($P < 0.001$). Based on the Elixhauser Comorbidity Index score, there were more comorbidities among AP with a secondary diagnosis of VTE as compared to AP patients without VTE (76% vs 45%). Eight point one percent and 46.2% of patients in AP with noninfected and infected necrosis underwent surgical interventions during hospital courses, respectively. The median income for all four categories was significantly comparable in AP patients with or without a secondary diagnosis of VTE. The distribution of AP population among hospital regions was higher in the Southern US for both the VTE and no VTE cohorts ($P < 0.001$). Acute VTE distribution based on hospital teaching status is shown in Additional Table 1, http://links.lww.com/JP9/A18.

Hospital length of stay

The mean LOS of patients with VTE in the AP was 10.6 days versus 4 days in those without VTE. After adjusting for potential confounders, the difference in length of stay in days was 5.9 ± 0.26 ($P < 0.001$). Subgroup analysis revealed that the mean LOS of patients with VTE in the AP without necrosis was 7.8 days versus 4 days in those without VTE. After adjusting for potential confounders, the difference in length of stay in days was 3.4 ± 0.21 ($P < 0.001$). The mean LOS of patients with VTE in the AP with noninfected necrosis was 14.3 days versus 8 days in those without VTE. With adjustment for potential confounders, the difference in length of stay in days was 5.6 ± 0.6 ($P < 0.001$). The mean LOS of patients with VTE in the AP with infected necrosis was 27.9 days versus 14 days in those without VTE. After adjusting for potential confounders, the difference in length of stay in days was 11 ± 1.8 ($P < 0.001$) (Table 2). Additionally, LOS in categorized pancreatitis in our study depending on VTE subtype are shown in Additional Table 2, http://links.lww.com/JP9/A18.

Total inpatient cost

It was estimated that the total healthcare burden of AP (without VTE) was $2.52 billion in 2016, and this has increased to $11 billion in 2019 for patients included in NIS (340% increase). A total of $130 million was spent on hospitalizations in AP with VTE in 2016, this increased to $750 million in 2019 per NIS (477% increase). The mean inpatient costs of an AP patient with acute VTE were $118,324 versus $38,682 in those without VTE. After adjusting for potential confounders, the analysis showed that patients with VTE had an increased hospital charge of $\$71{,}914 \pm 4702$ compared to AP patients with no VTE ($P < 0.001$). Subgroup analysis revealed that the mean inpatient cost of patients with VTE in the AP without necrosis was $78,337 versus $36,542 in those without VTE. After adjusting for potential confounders, the difference in total cost was $\$37{,}451 \pm 3458$ ($P < 0.001$). The mean inpatient cost of patients with VTE in the AP with noninfected necrosis was $170,797 versus $80,024 in those without VTE ($P < 0.001$). The difference in total cost after adjusting for potential confounders was $\$76{,}340 \pm 12455$ ($P < 0.001$). The mean inpatient cost of patients with VTE in the AP with infected necrosis group was $362,172 versus $163,300 in those without VTE ($P < 0.001$). Following adjustment for potential confounders, the difference in total cost was $\$164{,}141 \pm 31936$ ($P < 0.001$) (Table 3). Additionally, hospital charges in categorized pancreatitis in our study depending on VTE subtype are shown in Additional Table 3, http://links.lww.com/JP9/A18.

Inpatient mortality in AP patients

In AP patients, secondary diagnosis of acute VTE was associated with significant elevation in mortality (AOR 4.2, 95% CI 3.4–5.3, $P < 0.001$). Subgroup analysis revealed that VTE in AP without necrosis and noninfected necrosis was also associated with increased inpatient mortality ($P < 0.001$). However, acute VTE in AP with infected necrosis did not significantly increase mortality compared with patients without VTE (Fig. 2). Additional independent predictors of inpatient mortality in AP patients with acute VTE were age, black race, increased number of comorbidities, Medicare, cardiac arrhythmias, pulmonary circulation disorders, liver disease, coagulopathies, history of weight loss, and fluid/electrolyte imbalance ($P < 0.001$) (Fig. 2).

Association of VTE subcategories in AP patients

Overall, total acute VTE was significantly associated with AP (AOR 1.06, 95% CI 1.04–1.1, $P < 0.001$). Incidence and association of acute VTE based on AP severity are given in Additional Table 3, http://links.lww.com/JP9/A18, categorized by gender. Subgroup analysis revealed decreased association of total VTE with AP without necrosis (AOR 0.77, 95% CI 0.74–0.81, $P < 0.001$). The association was significantly increased in

Table 1

Summarization of patient characteristics included in the study

Patient characteristics	No VTE	VTE	*P*-value
N	890,599 (97.9)	18,755 (2.1)	<0.001
Sex			
Male	476,769 (54)	11,585 (62)	
Female	413,829 (46)	7170 (38)	
Age (yr)	51.9 ± 0.04	51.6 ± 0.25	
Pancreatitis without necrosis	857,094 (96)	13,450 (71)	<0.001
Pancreatitis with noninfected necrosis	29,294 (3)	4110 (22)	<0.001
Pancreatitis with infected necrosis	5530 (1)	1415 (7)	<0.001
Race/ethnicity			<0.001
White	554,529 (64)	12,605 (70)	
Black	147,665 (17)	2745 (15)	
Hispanic	114,089 (13)	1795 (10)	
Asian or Pacific Islander	18,374 (2)	360 (2)	
Native American	7505 (1)	165 (1)	
Other	25,249 (3)	415 (2)	
Elixhauser Comorbidity Index score			<0.001
0	63,784 (7)	450 (2)	
1	127,484	(14)	1375 (7)
2	175,934 (20)	2610 (14)	
≥3	523,484 (45)	14330 (76)	
Median annual income in patient's zip code			<0.0001
$1–24,999	284,319 (32)	5095 (28)	
$25,000–34,999	234,509 (27)	5000 (27)	
$35,000–44,999	206,354 (24)	4660 (25)	
$45,000 or more	150,464 (17)	3635 (20)	
Insurance type [n (%)]			<0.001
Medicare	272,304 (32)	5455 (30)	
Medicaid	215,714 (25)	4705 (26)	
Private	283,559 (33)	6395 (35)	
Uninsured	84,519 (10)	1505 (8)	
Hospital characteristics			
Hospital region			<0.001
Northeast	148,419 (17)	3345 (18)	
Midwest	200,179 (22)	4850 (26)	
South	364,125 (41)	6860 (37)	
West	177,964 (20)	3710 (20)	
Hospital bed size			<0.001
Small	224,589 (25)	3439 (18)	
Medium	224,589 (31)	4710 (25)	
Large	393,695 (44)	10,615 (57)	
Hospital status			<0.001
Rural	104,874 (12)	1085 (6)	
Urban non-teaching	217,499 (24)	3260 (17)	
Urban teaching	568,314 (64)	14,420 (77+)	

Data are expressed as number (percentage) with the exception of age (mean ± SD). SD = standard deviation, VTE = venous thromboembolism.

AP with noninfected necrosis (AOR 6.9, 95% CI 6.4–7.4, $P < 0.001$), and AP with infected necrosis (AOR 12.2, 95% CI 10.6–14.1, $P < 0.001$). PVT was significantly associated with AP (AOR 6.9, 95% CI 6.5–7.2, $P < 0.001$). Subgroup analysis revealed increased association of PVT with AP without necrosis (AOR 5.02, 95% CI 4.7–5.3, $P < 0.001$), AP with noninfected necrosis (AOR 42.9, 95% CI 38.8–47.4, $P < 0.001$), and AP with infected necrosis (AOR 54.7, 95% CI 45.1–66.4, $P < 0.001$).

Table 2

Length of stay in acute pancreatitis patients with and without venous thromboembolisms (VTE) using multivariable linear regression

Outcome	No VTE length of stay (d)	VTE length of stay (d)	Crude mean difference in length of stay (d)*	Adjusted mean difference in length of stay (d)*
Total	4.1 ± 0.01	10.6 ± 0.30	6.5 ± 0.25	5.90 ± 0.26
Pancreatitis without necrosis	3.9 ± 0.01	7.8 ± 0.19	3.9 ± 0.20	3.40 ± 0.21
Pancreatitis with noninfected necrosis	7.9 ± 0.12	14.3 ± 0.57	6.30 ± 0.58	5.60 ± 0.60
Pancreatitis with infected necrosis	14.0 ± 0.60	27.9 ± 1.70	13.40 ± 1.80	11.00 ± 1.80

Data are expressed as the mean ± SE. * Difference in length of stay comparing patients who had VTE with those who did not (all $P < 0.001$).

Table 3

Total inpatient cost in acute pancreatitis patients with and without venous thromboembolisms (VTE) using multivariable linear regression

Outcome	No VTE Mean charges	VTE Mean charges	Crude mean difference in total inpatient charge (USD)*	Adjusted mean difference in total inpatient charge (USD)*
Total ($)	38,682 ± 243	118,324 ± 4709	79,641 ± 4672	71,914 ± 4702
Pancreatitis without necrosis ($)	36,542 ± 217	78,337 ± 3326	41,794 ± 3306	37,451 ± 3458
Pancreatitis with noninfected necrosis ($)	80,024 ± 1839	170,797 ± 12,777	90,772 ± 12799	76,340 ± 12,455
Pancreatitis with infected necrosis ($)	163,300 ± 8655	362,172 ± 32,460	198,871 ± 33,459	164,141 ± 31,936

Data are expressed as the mean ± SE. VTE = venous thromboembolism. * Difference in total charge comparing patients who had VTE with those who did not (all $P < .001$).

Other DVTs were significantly associated with AP (AOR 1.8, 95% CI 1.7–1.97, $P < 0.001$). Subgroup analysis revealed increased association of other DVTs with AP without necrosis (AOR 1.2, 95% CI 1.1–1.3, $P < 0.001$), AP with noninfected necrosis (AOR 16.6, 95% CI 14–18.75, $P < 0.001$), and AP with infected necrosis (AOR 24.4, 95% CI 19.4–29.8, $P < 0.001$). Lower extremity DVTs had a significant decrease associated with AP (AOR 0.27, 95% CI 0.25–0.31, $P < 0.001$). Subgroup analysis revealed the decreased association of lower extremity DVTs with AP without necrosis (AOR 0.21, 95% CI 0.19–0.7, $P < 0.001$); however increased association with AP with infected necrosis (AOR 5.3, 95% CI 4.1–6.9, $P < 0.001$). Upper extremity DVTs had a significant decrease associated with AP (AOR 0.59, 95% CI 0.51–0.65, $P < 0.001$). Subgroup analysis revealed decreased association of upper extremity DVTs with AP without necrosis (AOR 0.47, 95% CI 0.41–0.53, $P < 0.001$); however increased association with AP with noninfected necrosis (AOR 2.6, 95% CI 2–3.4, $P < 0.001$), and AP with infected necrosis (AOR 6.4, 95% CI 4.4–9.2, $P < 0.001$). Pulmonary embolisms (PE) had a significant decreased association with AP (AOR 0.46, 95% CI 0.42–0.51, $P < 0.001$). Subgroup analysis revealed decreased association of PE with AP without necrosis (AOR 0.38, 95% CI 0.34–0.41, $P < 0.001$); however increased association with AP with noninfected necrosis (AOR 1.86, 95% CI 1.45–2.4, $P < 0.001$), and AP with infected necrosis (AOR 4.9, 95% CI 3.5–6.8, $P < 0.001$).

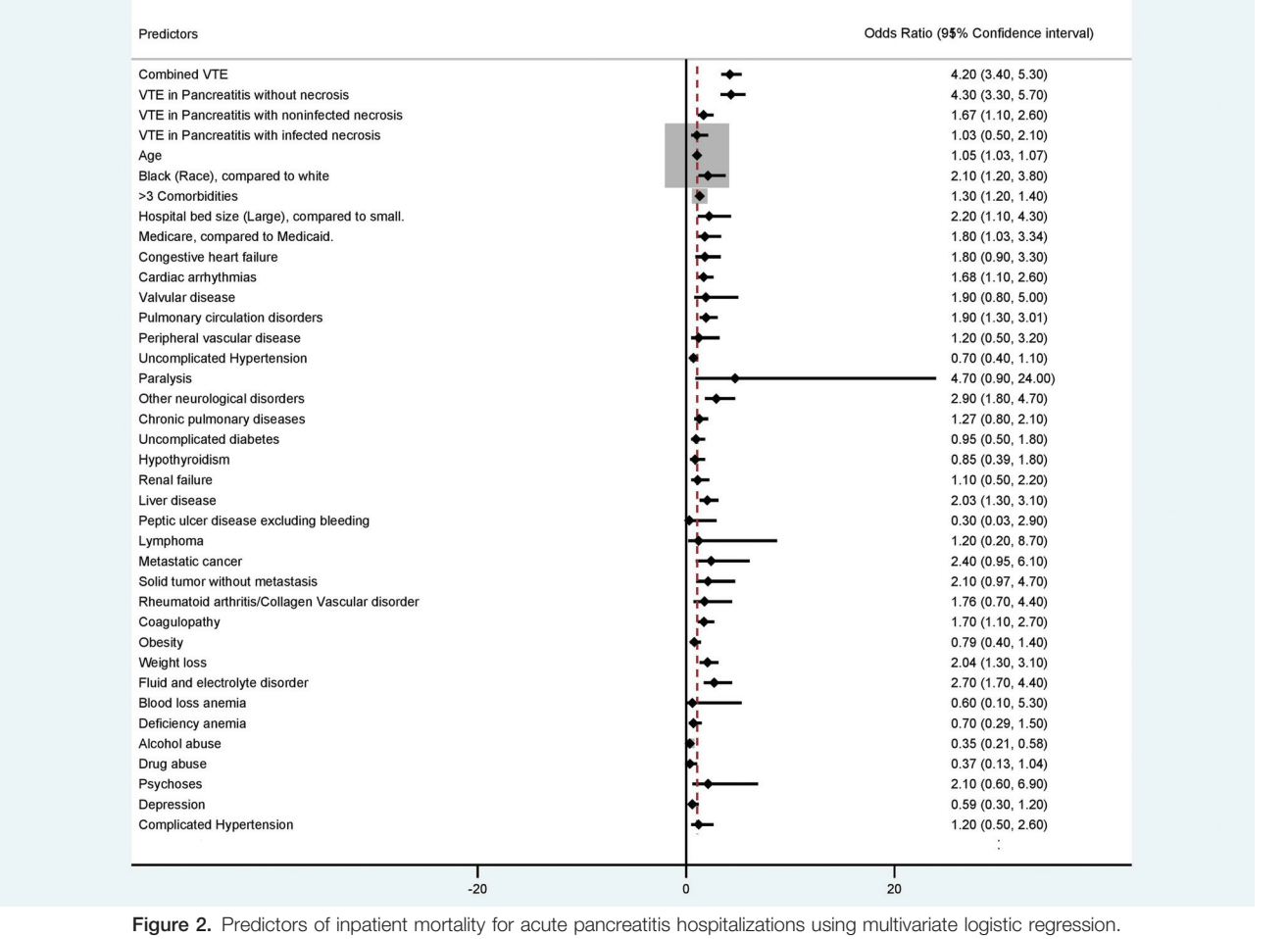

Figure 2. Predictors of inpatient mortality for acute pancreatitis hospitalizations using multivariate logistic regression.

Trends of acute VTE in AP based on severity

In patients with AP, VTE rate increased between 2016 and 2019. The rate of all acute VTE increased from 17.4 to 24 per 1000 AP admissions ($P < 0.001$). Among AP without necrosis, rates of VTE increased from 13 to 17.1 per 1000 AP admissions (Fig. 3). Acute VTE rates were highest in AP with noninfected and infected necrosis per 1000 AP admissions (123 and 204 respectively, $P < 0.001$). A comparison of trends can be seen in Figure 3, and rates can be seen in Additional Table 4, http://links.lww.com/JP9/A18.

Discussion

The Atlanta classification system identifies three severities of acute pancreatitis, which are mild, moderate, and severe.[15] Mild AP has no organ failure or local or systemic complications; moderately severe AP has organ failure resolving within 48 hours and can have local or systemic complications. Finally, severe AP is classified as having persistent >48 hours of organ failure that can be isolated to a single organ or involve multiple organs.[16] Both AP with necrosis and AP with infected necrosis fall under the category of moderate to severe pancreatitis according to the Atlanta classification, meaning that they are associated with organ failure.

We observed that hospitalized patients with AP have an increased association with the development of acute VTE. The total incidence of patients with AP developing VTE was 2.1%. AP without necrosis was most common. Furthermore, our analysis showed that patients who developed AP with VTE had significantly higher hospital LOS, hospital cost, healthcare utilization, and mortality levels than those with AP without VTE. A closer examination of subtypes of VTE revealed that PVT was the most common type of VTE occurring in these patients. The more severe form of AP (with infected necrosis) had the highest association with VTE.

The underlying pathophysiology of how AP instigates VTE formation is complex. Due to pancreatitis, the systemic acute inflammatory process increases pro-inflammatory markers such as TNF-alpha, IL-1, IL-6, IL-10, which then trigger the activation of the coagulation cascade, prevent fibrinolysis, and prevent regular anticoagulation pathways from functioning.[5] Endothelial vasculature is disrupted through the activation of inflammatory markers, leading to the weakening of vessel walls. This, in turn, leads to impediment of blood flow and stasis which allow for ensuing thrombus formation. When the pancreas is damaged, pancreatic enzymes are released, causing pro-thrombotic clotting factors to occur, which facilitates an increase in vascular events.[17]

The incidence rates of VTE development in patients with AP were higher in males than females, in the white race, those with multiple comorbidities, in higher income brackets, and those with private health insurance. Literature review reveals that AP due to alcohol abuse diagnosis occurred more frequently in males and those with Medicaid, self-pay, or another form of insurance.[18] This may explain why we observed a higher incidence of VTE development in these groups during our study, as rates of alcohol abuse are greater in men than in women.[19] When hospital characteristics were examined, the incidence of VTE in AP was higher in larger hospitals, those in an urban setting, and that was in southern regions. The regional distribution of VTE in AP among the southern US could be secondary to the increasing number of comorbidities associated with VTE development in this region, for example, obesity.[20,21]

When patients are hospitalized for AP, they have prolonged immobilization, which contributes to VTE development. Thus, the increased likelihood of VTE in AP can be attributed to the severe state of inflammation associated with the disease and prolonged immobilization of patients as a consequence of hospitalization. Reciprocally, VTE itself prolongs inpatient stays. Gigout et al[22] reported that in patients with AP complicated by necrosis, the LOS was more than 1 month. When looking at LOS divided by severity of pancreatitis, we demonstrated that pancreatitis with infected necrosis and VTE had the most prolonged LOS at 27.9 ± 1.7 days compared to

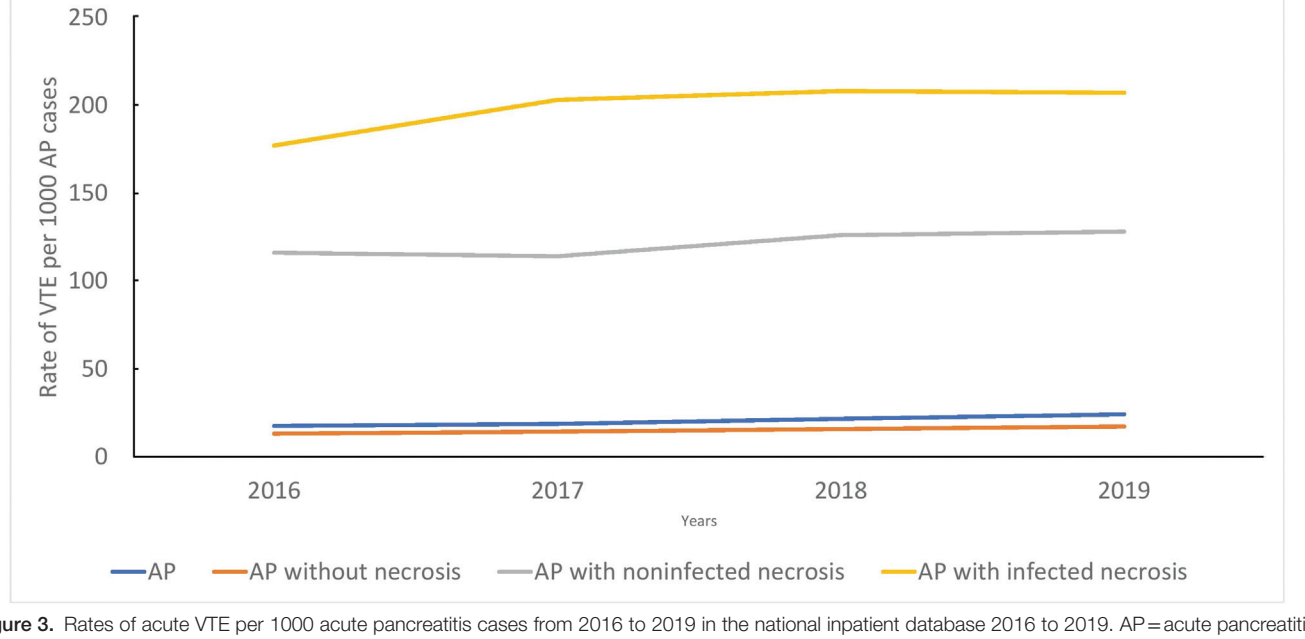

Figure 3. Rates of acute VTE per 1000 acute pancreatitis cases from 2016 to 2019 in the national inpatient database 2016 to 2019. AP = acute pancreatitis, VTE = venous thromboembolisms.

pancreatitis without necrosis which had a hospital stay of 10.6 ± 0.3 days. This LOS reduces to half (14 days) in the case of AP with infected necrosis without VTE. The prolonged LOS in more severe forms of AP prevents early ambulation, increases inflammatory state, resulting in increased VTE risk. In the VTE cohort, compared to AP without necrosis, the AP with noninfected and infected necrosis had increased LOS (6 and 18.4 days respectively, $P < 0.001$) in our study (results not shown).

The most common cause of gastrointestinal disease admissions in the United States is AP, costing approximately 9.3 billion annually.[23,24] Our study revealed a substantial increase in cost from 2016 to 2019 in AP with and without VTE (percent increased 340% and 477% respectively). A previous study reports that VTE in AP substantially increases costs, up to $44,882 per patient, consistent with our analysis.[17] However, the effect of AP severity on hospital cost has not been studied previously. AP with noninfected and infected necrosis, compared to AP without necrosis had increased per-patient cost ($82,034 and $251,207 respectively, $P < 0.001$) (results not shown). We believe that the increase in cost is not a result of only VTE but also due to the severity of AP.

The global incidence of AP continues to increase and is currently studied to be at 34 affected individuals per 100,000 person-years.[23] Even though the incidence of AP continues to rise, the mortality rate for the disease has been steadily decreasing from 1.6% to 0.8% over the past decade, presumably from adequate care and VTE prophylaxis. However, there has been no decrease in mortality of AP patients who have simultaneous VTE.[17] This study has reported that VTE occurring in patients hospitalized with AP is associated with significantly increased mortality. While VTE in AP without necrosis and noninfected necrosis was significantly associated with increased mortality, VTE did not significantly increase mortality in AP with necrosis but our results showed a positive trend, nearing significance (AOR 1.03, 95% CI 0.5–2.1, $P = .06$).

In this study, we demonstrated a significant association between AP and the development of VTEs. There have been well-established reports on complications of AP such as pancreatic necrosis, pseudocysts, acute lung injury, hypovolemia, but large-scale studies that have undertaken the task of studying the risk of VTE in AP are lacking. In our study, we saw that VTEs incidence rates per 1000 AP patients were higher in those admitted with pancreatitis with noninfected and infected necrosis ($P < 0.001$). Interestingly, we also found that mild AP had a lower association with upper and lower DVTs versus AP with necrosis, which was associated with higher levels of upper and lower extremity DVTs. As we have already noted, the inflammatory response elicited by AP is the factor predisposing patients with AP to develop VTE. It has been shown that almost all patients with persistent organ failure have persistent systemic inflammatory response syndrome.[25] Therefore, we observed increased upper and lower DVTs in AP with necrosis likely due to significantly elevated and sustained inflammatory response seen in AP with necrosis that does not occur to the same extent in mild AP. Severe presentations of pancreatitis such as severe AP, necrotizing pancreatitis, and recurrent pancreatitis have been shown to have higher occurrences of splanchnic vein thrombosis (SVT) in literature.[26] It was also demonstrated that the most common type of VTE occurring in AP was PVT, which is a type of SVT.[26] A systematic review by Anis et al showed that the pooled incidence of SVT at the first incidence of AP was 15% compared to the overall pooled incidence of SVT, which was 17%.[26]

There is currently no consensus on the management of AP complicated by VTE. There have been studies that suggest anticoagulating patients based on the severity of pancreatitis. Some studies showed that AP automatically requires anti-coagulation due to association with higher rates of development of VTE, particularly SVTs.[27,28] Other studies argue that there is no benefit of anticoagulation in the management of AP-induced VTEs due to risk for hemorrhagic conversion and because there have been no findings to suggest improvement in mortality or morbidity with anticoagulation.[29] Further studies regarding comprehensive management strategy for preventing AP, treating VTE in AP, and managing comorbidities leading to AP are needed.

The strengths of this study are the large sample size and extensive patient population that can be accessed with the NIS database. The findings from this study are easily applicable to a wide geographic distribution allowing it to be impactful throughout various regions of the country. Univariate and multivariate regression allowed for adjustment of various confounding variables to minimize bias. There are several limitations to this study. The present study identified cohorts retrospectively and cannot determine causality. The study did not have randomization and blinding, impacting the result interpretation. The data extracted is based on ICD 10 codes; therefore, misclassification may have occurred. There is the potential for missing data in the NIS.

In conclusion, acute VTE during AP hospitalizations is associated with poor inpatient outcomes. They increase the length of stay, hospital cost, and inpatient mortality. AP with noninfected and infected necrosis tends to have a higher association with VTE; however, AP with noninfected necrosis has a lower association with acute VTE. Moreover, AP with noninfected necrosis is associated with lower upper and lower extremity VTE incidence during hospitalizations. The rate of VTE in AP has been increasing in recent years, with the highest being in AP with infected necrosis. Acute VTE in AP patients can worsen prognosis, and gastroenterologists need vigilance to raise awareness about VTE among patients with AP.

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Author contributions

HA: Conceptualization, Writing-Review, Supervision, Project Administration; SM: Writing Original Draft, Writing-Review & Editing; RP: Writing-Original Draft, Writing-Review & Editing; MFF: Writing-Original Draft, Writing-Review & Editing; WL: Investigation, Supervision, Editing, Proof reading. All authors approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

The University and Medical Center IRB at East Carolina University Research Ethics Committee has confirmed that no ethical approval is required.

Declaration of participant consent

Patient consent was waived due to the public availability of data.

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