



Incidence and mortality rates of splanchnic vein thrombosis

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Introduction

Thrombosis of splanchnic veins encompasses hepatic (Budd-Chiari syndrome, BCS), portal, mesenteric, and splenic veins. In the general population, splanchnic vein thrombosis (SVT) is rare. BCS and portal vein thrombosis (PVT) are listed in Orphanet (Orpha 131 and Orpha 854, respectively) (1). However, there is no internationally accepted definition of rare disease, and the prevalence rate employed in national legislations varies from less than 200,000 (approximately 1 in 1,500 individuals) in the United States to 1 in 10,000 individuals in Australia and Taiwan (2,3). In Europe, a disease is defined as rare when it affects less than 1 in 2,000 individuals (4).

Studies on the prevalence, incidence, and mortality rate of diseases are based on three main activities: identification of the study cohort, case ascertainment, and quantification of the number of events. The type of data source (e.g., in-patients or out-patients), age or other demographic limits, geographic location, and time interval investigated are the main elements to consider in cohort identification. Studies that identify cases solely from the review of in-patient medical records may underestimate the true incidence since patients that are not hospitalized and patients who suddenly died can be missed.

Moreover, the use of administrative data as a source to estimate disease prevalence and incidence is subject to errors in case ascertainment (5,6). Coding errors, diagnostic uncertainty or misclassification, diagnoses of exclusion, limits in the number of diagnoses included in the patient chart, multiple records of initial or recurrent events in the same patient and discovery of missed events during autopsy can contribute to errors in administrative data and result in low accuracy, leading to the underestimation or

overestimation of incidence rate.

Case fatality rate (CFR), also called case fatality ratio, represents the proportion of patients who die from a specified disease among all individuals diagnosed with the disease over a certain period of time. CFR is used as a measure of disease severity and is calculated by dividing the number of deaths from a specified disease by the number of individuals diagnosed with the disease over a defined period of time; the resulting ratio is then multiplied by 100 to yield a percentage. For diseases that have a spectrum of clinical presentation, the cases that are preferentially enrolled into investigational databases will typically involve patients who have the most severe symptoms, who seek medical care, who are admitted to hospital, or who die (7). Therefore, the CFR is typically higher among these cases with respect to those with mild, subclinical, and asymptomatic presentations, leading to an important selection bias and overestimation of the actual rate in the entire patient population. In this setting, addressing the CFR based on a hospitalized population can typically be biased due to overestimation (cases with less severe presentation are missed) or underestimation (cases with sudden death are missed); additionally, in certain cases, recording the ultimate cause of death can lead to misinterpretation when using administrative data (e.g., intracranial haemorrhage due to anticoagulant treatment prescribed for cancer-related venous thromboembolism).

Incidence rate of BCS and PVT

The incidence rate of BCS has been reported to be less than

Table 1 Incidence rate of Budd-Chiari syndrome (BCS) in different countries

Reference	Period	Country	Disease	Incidence rate (per million/year)	Source
(8)	1989	Japan	BCS	0.13	National hospital survey questionnaire (>200 beds)
(9)	1989	France	BCS	0.36	National hospital survey questionnaire (unpublished data from the Observatoire National du Syndrome de Budd-Chiari)
(10)	1981–1985	Denmark	BCS	0.50	National computerized hospital registry based on unique person number (in-patients only)
(11)	1990–2001	Sweden	BCS	0.80	National computerized hospital registry based on unique person number, including in-patient and out-patient registries
(12)	1990–2013	China	BCS	0.28–0.88	Analysis of 20,191 BCS cases published in China. Range of rates according to the inclusion or not of geographical areas with highest prevalence
(13)	1994–2013	Denmark	BCS	0.30	National computerized hospital registry based on unique person number, including in-patient and out-patient registries
(14)	2002–2012	Italy	BCS	2.0 (males), 2.2 (females)	Regional computerized hospital registry based on the ICD-9-CM code (in-patients only)

Table 2 Incidence rate of portal vein thrombosis (PVT) in different countries

Reference	Period	Country	Disease	Incidence rate (per 100,000/year)	Source
(10)	1981–1985	Denmark	PVT	0.27	National computerized hospital registry based on unique person number (in-patients only).
(13)	1994–2013	Denmark	PVT	21	National computerized hospital registry based on unique person number, including in-patient and out-patient registries.
(15)	1995–2003	Sweden	PVT	0.70	National computerized hospital registry based on unique person number, including in-patient and out-patient registries.
(14)	2002–2012	Italy	PVT	3.78 (males), 1.73 (females)	Regional computerized hospital registry based on the ICD-9-CM code (in-patients only).

1 case per million individuals per year (8-13) (*Table 1*), and that of PVT to be between 0.27 and 0.70 cases per 100,000 individuals per year (10,15) (*Table 2*). An exceedingly high incidence of PVT at 21 cases per 100,000 individuals per year has been reported in a recent nationwide population-based study conducted in Denmark from 1994 to 2013 (13) (*Table 2*). However, in a population-based autopsy study carried out in Malmö, Sweden in 1970–1982, the prevalence rate for PVT was as high as 1.0% (n=23,796 representing 84% of all in-hospital deaths), suggesting a higher lifetime risk than previously thought (16).

Ageno and colleagues (14) performed a large epidemiologic study based on hospital admission due to BCS or PVT during the period from 2000 to 2012 in two regions in Italy

(total population 13 million) that included 287 cases of BCS and 3,535 cases of PVT. The method for ascertainment of cases was accurate and included the development of an ad hoc identification number to allow for the recognition of repeated hospital admissions for each patient and the distinction of initial incidences from recurrences. The incidence rate of BCS was higher than that in previous studies, and the incidence rate of PVT was intermediate among a wide range of estimates (*Tables 1,2*). This may be due to several reasons.

First, in the last two decades, non-invasive imaging methods, such as Doppler ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have been substantially improved and broadly employed, so it is now

much easier to obtain information on abdominal vessels and their flow characteristics. For example, in one study, the proportion of PVT diagnosed in an early phase was 7% in patients evaluated before 1990 and 56% after 1994 (17). A nationwide population-based study conducted in Denmark from 1994 to 2013 identified 1,915 patients with SVT; among them, 14.1% were diagnosed from 1994 to 1999, 23.2% from 2000 to 2005, and 62.7% from 2006 to 2013 (13). Therefore, comparison with studies that report data from populations investigated before 1990 or 2000 is not adequate (*Tables 1,2*).

Second, the study by Ageno and colleagues (14) refers only to hospitalized patients. Two population-based studies including in-patient and out-patient datasets have been carried out in Sweden from 1990 to 2001 for BCS (11) and from 1995 to 2003 for PVT (15), based on the national registration number, which is unique for each citizen (18); another nationwide population-based study conducted in Denmark from 1994 to 2013 identified all in-patients and out-patients with first-time SVT (13). The incidence rate estimated in those studies is likely to be the most accurate for BCS and PVT in the general population so far, although the time period in which the studies have been conducted seems to be an important confounding factor (*Tables 1,2*). However, in spite of the different source populations (in-patients only *vs.* in-patients and out-patients), in the study by Ageno and colleagues, the incidence rate of BCS was higher than that previously reported (11,13); on the other hand, the incidence rate of PVT was much lower than that previously reported (13). There are other differences between the Italian study and the nationwide Swedish and Danish studies that should be taken into consideration. First, the Italian cohort was assembled a decade later than the Swedish cohort, and it may have taken advantage of improvements in diagnostic imaging tools; however, in the Italian study, a trend in the incidence of events from 2002 to 2012 was not evident, suggesting that progress in imaging techniques was less rapid during those years than that in the past. Second, the incidence rate of events was estimated from background populations with very different sizes, 13 million in the Italian study (14), 1.3 million (BCS cases) or 4.4 million (PVT cases) in the Swedish studies (11,15) and 7.3 million in the Danish study (13). Third and most important, in the Italian study, the patients were included on the basis of either primary and up to five secondary discharge ICD-9-CM diagnosis codes for BCS or PVT (14), whereas in the Swedish studies, the patients were included on the basis of the primary discharge ICD-9 and ICD-10

diagnosis codes only (11,15); in the Danish study (reporting a much higher incidence of PVT), the patients with SVT were included on the basis of primary and up to 19 secondary discharge ICD-8 and ICD-10 diagnosis codes for BCS or PVT (13).

In a recent prospective survey on 597 patients with SVT conducted from 2008 to 2012, one-third of the patients had an incidental diagnosis (19,20); a previous diagnosis of incidental SVT is likely to be coded as secondary diagnosis in the case of hospitalization for other medical reasons. In this survey, diagnosis of liver cirrhosis or solid cancer was present in 46% and 35%, respectively, of the incidental cases of SVT (20). In the study by Ageno and colleagues (14), the proportion of patients with liver cirrhosis and cancer was comparable (33% and 39%, respectively); the method of data collection did not allow the distinction between diagnoses due to clinical suspicion or incidental detection; however, patients with these conditions undergo frequent imaging procedures for diagnostic work-up or follow-up reasons, and some of these procedures could have been carried out while they were hospitalized. It is reasonable to speculate that clinically suspected SVT leading to hospitalization for acute symptoms might result in primary discharge diagnosis, whereas incidental thromboses might result in secondary discharge diagnosis, and this could have contributed to the higher incidence rate than that reported in studies that only recorded primary discharge diagnoses (11,15); notably, a large majority of incidentally diagnosed SVT are PVT; thus, studies that include secondary diagnosis codes are more likely to identify such cases, with a change in the measured rate depending on the number of secondary diagnosis codes considered, which were five in the Italian study (14) and up to 19 in the Danish study (13).

Fatality rate of BCS and PVT and predictors of mortality

In the cohort investigated by Ageno and colleagues (14), the proportion of fatal cases during hospitalization was 4.9% in patients with BCS and 7.3% in patients with PVT during a study interval of 10 years [2002–2012]. The highest rate of fatality was reported for patients with solid cancer (28%), haematologic neoplasia (13%) and autoimmune disease (10%); the fatality rate in patients with cirrhosis was 7%.

In a large retrospective analysis of 832 patients with SVT admitted to a single center from 1980 to 2000, the survival rate at 10 years was 60% (21). In that study, patients with isolated BCS (n=45) had the highest 10-year survival rate

(82%), whereas patients with isolated PVT ($n=329$) had the lowest (63%) (21). In a population-based studies carried out in Sweden, the survival rate among 43 patients with BCS identified from 1990 to 2001 was 56% (11). and among the 173 patients with PVT identified from 1995 to 2004, it was 57% (15). In the aforementioned nationwide Danish study [1994–2013] after a 5-year follow-up, 458 patients with SVT (24%) were still alive (43% of 204 with BCS, 24% of 1,500 with PVT, and 7% of 211 with mesenteric vein thrombosis). The most frequent cause of death was circulatory system disease (24.3%), respiratory system disease (14.6%), and cancer (12.4%) (13). Therefore, in the Italian study, the mortality rate among hospitalized patients with BCS and PVT was far lower than that reported in the general population (11,13,15) or in the patient cohort referred to a tertiary center (21). This discrepancy remains difficult to explain; however, different study designs do not allow for a meaningful comparison between the different estimates.

In the study by Ageno and colleagues (14), the only independent risk factors for in-hospital mortality using the first multivariate model including age, gender, site of thrombosis and all co-morbidities were age, male gender, haematological neoplasia, and non-abdominal solid cancer for BCS and age and the presence of non-abdominal solid cancer for PVT. In the second multivariate model, which included age, gender, site of thrombosis and the Charlson comorbidity index (CCI) modified for ICD-9-CM database, age was confirmed to be an independent risk factor for mortality in both BCS and PVT patients, and male gender was confirmed to be a risk factor in BCS patients only; a CCI of 4 or more was a significant risk factor for PVT patients (odds ratio, 3.48; 95% CI, 2.50–4.80), but it reached only a borderline level of statistical significance in BCS patients (odds ratio, 3.06; 95% CI, 0.91–10.2) (14). Older age and presence of active cancer and myeloproliferative neoplasm have been previously reported to be independent predictors of mortality in a referral cohort of patients with SVT (21).

The CCI was developed to predict 1-year patient mortality using comorbidity data obtained from hospital chart review; the final Charlson index score is the sum of 19 predefined comorbidities that are assigned different weights based on the magnitude of the adjusted relative risk associated with each comorbidity in a Cox proportional hazards regression model (22); administrative database adaptations of the CCI are now commonly used. In comparison to chart review, the use of the CCI based

on the ICD-9-CM discharge code showed a reduction in precision with a high variability of positive predictive values for the Charlson conditions, ranging from 44% to 96% (23,24); the database adaptation of the ICD-10 code demonstrated an improved positive predictive value for the Charlson conditions from 82% to 100% (25). Therefore, as acknowledged by Ageno and colleagues (14), the use of the ICD-9-CM is a strong limitation of their study.

The design of the study did not allow the medical or interventional treatments to impact the mortality rate. However, treatment modalities heavily influence the outcome of SVT. The introduction of liver transplantation, percutaneous angioplasty and routine anticoagulation and transjugular intrahepatic portosystemic shunt to the clinical practice is associated with a progressive and significant improvement of the survival rate among BCS patients (26). In PVT, the treatment modalities are heterogeneous and mostly depend on a contemporary diagnosis of cirrhosis (27); additionally, patients with SVT and liver cirrhosis have a lower mortality rate than patients with SVT and cancer, but it is definitely higher than that of patients with non-cirrhotic and non-malignant SVT (13,19). A systematic review of 79 studies on BCS patients addressed the effect of treatment modalities on the survival rate of patients. According to the treatment modalities, the median 1-, 5- and 10-year survival rate was 93%, 83% and 73% after interventional radiological treatment; 81%, 75% and 72.5% after surgery other than liver transplantation; 82.5%, 70.2% and 66.5% after liver transplantation and 68.1%, 44.4% and unavailable after medical therapy alone, respectively (28).

Conclusions

The estimation of incidence rate and mortality rate of BCS and PVT in the general population remains challenging because of the heterogeneity in the patient cohorts investigated, in the methods of case ascertainment, and in the background populations. Another confounding factor is the time period of diagnosis; in fact, there is continuous improvement in diagnostic imaging tools frequently allowing earlier and/or incidental diagnoses. Moreover, treatment modalities strongly influence outcomes, especially in BCS patients. However, the study by Ageno and colleagues (14) has been carried out on the largest population investigated so far, assembling an impressive number of 287 BCS cases and 3,535 PVT cases. Therefore, their results concerning the hospitalized population with BCS and PVT are based on a sample size that should ensure

reliable information; unfortunately, nationwide registries that can uniquely identify a citizen and procure relevant data on in-patients or out-patients are not active in most countries with the largest populations.

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