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Splanchnic Vein Thrombosis in Acute Pancreatitis and Its Consequences

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Abstract

Splanchnic vein thrombosis (SVT) is a serious vascular complication that can occur in patients with acute pancreatitis. We assessed the incidence of SVT and its relationship with acute pancreatitis (AP) and associated complications. We carried out a retrospective analysis of medical histories from patients hospitalized with AP in a single surgical center. Histories were acquired from patients with abdominal and pelvic computed tomography scans performed between the 2nd and 3rd day of hospitalization. We assessed the impact and extent of thrombosis over the disease course. We found a strong positive correlation (Cramer's V coefficient = 0.34) between SVT and disease severity. Mortality in the study group was 7.2% (8 patients) of which 5 patients (62.5%) were diagnosed with SVT. We observed an increased incidence of death among patients with thrombosis, with results approaching significance ($P = 0.056$). In our study, we found that SVT has a negative effect on the course of AP and is associated with more severe disease and increased mortality.

Keywords

anticoagulation, pancreatitis, portal vein, splanchnic vein, thrombosis, computed tomography

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Introduction

Acute pancreatitis (AP) can result in autoactivation of pancreatic enzymes and the onset of a cascade reaction that leads to pancreatic cell auto-digestion, pancreatic parenchymal necrosis, and vasculitis. Vasculitis plays a major role in triggering the inflammatory processes[1,2] which can damage blood vessels located in the peripancreatic space resulting in bleeding into the pancreas and peripancreatic tissues, as well as episodes of bleeding into the gastrointestinal tract.[3] Inflammation promotes blood clotting which, when combined with ileus and hypovolemia, can lead to thrombosis of veins near organs including splanchnic vein thrombosis (SVT).[4]

SVT is common among patients with cancer, liver cirrhosis and systemic inflammation.[5] SVT can influence the course of many pancreatic diseases. Pancreatitis-induced splanchnic vein thrombosis (PISVT) is found in 22.6% of AP cases and 12.4% of chronic pancreatitis (CP).[5] PISVT can involve the portal vein, splenic vein and superior mesenteric vein in combination or separately.[6] To a large extent, the clinical consequences of SVT depend on the number of affected vessels and the potential to produce collateral circulation. The latter applying to all chronic processes.[7] SVT can lead to life threatening complications such as gastrointestinal bleeding, intestinal ischemia, necrosis and those related to portal hypertension such as ascites, splenomegaly, encephalopathy.[8,9] Taking into consideration the clinical significance of these issues, we examined the connection between SVT and the severity of AP.

Materials and Methods

Study Group

We conducted a retrospective analysis of 476 medical histories from patients who were hospitalized with AP at a single surgical center. The study included 111 patients who underwent abdominal and pelvic computed tomography (CT) between the 2nd and 3rd day of hospitalization.[10] The rest of the patients did not have a CT scan in the time period (222 patients), did not agree to the procedure (14 patients), were disqualified because

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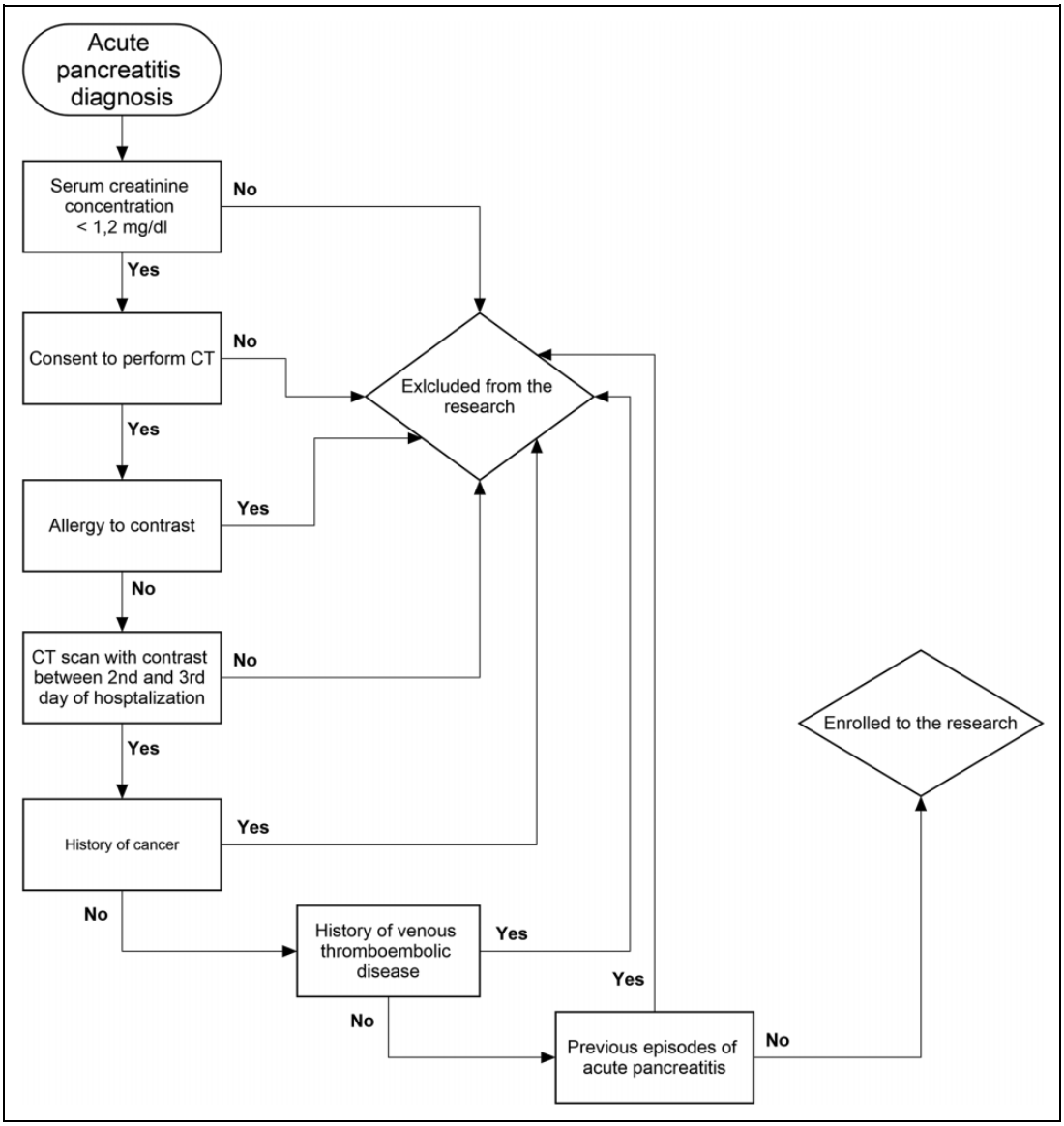

Figure 1. Flow chart for study participants.

of an allergy to contrast (12 patients) or they had an elevated serum creatinine concentration (above 1.2 mg/dl—upper limit in our laboratory) (117 patients). None of the patients had a history of venous thromboembolic disease, liver cirrhosis, cancer, or previous episodes of acute pancreatitis. Figure 1 shows the flow chart for inclusion of study participants.

Computed Tomography Examination Protocol

CT scans were acquired in 3 phases: (1) without application of contrast dye, (2) in the arterial phase—15-25 seconds after contrast application, and (3) in the portal phase—approximately 40 seconds after contrast application. The contrast dye (Iomeron 350 or Omnipaque 350) was administered in a peripheral vein at a rate of 3.5-5 ml/s and at a dose of approximately 1 ml/kg of body weight. Each CT study was interpreted by the same radiology specialist and reevaluated twice by the head chief of the Radiology Department.

Acute Pancreatitis and Splanchnic Vein Thrombosis Classification

AP was diagnosed and divided into severity grades based on the Atlanta 2012 criteria as follows: mild (MAP), moderately severe (MSAP) and severe acute pancreatitis (SAP).[11]

SVT was divided into 3 groups:

1. Portal vein thrombosis (PVT).
2. Splenic vein thrombosis (SpVT).
3. Superior mesenteric vein thrombosis (SMVT).

In the radiological studies conducted, concomitant thrombosis in more than 1 vessel was not reported.

Table 1. Basic Parameters of the Analyzed Group (n = 111).

Splanchnic vein thrombosis	Gender		Age: median (minimum-maximum)	Disease severity			Etiology		
	Male	Female		Mild	Moderately severe	Severe	Alcohol	Gallstones	Other
Present (n = 34; 30.6%)	29 (85.3%)	5 (14.7%)	45.5 (18-85)	0 (0%)	16 (47%)	18 (53%)	22 (64.8%)	6 (17.6%)	6 (17.6%)
Absent (n = 77; 69.4%)	56 (72.7%)	21 (27.3%)	54 (25-89)	11 (14.3%)	49 (63.6%)	17 (22.1%)	42 (54.5%)	26 (33.8%)	9 (11.7%)

Anticoagulation Therapy

All patients developed nonocclusive thrombosis. Immediately after the diagnosis of AP, all patients received antithrombotic prophylaxis in the form of low-molecular-weight heparin (LMWH)—2850 I.U. of nadroparin daily, independent of body weight. In cases where anticoagulants were used for other reasons (atrial fibrillation, implanted pacemaker), they were switched to body weight dependent LMWH (nadroparin) dosing: <70 kg—3800 I.U. twice a day, >70 kg—5700 I.U. twice a day. After diagnosis of SVT, the dose of LMWH in patients who did not receive previous antithrombotic treatment was changed to the aforementioned therapeutic dose. The correlation between the extent of thrombosis (listed above) and disease course, mortality and etiological factors was investigated.

Statistical Analyses

Statistical analyses were conducted using the IBM SPSS Statistics 20 program. Basic descriptive statistics were performed using the Kolmogorov-Smirnov test for normality, followed by Kruskal-Wallis, Mann-Whitney U, χ^2 and Fisher's exact tests where appropriate. A value of $P < 0.05$ was considered statistically significant, however, the results of statistical probability tests in the $0.05 < P < 0.1$ range were interpreted as significant based on trend analyses. The association between nominal variables relied on Cramer's V coefficient. Strength of association was characterized as follows:

1. 0 to 0.1—little if any association;
2. 0.1 to 0.3—low association;
3. 0.3 to 0.5—moderately strong association;
4. >0.5—very strong association.

The main analyses were:

5. Incidence of SVT and its influence on AP
6. Time of hospitalization
7. Local changes occurring in the course of AP
8. Mortality

Results

General Description of the Patient Cohort

One hundred and eleven patients were enrolled in our study. The study included 85 men and 26 women. SVT was found in 34 cases (30.6%). Localization revealed SMVT in 3 patients (8.8%), SpVT in 15 patients (44.1%) and PVT in 16 patients (47.1%). As mentioned above, there were no cases of simultaneous thrombosis in more than 1 vessel. Alcohol was a contributing etiological factor for AP complicated by SVT in 22 cases (64.8%) and the remaining were attributed equally to gallstones and other factors (17.6% each). The features of the described group are shown in Table 1. At the time of CT examination, no patients had symptoms directly related to SVT.

Table 2. Time of Hospitalization Related to Presence of Thrombosis.

Presence of thrombosis	No (n = 77)		Yes (n = 34)				
	M	SD	M	SD	Z	r	*P*
Hospitalization time	10.27	8.03	28.91	34.77	<0.001	0.00	0.00

Abbreviations: M, mean; SD, standard deviation; Z, normal distribution; *P*, significance; r, correlation coefficient.

Relationship Between SVT and Time of Hospitalization

We initially examined the relationship between the diagnosis of thrombosis and patient hospitalization time (HT). The result was statistically significant (Table 2). The average hospitalization time for patients without SVT was 10.27 days, compared with 28.91 days for patients with SVT. The association of the observed effect was strong. Furthermore, we assessed whether the extent of thrombosis has an influence on HT. The hospitalization time of patients with PVT was significantly longer than those without thrombosis ($P = 0.001$). In addition, there was a significant difference between patients with SpVT and those without thrombosis ($P = 0.065$). Other differences between the groups were not statistically significant (Figure 2).

Relationship Between SVT and AP Severity

The relationship between SVT and AP severity is shown in Table 3. There was a strong positive correlation between these 2 variables ($V = 0.34$). We also examined the relationship between the extent of SVT and the severity of AP (Table 4). SMVT was associated with MSAP in all cases. Moreover, PVT was associated with more severe form of the disease ($P = 0.008$).

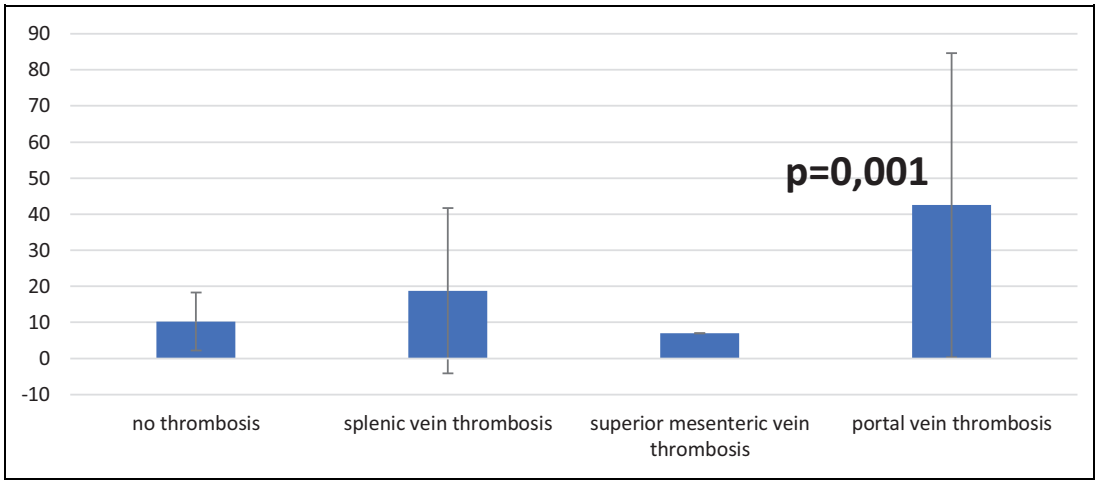

Figure 2. Kruskal-Wallis test to determine whether the extent of the thrombosis has an impact on time of hospitalization.

Table 3. Severity of the Disease and the Presence of Thrombosis.

		Thrombosis		
Disease severity		No	Yes	
MAP	*N*	11	0	
	%	14.30%	0.00%	$\chi^2(2) = 13.09$,
MSAP	*N*	49	16	$P = 0.001$,
	%	63.60%	47.10%	$V = 0.34$
SAP	*N*	17	18	
	%	22.10%	52.90%	

Abbreviations: *P*, significance; V, Cramer's V contingency; $\chi^2(2)$, chi-square distribution.

Table 4. Severity of Disease and Extent of Thrombosis.

		Extent of thrombosis				
Severity		No thrombosis	SpVT	SMVT	PVT	
MAP	*N*	11	0	0	0	
	%	14.30%	0.00%	0.00%	0.00%	
MSAP	*N*	49	7	3	6	$P = 0.008$,
	%	63.60%	46.70%	100.00%	37.50%	$V = 0.28$
SAP	*N*	17	8	0	10	
	%	22.10%	53.30%	0.00%	62.50%	

Abbreviations: *P*, significance; V, Cramer's V contingency.

Relationship Between SVT and Mortality

Eight patients died during the observation phase. All the fatal cases occurred in patients diagnosed with SAP. SVT was reported in 5 patients (62.5%). In 3 cases, we observed SpVT and the causes of death were respiratory failure, kidney failure and multiorgan failure, respectively. The remaining 2 fatal cases were related to respiratory failure. The cause of death of patients without SVT was also respiratory failure. None of the fatal cases were directly related to thromboembolic complications. A slightly higher proportion of death was reported in patients with thrombosis, with results approaching significance ($P = 0.056$). We examined whether mortality is associated with the extent of thrombosis, with the results shown in Table 5.

Table 5. Death and Extent of Thrombosis.

		Extent of thrombosis				
Death		No thrombosis	SpVT	SMVT	PVT	
No	*N*	74	12	3	14	
	%	96.1%	80%	100%	87.5%	$P = 0.075$,
Yes	*N*	3	3	0	2	$V = 0.23$
	%	3.9%	20%	0%	12.5%	

Abbreviations: *P*, significance; V, Cramer's V contingency.

Table 6. Local Changes and the Presence of Thrombosis.

		Thrombosis		
Local changes		No	Yes	
Absent	*N*	24	1	
	%	31.2%	2.9%	$x^2(1) = 10.77$,
Present	*N*	53	33	$P = 0.001$,
	%	68.8%	97.1%	$V = 0.31$

Abbreviations: *P*, significance; V, Cramer's V contingency; $\chi^2(1)$, chi-square distribution.

Relationship Between SVT and Other Local Complications (Excluding Necrosis)

Other local complications were observed in almost all cases diagnosed with thrombosis (33 out of 34 patients developed acute fluid collection) and in 35 out of 77 cases without thrombosis (45%). The association of the observed effect was moderately strong (Table 6). A moderately strong association was also found between the extent of thrombosis and other local complications (Table 7).

Table 7. Local Changes and Extent of Thrombosis.

Local changes		No thrombosis	SpVT	SMVT	PVT	
Absent	*N*	24	0	0	1	
	%	31.20%	0.00%	0.00%	6.30%	$P = 0.007$,
Present	*N*	53	15	3	15	$V = 0.31$
	%	68.80%	100.00%	100.00%	93.80%	

Abbreviations: *P*, significance; V, Cramer's V contingency.

Table 8. Pancreatic Necrosis and the Presence of Thrombosis.

Pancreatic necrosis		Thrombosis: No	Thrombosis: Yes	
Absent	*N*	59	13	$x^2(1) = 15.25$,
	%	76.60%	38.20%	$P < 0.001$,
Present	*N*	18	21	$V = 0.37$
	%	23.40%	61.80%	

Abbreviations: *P*, significance; V, Cramer's V contingency, $\chi^2(1)$, chi-square distribution.

Table 9. Pancreatic Necrosis and Type of Thrombosis.

Pancreatic necrosis		No thrombosis	SpVT	SMVT	PVT	
No	*N*	59	6	2	5	
	%	76.60%	40.00%	66.70%	31.30%	$P = 0.001$,
Yes	*N*	18	9	1	11	$V = 0.39$
	%	23.40%	60.00%	33.30%	68.80%	

Abbreviations: *P*, significance; V, Cramer's V contingency.

Relationship Between SVT and Pancreatic Necrosis

Twenty-three patients developed necrosis that included less than 30% of the organ: 13 in the MSAP and 10 in the SAP group. In each, 5 patients were diagnosed with SVT. There were 20 cases where the extent of necrosis was greater than 30%: 18 in the SAP (61% also complicated by SVT) and 2 in the MSAP group (without SVT). Pancreatic necrosis was significantly more common in patients with thrombosis ($P < 0.001$) and the association was moderately strong ($V = 0.37$). Results are shown in Table 8. We also assessed whether the presence of pancreatic necrosis may be correlated with the extent of thrombosis, with the results shown in Table 9. Patients diagnosed with SpVT and PVT had approximately twice as high incidence of pancreatic necrosis ($P = 0.001$). The association of the observed effect was moderately strong.

SVT and Endoscopic Changes

Thirty-one patients had a gastroscopy during the first week of hospitalization that was performed after CT examination. Twelve patients were diagnosed with SVT. Each of the patients in the SVT group had endoscopic changes in their upper gastrointestinal tract. The most severe lesion was a gastric ulcer. None of the patients were diagnosed with esophageal or gastric varices. Nineteen patients that had an endoscopic examination did not develop SVT, however, only 1 of them had a normal endoscopic image. There was no significant correlation between SVT occurrence and presence of any endoscopic changes ($P > 0.999$). Furthermore, no significant relationship was confirmed between endoscopic image and type of SVT ($P = 0.189$). Type of SVT was also not significantly related to disease severity ($P = 0.705$) or CLO test ($P = 0.102$).

Discussion

Acute pancreatitis is one of the most common gastrointestinal diseases that may require hospitalization and can present in 1 of 3 types: mild, moderately severe or severe.[11] Local changes, including SVT, may occur in the latter 2 forms. Different studies have shown a wide incidence of this complication, from 1-2%, independently of the disease severity[12] up to 24% in SAP cases.[9,13] Color doppler imaging (CDI) is a screening examination to diagnose SVT and CT scanning is indispensable to assess the extent of thrombosis, the existence of anastomosis between the portal and systemic circulation, and to plan venous recanalization therapy.[9,14,15] Our radiology department does not provide the possibility to perform CDI which is an unfortunate weakness of our study. Angiography, which is considered the gold standard for diagnosis of SVT is, in our opinion, too invasive. In our study group, 30.6% of patients (47.1% MSAP and 52.9% SAP) developed SVT. It was found in a routine CT scan performed according to the guidelines between the 2nd and 3rd day of hospitalization.[10] The most common etiological factor in our study group was alcohol, similar to previous studies.[16] According to the recently released practice guidelines for diagnosis of SVT,[9] this complication occurs within 1-2 weeks after onset of MSAP or MAP. In our study all the patients included had a CT scan performed during the second or third day of hospitalization. This means that the development of SVT may have a great impact on the course of the disease.

Every patient diagnosed with SVT should have a gastroscopy because the prevalence of esophageal or gastric varices may exceed 20%.[9] In our study, none of the patients developed this complication, however, 12 patients (38.7%) from the group who had a CT and endoscopic examination developed changes in the endoscopic image.

According to recent published guidelines for the treatment of AP complicated by SVT, there is no need to administer antithrombotic treatment in the case of isolated SpVT.[9,17] On the other hand, taking into consideration the risk of intestinal ischemia, patients with SMVT should be administered antithrombotic therapy for 3 to 6 months. At our facility, a prophylactic LMWH dose (2850 I.U. of nadroparin) is administered directly after the diagnosis of AP. When SVT is revealed, the dose is changed to therapeutic (nadroparin: <70 kg—3800 I.U. twice a day, >70 kg—5700 I.U. twice a day). If a patient has

received previous anticoagulation therapy, they are treated with the therapeutic dose from the diagnosis of AP. Junare et al[17] did not observe any significant difference between patients with and without anticoagulation therapy. According to that study and a study by Harris et al,[18] the standard use of anticoagulation may increase the risk of bleeding. In our study we did not experience any cases of gastrointestinal bleeding nor adverse reactions to LMWH. Unfortunately, due to the retrospective nature of our analysis, we do not know how large the recanalization rate was during hospitalization. Patients who were discharged from the hospital received a therapeutic dose of LMWH for 3 months, according to The American College of Chest Physician guidelines.[19] We did not observe any rehospitalization due to SVT or AP within the first year following hospital discharge.

Currently, there is no standardized classification to help with stratifying risk or implementing a specific therapy for patients with thrombosis.[20] Therefore, for the purposes of this study, extent of thrombosis was divided into affecting the portal, superior mesenteric or splenic vein. We did not experience any case that included thrombosis of more than 1 vessel. Similar categorization was adopted in Zhou et al,[21] where they demonstrated that SpVT is associated with an increased risk of bleeding from esophageal varices, chronic ascites and enteral nutrition intolerance. As previously stated, we did not experience any gastrointestinal bleeding during hospitalization. We did not observe also esophageal or gastric varices. They can occur in 53% and 77.3% of PISVT cases, respectively.[5] The reason that none of the patients developed this complication in our study may be the early timing of the endoscopic examination. Another reason for this observation may be the variation in coronary vein drainage.[5,22] Ascites and enteral nutrition intolerance are inseparably associated with more severe forms of acute pancreatitis. Due to this, it is difficult to distinguish the reason for these complications. Nevertheless, our study indicates that SVT is highly associated with prolonged time of hospitalization and more severe forms of acute pancreatitis, especially for PVT. The mortality rate of patients with SMVT is high,[23] however, a previous study did not report any additional complications associated with SMVT.[16] In our study, SVT is associated with a higher incidence of death with results approaching significance ($P = 0.056$).

We also evaluated the association between the presence of different types of SVT and other local lesions (such as acute peripancreatic fluid collection) and pancreatic necrosis. In both cases, the results were statistically significant. The same observations were made by Gonzelez et al.[16] Furthermore, Zhou et al[24] reported that the presence of necrosis can indirectly cause thrombosis. In our study, we observed that patients with acute pancreatitis complicated by SVT have a worse prognosis and this was also shown in other studies.[16,18,25] In line with our conclusion, Zhou et al[24] highlighted the prolonged time of hospitalization among patients with SVT. Similar results were also presented in a study by Trikudanathan et al.[26]

Conclusions

SVT is a common local complication of AP occurring in up to 30.6% of cases. The most common etiological factor for AP in this patient cohort was alcohol. SVT is associated with more severe forms of the disease ($P = 0.001$), prolonged hospitalization time ($P = 0.001$), pancreatic necrosis ($P < 0.001$) and presence of other local complications ($P = 0.007$). Therefore, measures should be taken to prevent thrombosis or to ensure early recanalization of the portal system.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The study was approved by The Jan Kochanowski Institutional Review Board, number 43/2020 from 02.07.2020.

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Patient Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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