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ORIGINAL ARTICLE

Venous Thromboembolism in Necrotizing Pancreatitis: an Underappreciated Risk

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Abstract

Background Necrotizing pancreatitis (NP) is a severe systemic inflammatory process. We have observed a high incidence of venous thromboembolism (VTE) in NP patients. However, remarkably few data exist to document the true incidence of VTE—including splanchnic vein thrombosis (SVT), extremity deep venous thrombosis (eDVT), and pulmonary embolism (PE)—in NP. Therefore, we sought to determine the incidence and risk factors for VTE in NP patients.

Methods Retrospective review of all NP patients treated at a single academic center between 2005 and 2015. VTE diagnosis was confirmed by ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and/or ventilation/perfusion (V/Q) scan. Descriptive statistics and univariate analysis were applied where appropriate; p value < 0.05 was considered statistically significant.

Results Five hundred and forty-five NP patients (median age 53 years; 65% males) were reviewed. VTE was diagnosed in 312 patients (57%). SVT was found in 50%, eDVT in 16%, and PE in 6%. VTE in multiple sites was found in 22% of patients. VTE was diagnosed a median of 37 days following pancreatitis diagnosis. Seventy-nine percent of patients required at least one surgical procedure over the course of their NP. Patients requiring surgery had a DVT incidence of 58%; however, VTE was diagnosed preoperatively in 63%. Male gender, history of previous DVT, infected necrosis, development of organ failure, and development of respiratory failure were identified as risk factors for VTE ($p = 0.001$–0.04) by univariate analysis.

Conclusions Venous thromboembolism is extremely common in necrotizing pancreatitis. Regular ultrasound screening may be considered to facilitate early diagnosis in this extremely high-risk population.

Keywords Acute necrotizing pancreatitis · Venous thromboembolism · Deep venous thrombosis · Venous thrombosis

Introduction

Acute pancreatitis (AP) is a common condition with greater than 275,000 hospitalizations annually in the USA.[1] A variety of local and systemic complications are associated with AP accounting for the second highest cost of hospital stays: 2.2 billion dollars per year.[2] While most patients have a mild self-limited course, up to 20% develop necrotizing pancreatitis (NP)[2,3] with an associated mortality of 15–30%.[4,5]

Epidemiologic data show the development of extremity deep venous thrombosis (eDVT) and pulmonary embolism (PE) in 1.3% and 0.4% of hospitalized patients, respectively.[6] Splanchnic vein thrombosis (SVT) is seen in about 1.7% of all patients undergoing abdominal contrast-enhanced cross-sectional imaging.[7] Splanchnic vein thrombosis has been described in the setting of severe acute pancreatitis,[8] though its incidence has not been documented in high-volume studies of

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NP. The incidence of eDVT and PE in the setting of NP remains unknown.

Venous thromboembolism (VTE), which includes SVT, eDVT, and PE, can result from multiple pathophysiologic pathways. The traditional pathway of a prothrombotic/hypercoagulable state[9] applies to NP patients given the severity of acute illness. Factors unique to NP include the direct mass effect from the adjacent walled off necrosis as well as damage of the venous wall by pancreatic enzymes, increasing the splanchnic vein inflammation.

This association between NP and a high occurrence of VTE has several clinical implications. Although SVT is often an incidental finding on imaging studies performed to diagnose or assess the severity of NP, it may lead to severe morbid consequences, including ascites, mesenteric ischemia, portal hypertension, and/or gastrointestinal bleeding. Similarly, eDVT may be challenging to diagnose in intensive care patients, yet the potentially lethal risk of PE makes this diagnosis critical, as VTE is the leading cause of preventable hospital deaths in the USA.[10]

Venous thromboembolism has been described in the setting of acute pancreatitis; however, the available studies account for all degrees of severity. No study exists to define the incidence of VTE specifically in NP. Therefore, the aim of this study is to determine the true incidence of VTE in the high-risk population of NP patients and to identify risk factors for developing VTE. We hypothesized the incidence of VTE in NP is significantly higher than that in other hospitalized patients.

Materials and Methods

All patients with the diagnosis of NP treated at a single institution from 2005 to 2015 were included in this study regardless of management strategy (medical, percutaneous, endoscopic, or surgical). Electronic medical records and all imaging studies with emphasis on vascular structures were retrospectively reviewed. Patients with insufficient data for analysis were excluded from the series. Data were compiled and reported in strict compliance with patient confidentiality protocols set forth by Indiana University School of Medicine's Institutional Review Board, which approved the conduct of this study.

Diagnosis of Necrotizing Pancreatitis

Acute pancreatitis was defined according to the 2012 revision of the Atlanta classification as an association of two of the three following features: typical abdominal pain (acute onset of persistent, severe, epigastric pain, often radiating to the back), serum lipase/amylase at least three times greater than the upper limit of normal, and characteristic findings of acute pancreatitis on abdominal cross-sectional imaging studies.[11] Necrotizing pancreatitis was defined as parenchymal and/or peripancreatic necrosis represented by lack of pancreatic parenchymal enhancement and/or the findings of acute necrotic collection (ANC) or walled off necrosis (WON) on contrast-enhanced cross-sectional imaging.[11] All patients were included in the study regardless of the extent of necrosis. Infected pancreatic necrosis was defined as the presence of extraluminal gas in the pancreatic and/or peripancreatic tissue on contrast-enhanced computed tomography or with positive bacteria and/or fungal Gram stain and culture.[11]

Diagnosis of Venous Thromboembolism

In the present study, VTE included splanchnic vein thrombosis (SVT), extremity deep vein thrombosis (eDVT), and pulmonary embolism (PE). Venous thrombotic events were diagnosed by various imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasonographic venous duplex (US), and ventilation/perfusion scintigraphy (V/Q). All imaging studies were performed prospectively by senior radiologists experienced in abdominal imaging and necrotizing pancreatitis and reviewed retrospectively by a single, dedicated, experienced pancreatologist confirming the diagnosis. On contrast-enhanced cross-sectional imaging (CT, MRI), VTE was defined as the presence of a filling defect within the lumen of the vessel, non-visualization of the vein, and/or demonstration of multiple collateral veins. Splanchnic vein thrombosis included only thrombosis in the portal vein, superior mesenteric vein, or splenic vein. On extremity sonographic imaging (US), thrombosis was defined by loss of compressibility of the vein and abnormal or absent blood flow. On scintigraphy (V/Q), pulmonary embolism was defined as at least one segmental defect on perfusion scintigraphy with a normal ventilation scintigraphy.

Parameters Assessed

General demographic parameters recorded include age, gender, pancreatitis etiology, and medical comorbidities. Clinical parameters recorded include development of organ failure, infected necrosis, and number and type of intervention. Organ failure was defined according to the Modified Marshall scoring system for organ dysfunction: P_aO_2:F_iO_2 ratio of < 300 defined respiratory failure; serum creatinine > 1.9 mg/dL or two times baseline creatinine defined renal failure; and systolic blood pressure of < 90 mmHg after fluid resuscitation or need for vasoactive agents defined cardiovascular failure.[11,12] Information gathered on the VTE event includes date of diagnosis, location, and type of imaging study used for detection.

Venous Thromboembolism Prophylaxis

All patients admitted with NP are placed on mechanical and pharmacological VTE prophylaxis. Mechanical prophylaxis includes sequential compression devices and mobilization exercises, as able based on the patient's clinical condition. First-line choice of pharmacological prophylaxis is enoxaparin (Lovenox©) 40 mg once daily or unfractionated heparin 5000 U every 8 hours. Pharmacological prophylaxis varies from this only in the event of an allergy or contraindication.

Statistical Analysis

Data were recorded using Microsoft Excel® 2015 (Microsoft, Inc., Redmond, WA, USA) and analyzed with IBM SPSS statistics version 25.0® (Armonk, NY: IBM Corp). Descriptive statistics for continuous data included median, mean, range, and standard deviation. Categorical data were expressed as numbers and percentages. Where applicable, independent groups *t* tests and Pearson's correlation or Fisher's exact tests were performed for univariate subgroup analysis. Variables reaching *p* values of 0.10 or less in univariate analysis were included in multivariate analysis (binary logistic regression). Statistical significance was defined as $p < 0.05$.

Results

Population Characteristics

Five hundred and forty-five patients had complete data for analysis and were eligible for this study. Median age at diagnosis of NP was 53 years (range 13–95). Male gender was predominant ($n = 355$, 65%). The leading etiologies for NP in this series were biliary ($n = 292$, 54%), alcohol ($n = 95$, 17%), hypertriglyceridemia ($n = 31$, 6%), and post-ERCP ($n = 29$, 5%). In 15% ($n = 80$) of patients, the episode of NP was idiopathic or no formal cause was identified. Over the disease course, 429 (79%) patients required at least one surgical intervention.

Development of Venous Thromboembolism

Venous thromboembolism was diagnosed in 312 patients (57%) a median of 37 days (range 0–523) following initial diagnosis of NP. Two hundred and seventy-two (50%) patients were diagnosed with SVT, 85 (16%) with eDVT, and 32 (6%) with PE. The distribution of VTE is shown in Fig. 1. In the thrombosis population, 208 patients (67%) had SVT only, 32 patients (10%) had eDVT only, and 5 patients (2%) had PE without evidence of SVT or eDVT. A combination was seen in the remaining patients: SVT with eDVT ($n = 40$, 13%), SVT with PE ($n = 14$, 4%), eDVT with PE ($n = 3$, 1%), and SVT + eDVT + PE ($n = 10$, 3%).

In patients with SVT ($n = 272$), the most common vein involved with thrombosis was the splenic vein in 67% ($n = 182$) of patients followed by the superior mesenteric vein in 30% ($n = 82$) of patients and the portal vein in 28% ($n = 77$) of patients; a combination of two or more splanchnic veins was seen in 21% ($n = 58$) of patients. The complete pattern of SVT distribution is shown in Fig. 2.

In the surgical population ($n = 429$), VTE was observed in 58% (250/429) of patients. Venous thromboembolism was diagnosed preoperatively in 63% of those cases (157/250) a median of 18 days (range 1–499) preoperatively. The incidence of new post-operative VTE was 34% and was diagnosed a median of 32 days post-operatively (range 1–493). In patients developing post-operative VTE, SVT was present in 80% of patients and was diagnosed a median of 40 days (range 2–400) post-operatively and eDVT was present in 35% of patients and was diagnosed a median of 15 days (range 1–493) post-operatively.

Risk Factors for Venous Thromboembolism

Demographic and clinical factors and their correlation to the development of any VTE, SVT, eDVT, and PE are shown in Tables 1, 2, 3, and 4.

Any Venous Thromboembolism (Table 1)

Risk factors for the development of any VTE include male gender, history of previous VTE, infected necrosis, organ failure, and respiratory failure. In multivariate analysis, male gender, previous VTE, and infected necrosis remained significant risk factors.

Splanchnic Vein Thrombosis (Table 2)

The significant risk factor associated with development of SVT was male gender in both univariate and multivariate analysis.

Extremity Deep Vein Thrombosis (Table 3)

Significant risk factors for eDVT development are previous VTE, infected necrosis, any organ failure, respiratory failure, renal failure, cardiovascular failure, and increasing number of organ failure (Fig. 3). On multivariate analysis, significant risk factors include previous VTE and infected necrosis.

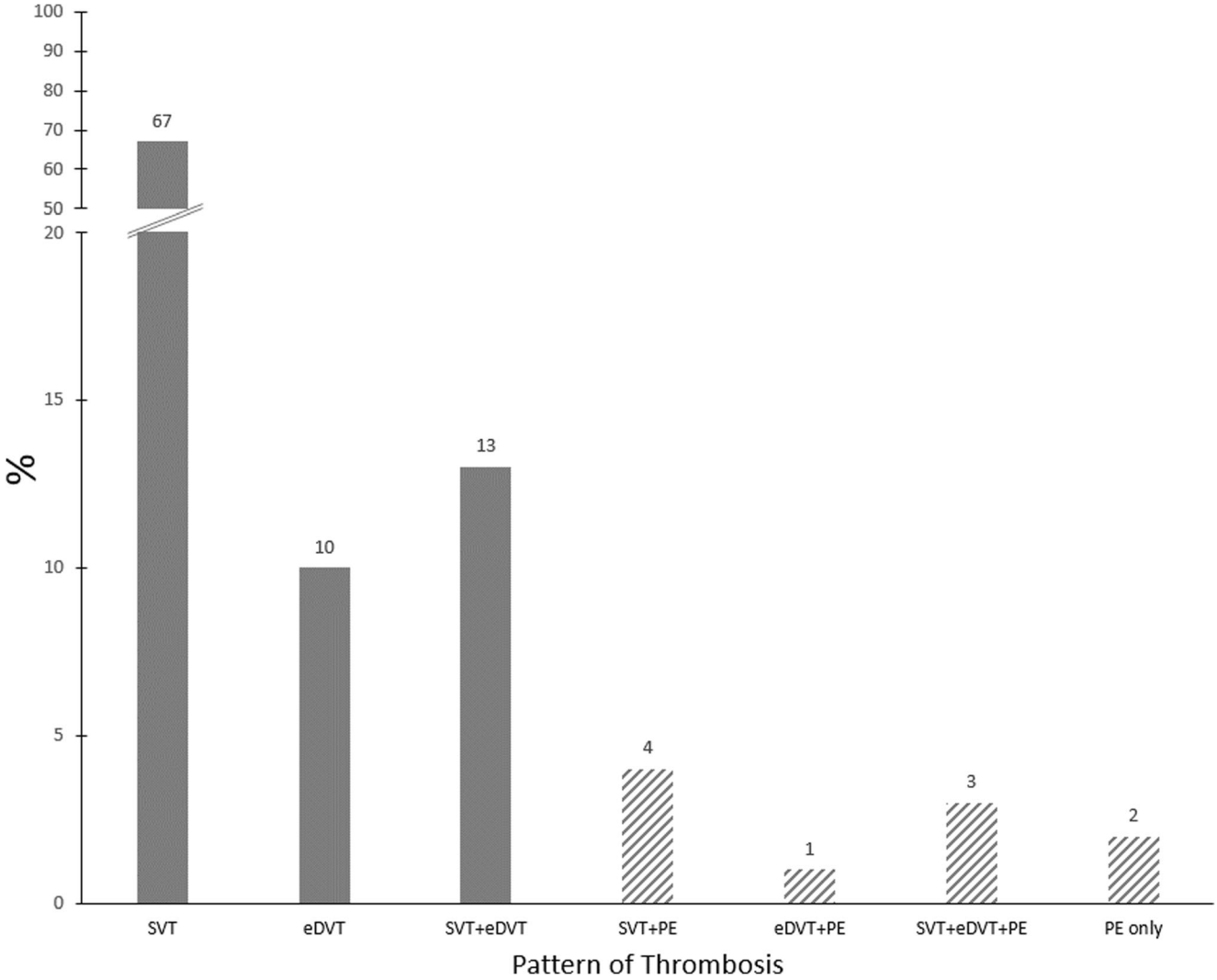

Fig. 1 Patterns of thrombosis in patients with venous thromboembolism ($n = 312$); splanchnic vein thrombosis (SVT), extremity deep vein thrombosis (eDVT), pulmonary embolism (PE)

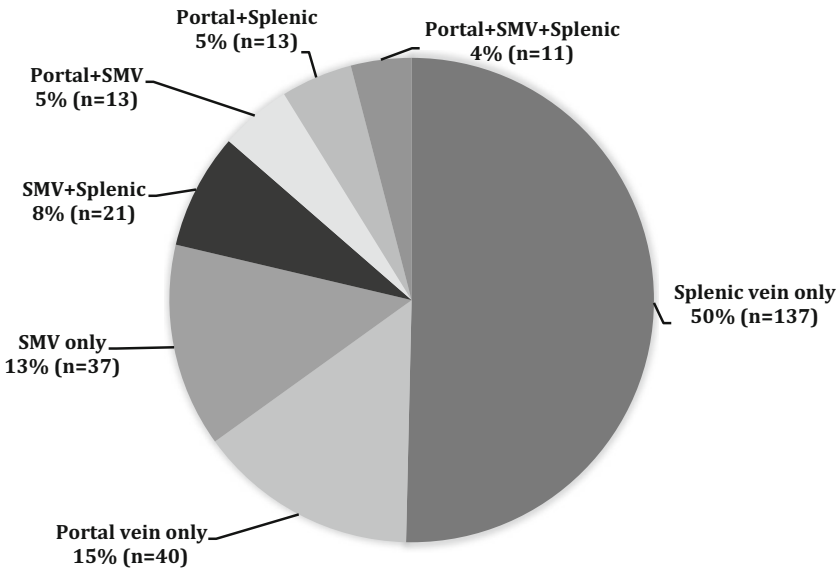

Fig. 2 Pattern of thrombosis in patients developing splanchnic vein thrombosis ($n = 272$); superior mesenteric vein (SMV)

Table 1 Incidence and risk factors for the development of venous thromboembolism (VTE); chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), venous thromboembolism (VTE), cardiovascular (CV). Values in italics represent statistical significance with $p < 0.05$

Variable	No VTE ($n = 233$)	VTE ($n = 312$)	p, univariate	p, multivariate
Age, mean (std dev)	52.6 (16.7)	52.4 (14.9)	0.88	
COPD, *n* (%)	19 (8.2%)	27 (8.7%)	0.87	
CAD, *n* (%)	24 (10.3%)	45 (14.4%)	0.19	
Hypertension, *n* (%)	141 (60.5%)	189 (60.6%)	1.00	
Diabetes, *n* (%)	61 (26.2%)	84 (26.9%)	0.92	
Alcohol abuse, *n* (%)	27 (11.6%)	44 (14.1%)	0.44	
Tobacco use, *n* (%)	93 (39.9%)	123 (39.4%)	0.93	
Obesity, *n* (%)	116 (49.8%)	157 (50.3%)	0.93	
Renal failure, *n* (%)	45 (19.3%)	79 (25.3%)	0.10	0.70
CV failure, *n* (%)	33 (14.2%)	48 (15.4%)	0.72	
Biliary etiology, *n* (%)	119 (51.1%)	173 (55.4%)		
Alcohol etiology, *n* (%)	41 (17.6%)	54 (17.3%)		
Triglyceride etiology, *n* (%)	12 (5.2%)	19 (6.1%)	0.43	
Male gender, *n* (%)	131 (56.2%)	224 (71.8%)	*< 0.001*	*< 0.001*
Previous VTE, *n* (%)	8 (3.4%)	24 (7.7%)	*0.04*	*0.04*
Infected necrosis, *n* (%)	82 (35.2%)	152 (48.7%)	*< 0.001*	*< 0.01*
Respiratory failure, *n* (%)	63 (27.0%)	118 (37.8%)	*0.01*	0.12
Any organ failure, *n* (%)	73 (31.3%)	128 (41.0%)	*0.03*	0.33

Pulmonary Embolism (Table 4)

Risk factors for the development of PE include *female* gender, coronary artery disease, obesity, and respiratory failure. Female gender remained significant on multivariate analysis.

Surgery as a Risk Factor

No difference was observed in VTE development between those patients who required surgery (41.7%) and those patients managed without surgery (46.6%), $p = 0.40$.

Table 2 Incidence and risk factors for the development of splanchnic vein thrombosis (SVT); chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), venous thromboembolism (VTE), cardiovascular (CV). Values in italics represent statistical significance with $p < 0.05$

Variable	No SVT ($n = 273$)	SVT ($n = 272$)	p, univariate	p, multivariate
Age, mean (std dev)	53.1 (16.6)	51.9 (14.7)	0.39	
COPD, *n* (%)	22 (8.1%)	24 (8.8%)	0.76	
CAD, *n* (%)	30 (11.0%)	39 (14.3%)	0.25	
Hypertension, *n* (%)	163 (59.7%)	167 (61.4%)	0.73	
Diabetes, *n* (%)	73 (26.7%)	72 (26.5%)	1.00	
Alcohol abuse, *n* (%)	32 (11.7%)	39 (14.3%)	0.38	
Tobacco use, *n* (%)	104 (38.1%)	112 (41.2%)	0.48	
Obesity, *n* (%)	142 (52.0%)	131 (48.2%)	0.39	
Renal failure, *n* (%)	57 (20.9%)	67 (24.6%)	0.31	
CV failure, *n* (%)	42 (15.4%)	39 (14.3%)	0.81	
Previous VTE, *n* (%)	14 (5.1%)	18 (6.6%)	0.47	
Infected necrosis, *n* (%)	107 (39.2%)	127 (46.7%)	0.08	0.18
Respiratory failure, *n* (%)	81 (29.7%)	100 (36.8%)	0.08	0.23
Any organ failure, *n* (%)	93 (34.1%)	108 (39.7%)	0.18	
Biliary etiology, *n* (%)	146 (53.5%)	146 (53.7%)		
Alcohol etiology, *n* (%)	44 (16.1%)	51 (18.8%)		
Triglyceride etiology, *n* (%)	14 (5.1%)	17 (6.3%)	0.66	
Male gender, *n* (%)	159 (58.2%)	196 (72.1%)	*0.001*	*0.01*

Table 3 Incidence and risk factors for the development of extremity deep vein thrombosis (eDVT); chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), venous thromboembolism (VTE), cardiovascular (CV). Values in italics represent statistical significance with $p < 0.05$

Variable	No eDVT ($n = 460$)	eDVT ($n = 85$)	p, univariate	p, multivariate
Age, mean (std dev)	52.1 (15.7)	54.8 (15.9)	0.15	
Male gender, *n* (%)	303 (65.9%)	52 (61.2%)	0.46	
COPD, *n* (%)	41 (8.9%)	5 (5.9%)	0.52	
CAD, *n* (%)	56 (12.2%)	13 (15.3%)	0.48	
Hypertension, *n* (%)	282 (61.3%)	48 (56.5%0	0.40	
Diabetes, *n* (%)	121 (26.3%)	24 (28.2%)	0.69	
Alcohol abuse, *n* (%)	66 (14.3%)	5 (5.9%)	0.04	
Tobacco use, *n* (%)	187 (40.7%)	29 (34.1%)	0.28	
Obesity, *n* (%)	223 (48.5%)	50 (58.8%)	0.10	
Biliary etiology, *n* (%)	235 (51.1%)	57 (67.1%)		
Alcohol etiology, *n* (%)	88 (19.1%)	7 (8.2%)		
Triglyceride etiology, *n* (%)	25 (5.4%)	6 (7.1%)	0.11	
Previous VTE, *n* (%)	22 (4.8%)	10 (11.8%)	*0.02*	*0.02*
Infected necrosis, *n* (%)	179 (38.9%)	55 (64.7%)	*< 0.001*	*0.002*
Respiratory failure, *n* (%)	137 (29.8%)	44 (51.8%)	*< 0.001*	0.11
Renal failure, *n* (%)	94 (20.4%)	30 (35.3%)	*0.01*	0.57
CV failure, *n* (%)	58 (12.6%)	23 (27.1%)	*0.001*	0.63
Any organ failure, *n* (%)	155 (33.7%)	46 (54.1%)	*0.001*	0.30

Mortality

The development of VTE did not increase mortality in patients with NP (Fig. 4).

Discussion

This large series identifies a remarkably high incidence of venous thromboembolism, including splanchnic vein

Table 4 Incidence and risk factors for the development of pulmonary embolism (PE); chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), venous thromboembolism (VTE), cardiovascular (CV). Values in italics represent statistical significance with $p < 0.05$

Variable	No PE ($n = 513$)	PE ($n = 32$)	p, univariate	p, multivariate
Age, mean (std dev)	52.4 (15.8)	53.8 (15.0)	0.70	
COPD, *n* (%)	42 (8.2%)	4 (12.5%)	0.34	
Hypertension, *n* (%)	314 (61.2%)	16 (50.0%)	0.26	
Diabetes, *n* (%)	137 (26.7%)	8 (25.0)	1.0	
Alcohol abuse, *n* (%)	69 (13.5%)	2 (6.3%)	0.41	
Tobacco use, *n* (%)	204 (39.8%)	12 (37.5%)	0.85	
Previous VTE, *n* (%)	29 (5.7%)	3 (9.4%)	0.42	
Infected necrosis, *n* (%)	215 (41.9%)	19 (59.4%)	0.07	0.28
Renal failure, *n* (%)	113 (22.0%)	11 (34.4%)	0.13	
CV failure, *n* (%)	73 (14.2%)	8 (25.0%)	0.12	
Biliary etiology, *n* (%)	271 (52.8%)	21 (65.6%)		
Alcohol etiology, *n* (%)	94 (18.3%)	1 (3.1%)		
Triglyceride etiology, *n* (%)	27 (5.3%)	4 (12.5%)	0.24	
Any organ failure, *n* (%)	184 (35.9%)	17 (53.1%)	0.06	0.96
Female gender, *n* (%)	173 (33.7%)	17 (53.1%)	*0.03*	*0.02*
CAD, *n* (%)	61 (11.9%)	8 (25.0%)	*0.04*	0.07
Obesity, *n* (%)	251 (48.9%)	22 (68.8%)	*0.04*	0.12
Respiratory failure, *n* (%)	165 (32.3%)	16 (50.0%)	*0.04*	0.59

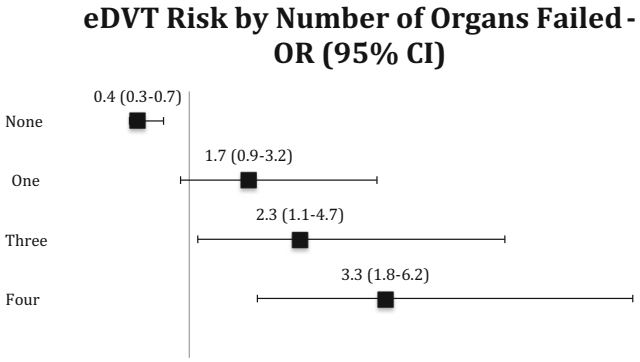

Fig. 3 Odds ratio (OR) with 95% confidence interval (CI) for the development of extremity deep vein thrombosis (eDVT) with progressing number of organs failed. *p* values: none < 0.001, one = 0.14, two = 0.02, three < 0.001

thrombosis, extremity deep vein thrombosis, and pulmonary embolism, in the setting of necrotizing pancreatitis. Identification of specific VTE risk factors may highlight patients who can benefit from aggressive mechanical and pharmacological prophylaxis. From a more practical standpoint, standardizing an assertive screening protocol in this population seems appropriate. The incidence of thrombotic events in this population mandates a change to the current clinical practice of VTE prevention and identification in NP.

Venous thromboembolism represents a significant and serious health condition. Regardless of comorbid conditions or pathology, nearly 25% of acute VTE patients die within 7 days of diagnosis.[13] Venous thromboembolism has been identified as the most common preventable cause of death in hospitalized patients.[10] As such, knowledge of VTE risk factors specific to NP may influence prophylaxis or screening strategy.

In the general medical population, risk factors for the development of VTE include acute medical illness, immobility, central venous catheter, obesity, surgical intervention, and systemic inflammation.[9] Unique to NP is a profound local splanchnic inflammatory response, mass effect from surrounding acute necrotic collection or walled off necrosis, and direct venous damage by pancreatic enzymes. The current study identifies risk factors specific to NP patients: male gender, history of previous VTE, infected pancreatic necrosis, organ failure, and respiratory failure. The presence of these risk factors should heighten the awareness to the presence of VTE in NP patients.

In this series, extremity deep vein thrombosis was identified in 16% of hospitalized patients with NP. This represents a tenfold increase when compared to the general hospitalized population (1.3%).[6] High-risk patients have been identified in other surgical populations; trauma and critical care physicians utilize the risk assessment profile (RAP) score to identify the highest-risk patient population who benefit from four-extremity duplex ultrasound screening for eDVT.[14] Given the extremely high incidence of eDVT in NP patients, a weekly, four-extremity duplex ultrasound screening protocol should strongly be considered. This practice has become standard of care at the author's institution and is the scope of an ongoing prospective study. The recommendation for screening ultrasound should be considered in light of reported evidence.

The most common VTE in NP patients is of the splanchnic veins (50%). This is not surprising given the local peripancreatic inflammation, direct mass effect, and venous damage from pancreatic enzymes. Splanchnic vein thrombosis in NP introduces several clinical dilemmas. Fear of hemorrhage upon initiation of therapeutic anticoagulation is a serious concern. While splenic vein thrombosis can often be observed, mesenteric and portal vein thrombosis can have potentially fatal consequences. Studies regarding the use of therapeutic anticoagulation remain inconclusive; rates of recanalization in acute pancreatitis are similar between patients

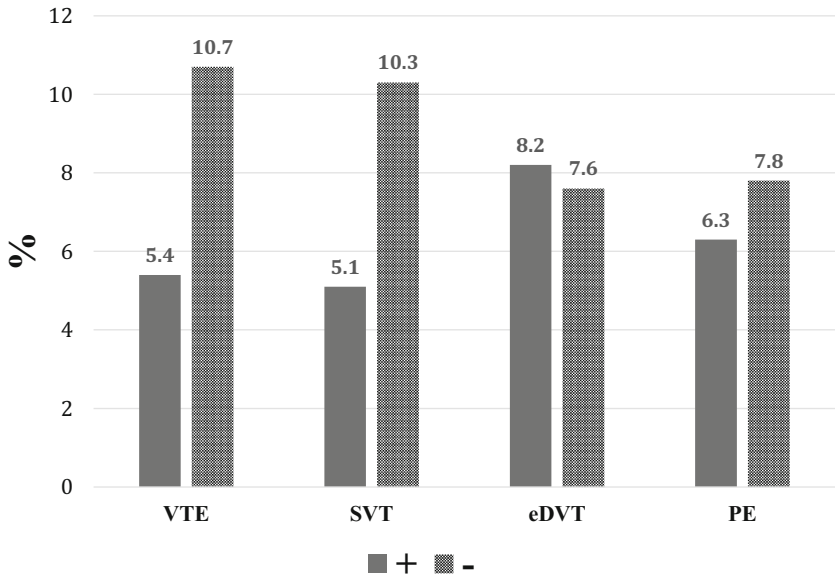

Fig. 4 Mortality rates by type of thrombosis: venous thromboembolism (VTE), splanchnic vein thrombosis (SVT), extremity deep vein thrombosis (eDVT), pulmonary embolism (PE). Patients with VTE ($p = 0.03$) or SVT ($p = 0.03$) had significantly decreased mortality rates when compared to those without VTE or SVT, respectively. No difference was seen in mortality between those with/without eDVT or PE

treated with therapeutic anticoagulation and those treated expectantly.[15,16] It is the practice of the authors to observe splenic vein thrombosis[17] and utilize anticoagulation selectively in portal vein and superior mesenteric vein thrombosis. Given the complexity of NP patients, the decision to fully anticoagulate patients with splanchnic vein thrombosis is always made on a case-by-case basis. This captivating topic is the subject of an ongoing, more in-depth analysis at the author's institution.

The overall incidence of pulmonary embolism in NP patients was 6% - a fifteen-fold increase compared to that of the general hospitalized population (0.4%).[6] The presentation of PE is variable and can develop in the presence of eDVT, SVT, a combination, or PE alone. Pulmonary embolism represents a potentially fatal problem; however, its development is possibly preventable with adequate prophylaxis. When present, swift diagnosis and aggressive treatment is critical to improving mortality.[18]

Prevention and early detection of VTE in NP patients requires a change from the current clinical practice to more aggressive prophylaxis and screening measures. Patients deemed high risk, particularly those with organ failure, infected pancreatic necrosis, previous history of VTE, and male gender, should be considered for weekly four-extremity duplex ultrasound studies. Future development of a VTE risk score will assist in preventing unnecessary screening of the lowest risk population of NP patients. Pharmacologic prophylaxis should consider including anti-factor-Xa level measurement and appropriate medication dose adjustments, as this has been shown in the high-risk trauma patients to decrease the incidence of VTE development.[19]

A significant proportion of patients required operative intervention (79%) and developed infected pancreatic necrosis (43%). Most patients were transferred to our facility, as it is a tertiary referral center with experience in the management of NP. As such, these transferred patients are often the most complex NP patients in which their clinical demands have exceeded the capabilities of the referring facility. The result is a high-incidence of infected necrosis and failed minimally invasive management, and thus, a high requirement for operative intervention as the last line of treatment. Additionally, the current study includes patients treated prior to the evolution of NP treatment strategy[20] further explaining the higher incidence of operative intervention. The requirement for operative intervention at our institution has decreased over the decade of this study.[21] In the current study, surgery itself was not a risk factor for VTE development; however, this relationship may change with the evolution of NP treatment.

This study is limited by its retrospective nature. Most patients treated at our institution are transferred from outside hospitals and it may be unclear in some cases whether thrombosis was present prior to development of NP. The relationship between VTE development and extent of necrosis or type of intervention was not evaluated. Mortality was found to be lower in patients with VTE. A significant portion of NP patients do not survive the initial insult and profound systemic inflammatory response and thus do not survive long enough to develop or establish the diagnosis of VTE. These patients are included in the non-VTE arm of this study; this limits the ability to evaluate the association between VTE development and mortality and may explain the increased mortality in non-VTE patients. Additionally, given the complexity of NP patients, mortality in this study could not be definitively attributed to VTE due to the retrospective nature. Finally, optimal treatment of splanchnic vein thrombosis was not evaluated in this study—further study is warranted to determine which patients should receive therapeutic anticoagulation.

Conclusion

Venous thromboembolism in necrotizing pancreatitis is extremely common. Mechanical and pharmacologic prophylaxis must be a priority in this high-risk patient population. A low threshold for venous thromboembolism workup is obligatory. Changes to clinical practice should include the addition of weekly, screening, four-extremity duplex ultrasounds and anti-factor-Xa guided dosing of pharmacologic prophylaxis.

Author Contribution Conception, design, data acquisition/analysis/interpretation: AMR, TKM, RAC, CLC, EPC, MGH, JL, AN, CMS, NJZ

Drafting/revision of work: AMR, TKM, RAC, CLC, EPC, MGH, JL, AN, CMS, NJZ

Final approval: AMR, TKM, RAC, CLC, EPC, MGH, JL, AN, CMS, NJZ

Accountability of work: AMR, TKM, RAC, CLC, EPC, MGH, JL, AN, CMS, NJZ

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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