

Portal vein thrombosis: Prevalence, patient characteristics and lifetime risk: A population study based on 23 796 consecutive autopsies

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Abstract

AIM: To assess the lifetime cumulative incidence of portal venous thrombosis (PVT) in the general population.

METHODS: Between 1970 and 1982, 23 796 autopsies, representing 84% of all in-hospital deaths in the Malmö city population, were performed, using a standardised protocol including examination of the portal vein. PVT patients were characterised and the PVT prevalence at autopsy, an expression of life-time cumulative incidence, assessed in high-risk disease categories and expressed in terms of odds ratios and 95% CI.

RESULTS: The population prevalence of PVT was 1.0%. Of the 254 patients with PVT 28% had cirrhosis, 23% primary and 44% secondary hepatobiliary malignancy, 10% major abdominal infectious or inflammatory disease and 3% had a myeloproliferative disorder. Patients with both cirrhosis and hepatic carcinoma had the highest PVT risk, OR 17.1 (95% CI 11.1-26.4). In 14% no cause was found; only a minority of them had developed portal-hypertension-related complications.

CONCLUSION: In this population-based study, PVT was found to be more common than indicated by previous clinical series. The markedly excess risk in cirrhosis and hepatic carcinoma should warrant an increased awareness in these patients for whom prospective studies of directed intervention might be considered.

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Key words: Epidemiology; Venous thrombosis; Portal hypertension; Cirrhosis; Gastrointestinal cancer

INTRODUCTION

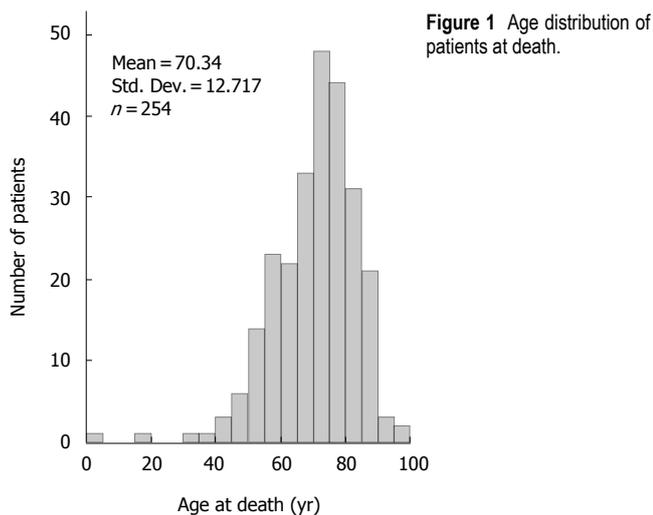
Extrahepatic portal vein thrombosis (PVT) may be caused by a variety of conditions including cirrhosis, cancer and abdominal infectious and inflammatory processes. In the wake of thrombus organisation and vessel involution follows development of tortuous collaterals, so called cavernous transformation^[1]. Symptom development is often insidious and related to the progression of portal hypertension. The concept of PVT as a rare disease is mainly based on clinical series and case reports^[2-7]. Estimates of frequency and of distribution of etiological fractions vary widely between studies^[2, 4,5,6, 8,9,10,11]. To some extent this may be explained by lack of precision in these small series, but a contribution of case selection and ascertainment bias should also be considered.

For several decades, the city of Malmö in southern Sweden has been a centre for epidemiological research, including clinical and autopsy-based studies of cardiovascular diseases^[12,13,14,15]. Between 1970 and 1982, close to 24 000 autopsies, comprising 84% of all in-hospital deaths in the city, were performed. All procedures followed a standardised protocol including examination of the portal vein and its major tributaries. In consequence with the course in PVT, the prevalence at autopsy can be regarded as a proxy for the cumulative incidence during lifetime to develop PVT. The size of the cohort together with the high autopsy rate thus provides a unique opportunity to yield a robust estimate of risk in the general population. Further aims have been to evaluate likely causes to PVT and clinical characteristics related to portal hypertension, and to estimate the absolute risk of PVT in high-risk disease categories as characterised by autopsy findings.

MATERIALS AND METHODS

Study cohort

Malmö is a city with a single referral centre for post-



mortem examinations, the Department of Pathology at Malmö University Hospital. Between January 1, 1970 and December 31, 1982, when the city population declined from 264 000 to 230 000 inhabitants, 35 784 deaths occurred in the Malmö population. Among the 28 196 deaths occurring among in-patients at the three hospitals, which served the Malmö population during this period, a total of 23 796 clinical autopsies were performed, corresponding to an autopsy rate of 84%.

All autopsies were performed using a standardised protocol and carried out or supervised by senior pathologists. All findings were classified and coded according to the Standardised Nomenclature of Pathology (SNOP), as defined by the College of American Pathologists in 1965. The death certificates were issued by the pathologist. Based on the clinical picture and on autopsy findings, an underlying cause of death and up to six contributing causes were determined and classified using the ICD-8 code.

Classification of PVT patients in relation to potential causes

All cases with SNOP code 48-80-3700/3703, denoting *portal vein thrombosis (PVT)*, were identified and validated individually. The following disease categories in the literature regarded as major causes of PVT were identified^[5]:

- cirrhosis*, where classification was based on SNOP codes 4850 - 4857 and/or cirrhosis as underlying or contributing death cause (ICD 8 code 571.00 - 571.99). PVT patients with cirrhosis were further classified according to presence or absence of *primary hepatic cancer* (hepatocellular carcinoma or intrahepatic cholangiocarcinoma);

- primary hepatobiliary cancer*, comprising primary hepatic cancer (with or without cirrhosis), extrahepatic cholangiocarcinoma and gall bladder carcinoma;

- secondary malignancy of the hepatobiliary region* (metastatic malignancy to the liver, biliary tract, gall bladder, duodenum or pancreas), further classified according to primary tumour location as expressed by SNOP code;

- myeloproliferative disorders*: non-specific myeloproliferative disorder (SNOP code 7690); agnogenic myeloid

metaplasia (7691); myelofibrosis (7692); histiocytic medullary reticulosis (7698); megablatic erythropoiesis (7706); neutrophilic (7711) and eosinophilic (7713) leukocytosis; leukaemoid reaction (7714); erythrocytosis (7715); reticulocytosis (7716); lymphocytosis (7718); thrombocytosis (7719); erythrophagocytosis (7763); erythroid (7771), granulocytic (7772), reticular cell (7777) and megakaryocytic (7778) hyperplasia; polycythaemia vera rubra (7779); and chronic myeloid leukaemia (9867);

- major abdominal infections and inflammations*, including liver abscess, abdominal abscess, purulent peritonitis, acute necrotising pancreatitis and ulcerative colitis.

In consequence with the possibility PVT being the result of more than one factor, a patient might be included in more than one of these categories. PVT patients in whom none of the above causes could be established were identified and analysed separately.

Classification of risk groups for PVT

PVT prevalence and risk, expressed as odds ratio, were assessed in relation to the following disease categories: *cirrhosis* (with and without primary hepatic cancer), *primary hepatobiliary cancer* (with and without cirrhosis), *secondary hepatic malignancy* (secondary malignancy of the hepatobiliary region not being readily definable in terms of SNOP codes) and *myeloproliferative disorders*. Presence of secondary hepatic malignancy was based on SNOP code 56-8006. Among these, patients with metastatic disease from pancreatic, gastric and colorectal carcinoma were further identified and similarly analysed. For the other disease categories, patients were classified using the definitions stated in the previous section.

Definition of clinical complications in PVT patients

In patients with PVT, the prevalence at autopsy of the following complications typically related to portal hypertension was ascertained and analysed in relation to disease categories: ascites, oesophageal varices and gastrointestinal bleeding.

Statistical analysis

Distributions of age at death were expressed in terms of means and variance and groups defined by presence or absence of potential causal factor compared with one-way analysis of variance (ANOVA). Proportions were compared using two-sided Fisher's exact test for univariate analyses. The PVT risks in relation to respective disease category were also expressed in terms of odds ratios with computation of 95% confidence intervals.

RESULTS

PVT prevalence and patient demographics

PVT was found at autopsy in 254 (1.1 %) of the 23 796 patients; in 125 (1.0 %) out of 12 157 men and 129 (1.1 %) of the 11 639 women ($P=0.57$). The age distribution is depicted in Figure 1. With the exception of one patient, who was less than 1 year old, the age ranged between 17 and 96 years. Mean (95 % CI) age was 68 (66-70) years in

Table 1 Prevalence in patients with portal vein thrombosis (PVT) of conditions known to be major causes: Age- and gender distribution within categories

Patient category	n (%) of PVT patients	n (%) within risk category	Age (yr) Median	Mean (95% CI)	Female gender (%)
Cirrhosis ¹	72 (28)		70	68.5 (65.8 - 71.3)	28 (39)
with primary hepatic cancer		26 (36)			
without primary hepatic cancer		46 (64)			
Primary hepatobiliary cancer ¹	59 (23)		72	72.1 (69.4 - 74.8)	26 (44)
hepatic carcinoma ²		38 (64)			
extrahepatic biliary / gall bladder carcinoma		21 (36)			
Secondary malignancy of the hepatobiliary region ¹	111 (44)		70	69.0 (66.7 - 71.2)	59 (52)
from pancreatic carcinoma		47 (42)			
gastric carcinoma		20 (18)			
colorectal carcinoma		11 (10)			
lung cancer		7 (6)			
malignant lymphoma		5 (4)			
mammary adenocarcinoma		4 (4)			
other primary cancer ³		17 (15) ¹			
Myeloproliferative disorders ¹	7 (3)		72	65.4 (44.2 - 86.6)	5 (71)
Major abdominal infection / inflammation ^{1,4}	25 (10)		73	71.9 (66.5 - 77.3)	15 (60)
No cause identified	36 (14)		73	70.8 (65.9 - 75.7)	21 (57)
All patients with PVT	254 (100)		72	69.9 (68.3 - 71.4)	129 (51)

¹ categories not mutually exclusive. ² hepatocellular carcinoma (26), intrahepatic cholangiocarcinoma (6), mixed (4), anaplastic (1) and unspecified (1) carcinoma. ³ malignant melanoma (3), female genital tract cancer (3), uroepithelial cancer (2), urinary bladder carcinoma (2), prostatic carcinoma (2), oesophageal cancer (1), duodenal cancer (1), renal cancer (1), adrenal cancer (1), sarcoma (1). ⁴ liver abscess (13), peritonitis (8), acute necrotising pancreatitis (4), abdominal abscess (2), ulcerative colitis (1) (more than one alternative possible).

Table 2 Prevalence and relative risk (odds ratio) of PVT in relation to disease condition with major risk of PVT

Patient category	n (%)	PVT (%)	O.R. (95% C.I.) ¹	P value	O.R. (95% C.I.)	P value
Cirrhosis	1193 (5.0)	72 (6.0)	7.9 (6.0 - 10.5)	<0.001		
with primary hepatic cancer	182	26 (14.3)	17.1 (11.1 - 26.4)	<0.001	3.5 (2.1 - 5.8)	<0.001
without primary hepatic cancer	1011	46 (4.5)	5.2 (3.7 - 7.2)	<0.001	1 ²	
Primary hepatobiliary cancer	698 (2.9)	59 (8.5)	10.8 (8.0 - 14.7)	<0.001		
hepatic carcinoma	392	38 (9.7)	11.5 (8.0 - 16.5)	<0.001		
with cirrhosis	182	26 (14.3)	17.1 (11.1 - 26.4)	<0.001	2.8 (1.3 - 5.6)	0.004
without cirrhosis	210	12 (5.7)	5.8 (3.2 - 10.6)	<0.001	1 ²	
extrahepatic biliary / gall bladder carcinoma	313	21 (6.7)	7.2 (4.5 - 11.4)	<0.001		
Secondary hepatic malignancy						
from all tumours	3446 (14.5)	113 (3.3)	4.9 (3.8 - 6.2)	<0.001		
from pancreatic carcinoma	312	36 (11.5)	13.9 (9.6 - 20.2)	<0.001	5.2 (3.4 - 7.8) ³	<0.001 ³
gastric carcinoma	316	18 (5.7)	5.9 (3.6 - 9.7)	<0.001	1.9 (1.2 - 3.2) ³	0.019 ³
colorectal carcinoma	637	13 (2.0)	2.0 (1.1 - 3.5)	0.028	0.5 (0.3 - 1.0) ³	0.063 ³
Myeloproliferative disorders	231 (1.0)	7 (3.0)	3.0 (1.4 - 6.3)	0.012		
All patients	23796 (100)	254 (1.0)				

¹ vs. all patients with absence of respective condition. ² reference category. ³ vs. patients with liver metastatic disease from other cancer forms.

men and 71 (69 - 74) years in women. Median age at death was 72 years; 70 years in men and 74 years in women.

Distribution of potential causative factors in PVT patients

Seventy-two (28 %) of the PVT patients had cirrhosis, and one third of those had also primary hepatic cancer (Table 1). In all 59 PVT patients (23 %) had primary hepatobiliary cancer and 111 (44 %) had secondary malignancy of the hepatobiliary region. Major abdominal infectious or inflammatory disease was present in 25 (10 %), 7 (3 %) had myeloproliferative disorders, whereas in 36 (14 %) of the patients with PVT, none of the above causal factors could

be identified. The age distribution in these categories was similar (Table 1). Sixty-one per cent of the PVT patients with cirrhosis were men ($P=0.018$), otherwise there were no gender differences.

PVT prevalence and risk in relation to presence of disease

Cirrhosis was present in 5 % (1193 / 23796) of the cohort and related to a 7.9 times increased odds for PVT (95 % CI: 6.0-10.5) (Table 2). Patients who also had primary hepatic cancer had a 3.5 times higher odds for PVT (95 % CI 2.1-5.8) than cancer-free cirrhosis patients, with a PVT prevalence of more than 14 %. Secondary hepatic malignancy was associated with 4.9 times increased odds (95 %

Table 3 Portal hypertension-related complications in categories of PVT based on likely etiology

Patient category	n	n	Complication		Oesophageal varices		Gastrointestinal bleeding	
			Ascites n (%)	P value ²	n (%)	P value ²	n (%)	P value ²
Cirrhosis ¹	72		45 (62)	<0.001	42 (58)	<0.001	34 (47)	<0.001
with primary hepatic cancer		26	21 (81)		13 (50)		7 (27)	
without primary hepatic cancer		46	24 (52)		29 (63)		27 (59)	
Primary hepatobiliary cancer ¹	59		34 (58)	0.016	15 (25)	0.18	15 (25)	0.72
without cirrhosis		33	13 (39)		2 (6)		8 (24)	
Secondary hepatobiliary malignancy ¹	111		46 (41)	0.61	4 (4)	<0.001	15 (14)	0.002
Myeloproliferative disorders ¹	7		4 (57)	0.47	2 (29)	0.62	2 (29)	0.67
Major abdominal infection / inflammation ¹	25		12 (48)	0.67	1 (4)	0.06	5 (20)	0.81
No cause identified	36		6 (17)	<0.001	2 (6)	0.036	3 (8)	0.02
All patients with PVT	254		110 (43)		48 (19)		59 (25)	

¹ Categories not mutually exclusive; ² in comparison with all PVT patients not belonging to category.

CI 3.8 - 6.2). Within this group, pancreatic cancer patients had a 6.7 times higher odds for PVT (95 % CI: 3.4 - 13.1) than patients with liver metastatic disease from colorectal cancer.

Complications related to portal hypertension

Among the patients with PVT, the highest rates of complications related to portal hypertension were found in the subgroup with concomitant cirrhosis: 62 % had developed ascites, 58 % had oesophageal varices and 47% terminal gastrointestinal bleeding (Table 3). Corresponding figures in all PVT patients were 43 %, 19 % and 25 % ($P < 0.001$ for all three comparisons), whereas of the 36 patients where no cause of PVT could be identified at autopsy only a minority had these signs of portal hypertension: ascites was only present in 6 (17 %; $P < 0.001$), oesophageal varices in 2 (6 %; $P = 0.036$) and only 3 (8 %; $P = 0.020$) had developed gastrointestinal bleeding.

DISCUSSION

Our finding of an overall risk in the general population of 1 % to develop PVT during lifetime does not corroborate the concept of PVT being a rare disease. The figure might even be an underestimation, since it cannot be ruled out that in some cases of partial thrombosis earlier in life a spontaneous resolution may have occurred. It should therefore be relevant to view these patients with renewed interest.

Among the major causes of PVT in adults, cirrhosis is generally named the most common, followed by neoplasia^[5-6]. In this study the order of magnitude was reversed, with cancer in two thirds of the patients. By nature of being an autopsy study it is a selection of the sickest patients, and in some of these the thrombosis may be a late event in advanced cancer disease. Discrepancies in proportion of cirrhosis patients compared with previously published case series might also reflect patient selection and ascertainment bias resulting from an increased diagnostic activity in high-risk categories, but one should also consider the impact of disease duration. An intriguing

finding was the heterogeneity of risk within the group of metastatic malignancy, with a significantly higher risk with pancreatic cancer in comparison with other major gastrointestinal adenocarcinomas.

When assessing the risk for a patient with a certain condition to develop an infrequent complication like PVT, knowledge from case series on the distribution of causes to that complication may be helpful and is sometimes the only available information. It may be misleading, though. In this study, secondary malignancies accounted for a twice as large fraction of PVT cases as primary hepatobiliary cancer, but the actual risk of PVT in patients with secondary malignancies was less than half of that associated with primary hepatic cancer. In patients with both cirrhosis and hepatic cancer the risks appeared to be additive resulting in a prevalence of 14%. Whether increased diagnostic and therapeutic activities would be effective to reduce this rate is to be considered for further studies. A recent study, though, indicates that even hepatocellular cancer patients, who have developed portal vein tumour thrombosis, may benefit from an active treatment if timely diagnosed with respect to hepatic function^[16].

In one sixth of the PVT patients no explanation could be found despite the thorough examination. This group differed from the other patients by a low frequency of complications typical to portal hypertension. A cross-sectional study like the present has obvious limitations for assessment of previous diseases, and this group may harbour some cases of juvenile PVT, though recent longitudinal studies indicate that PVT is an infrequent complication to umbilical vein sepsis, and in the western world the risk of this complication to umbilical vein catheterisation has declined considerably over time^[5,17-18]. Similarly, it cannot be ruled out that the thrombosis in the odd case might have been caused by surgical trauma not evident from the recent patient history. With increasing possibilities to detect various thrombophilic disorders the proportion of non-explainable, so called idiopathic PVT has gradually become smaller^[5,10,19-22]. The present study does not allow an investigation of markers of the haemostatic system, but it is not unreasonable that the

PVT in some of these cases may be an expression of a hypercoagulability state.

Autopsy rates have declined considerably also in Malmö, following changes in legislation, and it is unlikely that a similar study will ever be performed again. With regards to the setting in time, some limitations should be discussed. Apart from aspects of the design previously viewed, the potential effects on the epidemiology of an increasing use of antithrombotic therapies should be considered. The study does not allow an assessment of actual medications, but even today the majority of these conditions would not warrant primary or secondary anticoagulant prophylaxis according to guidelines^[23].

From this first population-based study we conclude that PVT is more common than previously indicated by clinical series. The greatly increased risk in patients with cirrhosis and hepatic carcinoma should warrant an increased awareness in these patients. While anticoagulation therapy might be considered for certain patient categories, this remains to be evaluated in prospective studies.

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