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Original Article

Splanchnic vein thrombosis-related mortality in the Veneto region (Italy), 2008–2019: Retrospective analysis of epidemiological data

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ABSTRACT

Background: Splanchnic vein thrombosis (SVT) is an uncommon manifestation of venous thromboembolism. Epidemiological data on SVT-related mortality rate is not available to date.
Methods: We investigated time trends in SVT-related mortality rate, 2008–2019, in Veneto, an Italian high-income region of approximatively 5,000,000 inhabitants. SVT-related deaths were identified by the following ICD-10 codes: I81 (portal vein thrombosis), K75.1 (phlebitis of portal vein), K76.3 (liver infarction), K76.5 (hepatic veno-occlusive disease) or I82.0 (Budd-Chiari syndrome).
Results: During the study period, a total of 557,932 deaths were recorded. SVT was reported in 823 cases; 776 (94%) consisted of portal vein thrombosis. The age-standardized SVT-related mortality rate varied from 1.47 (year 2008) to 1.52 (year 2019) per 100,000 person-years. An increase in the cause-specific annual mortality rate was observed in women (0.56 in 2008 to 1.04 per 100,000 person-years in 2019; average annual percent change +5.7%, 95%CI +3.1; +8.3%). In men, the cause-specific mortality rate moved from 2.53 in 2008 to 2.03 per 100,000 person-years in 2019 (average annual percent change −1.2%, 95%CI -4.0; +1.6%). After conditioning for age and sex, the odds of having a concomitant liver disease were higher for SVT-related deaths (OR 31.6; 95% CI 17.1–37.0) compared with non-SVT-related deaths. This also applies to gastrointestinal cancers (OR 1.28; 95% CI 1.07–1.55), although to a lesser extent.
Conclusions: We report first epidemiological estimates of SVT-related mortality in a Western country. These values will serve as a reference to weight novel potential factors associated with SVT-related death and interpret them from an epidemiological perspective.

1. Introduction

Splanchnic vein thrombosis (SVT) is an uncommon manifestation of venous thromboembolism (VTE) involving portal, splenic, and mesenteric veins, as well as the suprahepatic veins (Budd-Chiari syndrome, BCS). The annual incidence rate of SVT range between 0.7 and 21 per 100,000 general population for SVT [1–4] and between 0.8 and 2.2 per million general population for BCS [4,5]. Cirrhosis, abdominal cancer, and myeloproliferative neoplasms (MPN) are associated with incident SVT: the prevalence of SVT in these patient subgroups has been estimated to be 15%, 7%, and 4%, respectively [6–11]. The diagnosis of SVT is driven by a rather unspecific constellation of symptoms, including

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abdominal pain, ascites, and acute abdomen [1,12–14]. One third of SVT patients are diagnosed incidentally during imaging exams done for other reasons and explaining the heterogeneity in reported incidences [15,16]. Nonetheless, incidental SVT events seem to have a prognosis similar to symptomatic events [15].

The burden of SVT in terms of fatality is considerable. Søgaard et al. reported a 30-day case fatality rate of 20%. The 5-year case fatality was up to 25% [3]. Ageno et al. observed an overall case fatality of 7.3% for portal vein thrombosis and 4.9% for BCS in an 11-year time period [4]. A recent meta-analysis by Zhang et al. reported a case fatality rate of 16% in patients who developed SVT after abdominal surgery [17]. Ogren et al. reported a prevalence of SVT of 1% in 24,000 autopsies [18], thus raising the issue of possible SVT underdiagnosis. Currently, there is no available data concerning the burden of this disease on the general population, notably its annual mortality rate.

The availability of mortality and time-trend data is crucial for healthcare policy and study of risk factors allowing the identification of groups toward efforts should be oriented. Moreover, it is useful to study trends and have historical references to put changes in the exposure to novel potential or suspected thrombosis risk factors, for instance SARS-CoV2 vaccination [19,20], into an epidemiological perspective.

We conducted this study to investigate contemporary time trends in SVT-related mortality and used data from Veneto, a high-income region of Italy characterized by a homogeneous healthcare system, geography, and structure of the population as a proxy for other similar regions with an advanced healthcare structure.

2. Patients and methods

Veneto is a north-eastern Italy region of approximatively 5,000,000 inhabitants in 2019, with a public healthcare system organized into nine Local Health Units, two university hospitals, and a regional oncologic institute. For each Local Health Unit, a copy of death certificates of residents is routinely transmitted to the Regional Epidemiology Department for coding of the causes of death according to the International Classification of Diseases 10th Edition (ICD-10). Standard mortality statistics are based on internationally adopted rules, which identify the underlying cause of death (UCOD) among all conditions reported in the certificate. The UCOD usually corresponds to the underlying cause stated by the certifying physician, but could also correspond to another disease reported in the certificate, or a derived condition, if deemed more appropriate. For the period 2008–2017, such rules have been applied by means of the Automated Classification of Medical Entities (ACME), a program developed by the US National Center for Health Statistics to standardize assignment of the UCOD [21]. Since 2018, selection of the UCOD has been performed with the IRIS software, currently adopted in most European countries [22]. As well as the UCOD, the regional mortality database includes all diseases mentioned in the certificate (multiple causes of death, MCOD). No information on the prevalent use of autopsy are available in this database.

All death certificates from January 1, 2008 to December 31, 2019 were deemed to be SVT-related if codes I81 (portal vein thrombosis), K75.1 (phlebitis of portal vein), K76.3 (infarction of liver), K76.5 (hepatic veno-occlusive disease) or I82.0 (Budd-Chiari syndrome) had been reported in any position in the certificate (MCOD). The choice of the ICD-10 codes was made according to the previous epidemiological studies on SVT. No ICD-10 codes are currently available for mesenteric venous thrombosis and splenic vein thrombosis, which are currently encompassed by the general K55.0 (acute vascular disorders of the intestine), K55.1 (chronic vascular disorders of the intestine) and D73.5 (infarction of spleen) codes. Additionally, the following information was collected: sex, age, site, and year of death.

Age and sex specific mortality rates (number of patients with SVT in any position of the death certificate per 100,000 general population per year), age-standardized mortality rates (direct standardization, 2013 European standard population), and the proportionate mortality (share of SVT-related deaths out of all deaths), were calculated for the MCOD. The 95% Confidence Intervals (CI) for yearly age-adjusted mortality rates were calculated according to the method by Fay et al. [23]. The average annual percent change (AAPC) in age-standardized mortality rates through the study period with 95% CI was estimated using the Joinpoint software. The distribution of the most common UCOD in certificates with any mention of SVT was investigated.

For each death certificate, data about bleeding events was collected. The ICD-10 codes for bleeding events are reported in Supplementary Table 2, consistently with codes previously used in the literature [24]. The odds ratio (OR) with 95% CI for bleeding events in SVT (vs. non-SVT) patient was estimated by a conditional regression model stratified by sex and age at death.

Lastly, the association between liver diseases or gastrointestinal cancer (Supplementary Tables 1), known risk factors for SVT as identified from observational cohort studies, and SVT itself was estimated by age and sex-stratified conditional logistic regression models stratified by sex and age at death comparing the SVT vs. non-SVT populations. Data was analyzed with Microsoft Excel (version 16.54), Stata (version 15.0) and RStudio (version 1.4). The analysis of causes of mortality is included among mandatory activities of the Regional Epidemiology Department according to regional law; data used in this study were completely anonymized and their use did not require ethics or institutional review board approval.

3. Results

During the 2008–2019 period, a total of 557,932 deaths were recorded in Veneto: 293,455 in women and 264,477 in men. Splanchnic vein thrombosis was reported in 823 cases, corresponding to 0.14% of all deaths. The number of SVT-related deaths was higher in men (561 SVT-related deaths, 68.2%) than in women (262 SVT-related deaths, 31.8%). Portal vein thrombosis represented the vast majority (n = 776; 94.3%) of SVT events. Phlebitis of portal vein (n = 1), liver infarction (n = 23), hepatic veno-occlusive disease (n = 2), and Budd-Chiari syndrome (n = 21) have been much more rarely reported as a cause of death.

The annual crude SVT-related mortality rate was 1.41 per 100,000 person-years: 1.97 per 100,000 general population in men and 0.87 per 100,000 general population in women. SVT events were reported as the underlying cause of death in 54 (6.6%) patients with a mention of SVT in the death certificate (Table 1). Mortality rates peaked among men aged 70–79 years. In women, the increase in SVT-related mortality increased proportionally across age groups: however, these rates remained lower

Table 1
List of the selected underlying causes of death from death certificates in patients with splanchnic vein thrombosis (SVT).

Underlying cause of death	ICD-10 code	Men		Women	
		n	%	n	%
Splanchnic venous thrombosis	I81, I82.0, K75.1, K76.3, K76.5	26	4.6	28	10.7
Viral hepatitis, chronic liver diseases	B15-B19, K70, K73, K74	109	19.4	52	19.8
Liver cancer	C22	268	47.8	78	29.8
Biliary, pancreatic cancer	C23-C25	30	5.3	35	13.4
Other GI cancer	C15-C21, C26	31	5.5	12	4.6
Other neoplasms	C00-C14, C30-D489	38	6.8	24	9.2
Other GI diseases	A00-A09, K00-K99 (SVT, chronic liver dis. excluded)	24	4.3	11	4.2
Circulatory diseases	I00-I99 (SVT excluded)	16	2.9	13	5.0
Other causes	–	19	3.4	9	3.4
Total		561		262	

Abbreviations: GI, gastro-intestinal; SVT, splanchnic vein thrombosis.

compared to men of same age (Fig. 1).

Information on the place of death was available starting in 2012. Of 380,515 deaths since 2012, 579 were deemed to be SVT-related. Of these, 399 (68.9%) occurred in hospital, 79 (13.6%) at home, and 62 (10.7%) in a hospice; Table 2.

3.1. Trends in SVT-related mortality

The age-standardized SVT-related mortality varied from 1.47 in 2008 to 1.52 per 100,000 person-years in 2019. In the study period, an increase in the age-standardized SVT-related mortality rate was observed in women (from 0.56 to 1.04 per 100,000 person-years; AAPC 5.7%, 95% CI 3.1; 8.3%), whereas in men the trend was toward reduction, although without evidence of statistical significance (from 2.53 to 2.03 per 100,000 person-years; AAPC −1.2%, 95% CI −4.0; 1.6%), Fig. 2. In men, the median age at SVT-related death was 70 years (Q1–Q3 62–76); in women, it was 77 years (Q1–Q3 68–83).

Similar to age-standardized SVT-related mortality rate, SVT-related proportionate mortality (number of SVT-related deaths/total deaths) also increased over time in women, indicating that SVT represented a progressively more frequent cause of death among women. As shown in Table 3, SVT codes were reported in women in 0.07% of deaths in 2008–2011, increasing to 0.11% in 2016–2019. In men, we observed a rather stable prevalence (0.21%, 0.22%, and 0.21% for the periods 2008–2011, 2012–2015, and 2016–2019, respectively).

3.2. Prevalence of bleeding events in patients with and without SVT

Bleeding events, as defined by the ICD-10 codes presented in the Supplementary Table 2, were recorded in 114 (13.9%) out of 823 SVT-related deaths, vs. 32,988 (5.9%) out of 557,109 non-SVT-related deaths for an OR of 2.21 (95% CI 1.81–2.69). Of 114 bleeding events among SVT-related deaths, 92 (80.7% of bleeding events) occurred in the digestive tract and 25 (21.9% of bleeding events) were due to the presence of esophageal varices. In the non-SVT population, the percentage of gastrointestinal bleeding events was 26.8% of all bleeding events, whereas that of esophageal varices bleeding was 1.1%. Of all SVT-related deaths, the percentage of gastrointestinal bleeding was 11.2% (3.0% for bleeding from esophageal varices). Of all non-SVT-related deaths, the percentage of gastrointestinal bleeding was 1.6% (0.1% for bleeding from esophageal varices).

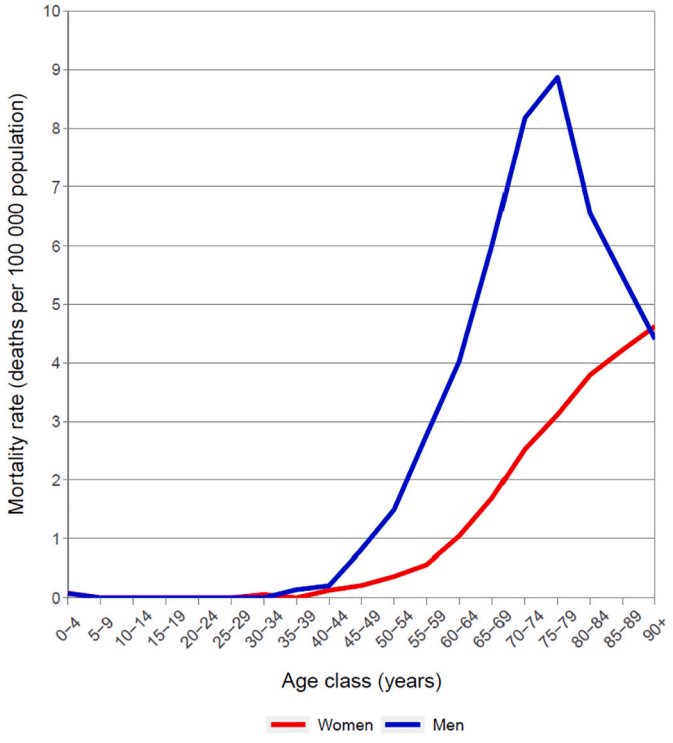

Fig. 1. SVT-related deaths per 100,000 population by age and sex, 2008–2019
Abbreviations: SVT, splanchnic vein thrombosis.

Table 2
Place of death in patients with and without splanchnic vein thrombosis (SVT).

	SVT	No SVT	Total
Total, N	579	379,936	380,515
Missing, n (% of column)	17 (2.9)	11,857 (3.1)	11,874
Home, n (%)	79 (13.6)	95,467 (25.1)	95,546
Hospital, n (%)	399 (68.9)	190,040 (50.0)	190,439
Hospice, n (%)	62 (10.7)	21,502 (5.7)	21,564
Nursing home, n (%)	18 (3.1)	54,715 (14.4)	54,733
Other, n (%)	4 (0.7)	6355 (1.7)	6359

This data refers to the period 2012–2019, for which information on the place of death was available.
Abbreviations: SVT, splanchnic vein thrombosis.

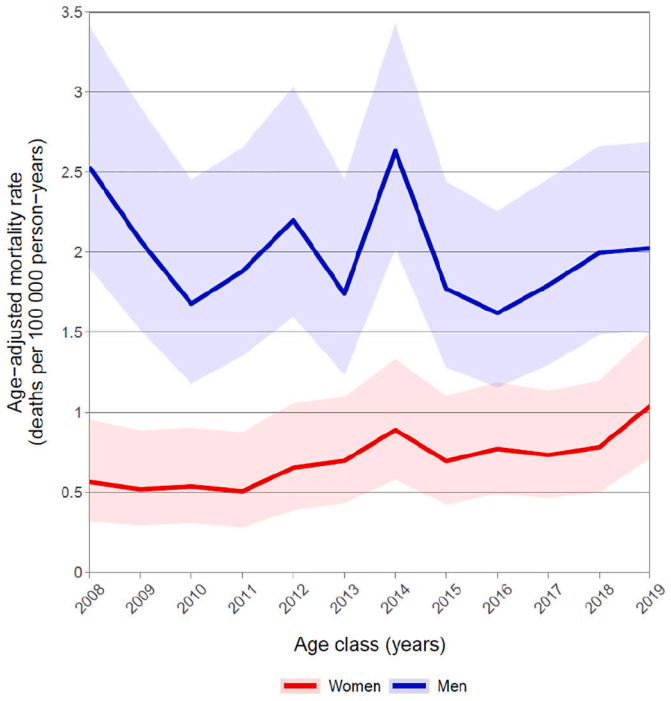

Fig. 2. Trend in age-standardized SVT-related mortality per 100,000 deaths by sex, 2008–2019
Abbreviations: SVT, splanchnic vein thrombosis.

3.3. Prevalence of concomitant diseases in patients with and without SVT

Among all deaths with SVT in any position of the certificate, the most prevalent underlying causes of death in women were liver cancer (n = 78, 29.8%), followed by viral hepatitis and chronic liver diseases (n = 52, 19.8%), biliary and pancreatic cancer (n = 35, 13.4%), other gastrointestinal cancer (n = 12, 4.6%), and other cancer subtypes (n = 24; 9.2%). In men, the most prevalent underlying causes of death were liver cancer (268 deaths; 47.8%), followed by viral hepatitis and chronic liver diseases (n = 109; 19.4%), biliary and pancreatic cancer (n = 30; 5.3%), other gastrointestinal cancer (n = 31; 5.5%), other cancers (n = 38; 6.8%) (Table 1).

The prevalence of liver diseases (Supplementary Table 1) in patients with SVT-related death was 76.3% in men and 55.0% in women. Compared to deaths without SVT, age- and sex-adjusted OR for liver

Table 3
Trends in SVT-related mortality rate and proportionate mortality in women and men by year groups, Veneto region.

	Years 2008–2011	Years 2012–2015	Years 2016–2019
Men			
UCOD, n	1	14	11
MCOD, n	180	193	188
Proportionate mortality, %	0.21	0.22	0.21
Crude mortality rate (deaths per 100,000 pop-yrs)	1.9	2.0	2.0
Age-standardized mortality rate (deaths per 100,000 pop-yrs)	2.0	2.1	1.9
Women			
UCOD, n	4	11	13
MCOD, n	64	90	108
Proportionate mortality, %	0.07	0.09	0.11
Crude mortality rate (deaths per 100,000 pop-yrs)	0.6	0.9	1.1
Age-standardized mortality rate (deaths per 100,000 pop-yrs)	0.5	0.7	0.8

SVT-related mortality rates are expressed as the number of SVT-related deaths per 100,000 population-years (pop-yrs). Proportionate mortality is expressed as the number of SVT-related deaths per 100 all-cause deaths in the general population.
Abbreviations: SVT, splanchnic vein thrombosis; UCOD, underlying cause of death; MCOD, multiple causes of death.

disease in deaths with SVT was 31.6 (95%CI 17.1–37.0). This association was stronger in men than in women and was stable through the study period (Table 4).

The prevalence of gastrointestinal cancer (excluding liver cancer and including biliary and pancreatic cancer; Supplementary Table 3) in patients with SVT-related death was 14.3% in men and 21.2% in women. Compared to deaths without SVT, age- and sex-adjusted OR for gastrointestinal cancer in deaths with SVT was 1.28 (95%CI 1.07–1.55). This association was present in women, but not in men (Supplementary Table 3).

4. Discussion

In this study, we provided epidemiological estimates of the annual mortality rate related to SVT and the relative impact of known risk factors on SVT. In Veneto, an Italian high-income region of nearly 5 million inhabitants, SVT contributed to approximately 1.4 deaths per 100,000 population year in the period 2008–2019. To our knowledge, this is the first study that analyzes SVT-related mortality and its trends. This data currently represents the most reliable population-level historical information for this condition and quantifies the relative impact of known risk factors on SVT-related deaths, including liver diseases and gastrointestinal cancers.

Table 4
Prevalence of liver disease (liver cancer included, ICD-10 codes B15-B19, C22, K70, K73, K74) in patients with SVT-related death and comparison with non-SVT-related deaths in the Veneto region, 2008–2019.

	Patients with liver disease and SVT, n (% of all SVT patients)	Odds Ratio for patients with vs. without SVT (95% CI)
Total	572 (69.7)	31.6 (27.1–36.0)
Sex		
Men	428 (76.3)	35.3 (28.9–43.1)
Women	144 (55.0)	26.4 (20.5–34.0)
Period		
2008–2011	175 (71.7)	31.4 (23.6–42-0)
2012–2015	202 (71.6)	35.2 (26.8–46.3)
2016–2019	195 (66.1)	30.5 (23.7–39.3)

Odds ratio are presented as age- and, where applicable, sex-adjusted values.
Abbreviations: SVT, splanchnic vein thrombosis; CI, confidence interval.

Lately, an increased awareness on the novel vaccine-induced immune thrombocytopenia and thrombosis (VITT) [25] has risen in concomitance of national vaccination campaigns against SARS-CoV2. However, it proved difficult to compare the observed fatal cases of venous thrombosis with expected cases based on appropriate reference mortality data [19,20,26]. For SVT, at least concerning its most prevalent manifestations, portal vein thrombosis and BCS, no epidemiological data on mortality is available although specific ICD-10 codes exist and incidence estimates vary considerably. Our trend data represent a reference for future analyses on contemporary SVT-related mortality rates, assuming that a deviation from the expected range for the year 2020–2021 based on current trends might be secondary novel potential risk factors, including COVID-19 and COVID-19 vaccines. For it has been recently shown that SVT was a major presenting thrombotic site in 41 (19%) for the UK's cohort of 220 definite and probable VITT cases who received the first dose of the ChAdOx1 nCov-19 [27].

In this population, SVT-specific mortality rate was twice as high in men compared to women. However, the annual cause-specific mortality trend increased among women during the study period, while it remained stable among men. Liver disease represented a key risk factor for SVT with an overall prevalence of 69.7% in SVT deaths and a 30-time increased risk compared with non-SVT patients. Gastrointestinal cancer seemed a much less relevant risk factor for SVT and indeed an association could be confirmed in women only. Differences in the prevalence of sex-specific risk factors were reflected by a corresponding difference in SVT-related mortality, which peaked in the 70–79 years age group among men, while in women we observed a steady increase in mortality rates with age. There are several possible explanations for these observations. First, in both sexes the most frequently reported underlying cause of death was a liver-related disease (unspecified chronic liver disease, viral or alcoholic hepatitis, and liver cancer). It is known that liver diseases-related mortality is higher in men than in women, particularly in this age group [28,29]. Second, preventive strategies, including campaigns to prevent alcohol abuse and the introduction of hepatitis B vaccine, contributed to an overall reduction in chronic liver disease, particularly among the younger generations [28,30,31]. Finally, the decrease of age-specific SVT mortality in men aged 80 or older might be explained by the presence of other severe conditions — namely cardiovascular diseases and non-liver cancer — acting as a competing risk, thus shifting the focus from SVT to other possible causes of death.

In women, the SVT-related mortality trend increased significantly during the study period. An increase in alcohol consumption in the general population may partly explain this observation [32,33]. The increase with age in SVT-related mortality in women extended to age classes >80 years. It is possible that this trend also reflects the higher risk of getting infected by HCV through contaminated blood transfusions before the year 1984, especially in pregnant women. Furthermore, the association between gastrointestinal cancers and SVT was stronger in women, possibly explaining sex-related differences in SVT patterns and time trends.

The prevalence of bleeding events was two-time higher in SVT patients compared with the non-SVT population. This difference was more pronounced for gastrointestinal bleedings, which were reported in 11.2% of deaths certificate from patients with SVT and in 1.6% of those from patients without SVT. This observation is consistent with data from prior cohort studies showing a higher risk of bleeding among SVT patients compared to patients with other types of VTE [34]: as previously demonstrated, this risk reflects the baseline gastrointestinal disease and may only minimally influenced by anticoagulation [13,15].

Our study has some limitations. First, the attribution of deaths to SVT as the underlying cause is difficult. It is more likely for subjects with SVT secondary to other diseases (i.e. liver diseases or cancer) to have these as the underlying cause of death. However, the use of MCOD allowed the inclusion in the study of a relevant number of subjects with SVT as a concomitant cause of death, thus partially reducing the risk of

underestimation. Second, the relatively small number of SVT-related deaths reported in any position of the death certificate did not allow further analyses on the association with specific comorbidities (e.g. alcoholic-related liver disease, viral hepatitis, and liver cancer). Therefore, we analyzed the association with clusters of diseases (Supplementary Table 1) already used in epidemiological studies. Built as a vital registration database, no information on the number of SVT diagnoses was available: therefore, no data on its incidence, prevalence, and fatality could be calculated. Third, being based on ICD-10 codes from death certificates, no information was available on the use or duration of anticoagulant therapy, presence of symptoms, or timing of bleeding in relation to the diagnosis of SVT. Finally, apparently specific ICD-10 codes for splanchnic thrombosis, including K55.0 (acute vascular disorders of the intestine) K55.1 (chronic vascular disorders of the intestine) and D73.5 (infarction of spleen) do not distinguish between venous and arterial disorders. Thus, and although these two thrombotic manifestations share different risk factors, it is impossible to distinguish between them. This also calls for an implementation of the coding system to be able to better categorize and study them.

In this study, we reported the time trend and the burden of SVT-related mortality in a large region of a Western country, showing marked age-sex differences, a strong association between SVT-related death and liver disease, and a high prevalence of gastrointestinal bleedings. Our data may serve as a reference value for future analyses studying the association between novel potential thrombosis risk factors, for instance COVID-19 vaccines/VITT and SVT on a population level.

Credit authorship contribution statement

Giacomo Turatti and Stefano Barco: concept and design, analysis, and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. Ugo Fedeli: design, analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. Luca Valerio: analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. Frederikus A. Klok, Alexander T. Cohen, Beverly J. Hunt, Paolo Simioni, Saskia Middeldorp, Walter Ageno, Nils Kucher, Stavros V. Konstantinides and Elena Schievano: interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.11.005.

References

[1] R. Rajani, E. Bjornsson, A. Bergquist, A. Danielsson, A. Gustavsson, O. Grip, T. Melin, P. Sangfelt, S. Wallerstedt, S. Almer, The epidemiology and clinical features of portal vein thrombosis: a multicentre study, Aliment. Pharmacol. Ther. 32 (2010) 1154–1162, https://doi.org/10.1111/j.1365-2036.2010.04454.x.

[2] S. Acosta, A. Alhadad, P. Svensson, O. Ekberg, Epidemiology, risk and prognostic factors in mesenteric venous thrombosis, Br. J. Surg. 95 (2008) 1245–1251, https://doi.org/10.1002/bjs.6319.

[3] K.K. Sogaard, B. Darvalics, E. Horvath-Puho, H.T. Sorensen, Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study, Thromb. Res. 141 (2016) 1–7, https://doi.org/10.1016/j.thromres.2016.02.024.

[4] W. Ageno, F. Dentali, F. Pomero, L. Fenoglio, A. Squizzato, G. Pagani, R. Re, M. Bonzini, Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari syndrome, Thromb. Haemost. 117 (2017), https://doi.org/10.1160/TH16-10-0781.

[5] R. Rajani, T. Melin, E. Björnsson, U. Broomé, P. Sangfelt, Å. Danielsson, A. Gustavsson, O. Grip, H. Svensson, L. Lööf, S. Wallerstedt, S.H.C. Almer, Budd-Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival - an 18-year experience, Liver Int. 29 (2009) 253–259, https://doi.org/10.1111/j.1478-3231.2008.01838.x.

[6] A. Mangia, M.R. Villani, G. Cappucci, R. Santoro, R. Ricciardi, D. Facciorusso, G. Leandro, N. Caruso, A. Andriulli, Causes of portal venous thrombosis in cirrhotic patients: the role of genetic and acquired factors, Eur. J. Gastroenterol. Hepatol. 17 (2005) 745–751, https://doi.org/10.1097/00042737-200507000-00009.

[7] M.A. Zocco, E. di Stasio, R. de Cristofaro, M. Novi, M.E. Ainora, F. Ponziani, L. Riccardi, S. Lancellotti, A. Santoliquido, R. Flore, M. Pompili, G.L. Rapaccini, P. Tondi, G.B. Gasbarrini, R. Landolfi, A. Gasbarrini, Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development, J. Hepatol. 51 (2009) 682–689, https://doi.org/10.1016/j.jhep.2009.03.013.

[8] R. Singh, T. Sousou, S. Mohile, A.A. Khorana, High rates of symptomatic and incidental thromboembolic events in gastrointestinal cancer patients, J. Thromb. Haemost. 8 (2010) 1879–1881, https://doi.org/10.1111/j.1538-7836.2010.03929.x.

[9] A. Afzal, L. Suhong, B.F. Gage, M.W. Schoen, K. Carson, T. Thomas, K. Sanfilippo, Splanchnic vein thrombosis predicts worse survival in patients with advanced pancreatic cancer, Thromb. Res. 185 (2020) 125–131, https://doi.org/10.1016/j.thromres.2019.11.023.

[10] N. Gangat, A.P. Wolanskyj, A. Tefferi, Abdominal vein thrombosis in essential thrombocythemia: prevalence, clinical correlates, and prognostic implications, Eur. J. Haematol. 77 (2006) 327–333, https://doi.org/10.1111/j.1600-0609.2006.00715.x.

[11] A. Alvarez-Larran, A. Pereira, M. Magaz, J.C. Hernandez-Boluda, M. Garrote, B. Cuevas, F. Ferrer-Marin, M.T. Gomez-Casares, V. Garcia-Gutierrez, M.I. Mata-Vazquez, F. Turon, V. Hernandez-Gea, E. Arellano-Rodrigo, F. Cervantes, J. C. Garcia-Pagan, R.groups <collab>Gemfin, Natural history of polycythemia vera and essential thrombocythemia presenting with splanchnic vein thrombosis, Ann. Hematol. 99 (2020) 791–798, https://doi.org/10.1007/s00277-020-03965-z.

[12] M.R. Thatipelli, R.D. McBane, D.O. Hodge, W.E. Wysokinski, Survival and recurrence in patients with splanchnic vein thromboses, Clin. Gastroenterol. Hepatol. 8 (2010) 200–205, https://doi.org/10.1016/j.cgh.2009.09.019.

[13] M. Senzolo, N. Riva, F. Dentali, K. Rodriguez-Castro, M.T. Sartori, S.M. Bang, I. Martinelli, S. Schulman, A. Alatri, J. Beyer-Westendorf, M.N.D. di Minno, W. Ageno, I. study investigators, Long-term outcome of splanchnic vein thrombosis in cirrhosis, Clin. Transl. Gastroenterol. 9 (2018) 176, https://doi.org/10.1038/s41424-018-0043-2.

[14] L. Amitrano, M.A. Guardascione, M. Scaglione, L. Pezzullo, N. Sangiuliano, M. F. Armellino, F. Manguso, M. Margaglione, P.R. Ames, L. Iannaccone, E. Grandone, L. Romano, A. Balzano, Prognostic factors in noncirrhotic patients with splanchnic vein thromboses, Am. J. Gastroenterol. 102 (2007) 2464–2470, https://doi.org/10.1111/j.1572-0241.2007.01477.x.

[15] N. Riva, W. Ageno, S. Schulman, J. Beyer-Westendorf, R. Duce, A. Malato, R. Santoro, D. Poli, P. Verhamme, I. Martinelli, P. Kamphuisen, F. Dentali, group International Registry on Splanchnic Vein Thrombosis study, Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry, Lancet Haematol. 3 (2016) e267–e275, https://doi.org/10.1016/S2352-3026(16)30020-5.

[16] W. Ageno, A. Squizzato, A. Togna, F. Magistrali, M. Mangini, C. Fugazzola, F. Dentali, Incidental diagnosis of a deep vein thrombosis in consecutive patients undergoing a computed tomography scan of the abdomen: a retrospective cohort study, J. Thromb. Haemost. 10 (2012) 158–160, https://doi.org/10.1111/j.1538-7836.2011.04565.x.

[17] B. Zhang, M. Kim, C. Griffiths, Q. Shi, E. Duceppe, L. Ruo, P.E. Serrano, Incidence of splanchnic vein thrombosis after abdominal surgery: a systematic review and meta-analysis, J. Surg. Res. 245 (2020), https://doi.org/10.1016/j.jss.2019.07.086.

[18] M. Ogren, D. Bergqvist, M. Bjorck, S. Acosta, H. Eriksson, N.H. Sternby, Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies, World J. Gastroenterol. 12 (2006) 2115–2119, https://doi.org/10.3748/wjg.v12.i13.2115.

[19] M. Porres-Aguilar, A. Lazo-Langner, A. Panduro, M. Uribe, COVID-19 vaccine-induced immune thrombotic thrombocytopenia: an emerging cause of splanchnic vein thrombosis, Ann. Hepatol. 23 (2021), https://doi.org/10.1016/j.aohep.2021.100356.

[20] O. Öcal, S.-S. Stecher, M. Wildgruber, Portal vein thrombosis associated with ChAdOx1 nCov-19 vaccination, Lancet Gastroenterol. Hepatol. (2021), https://doi.org/10.1016/S2468-1253(21)00197-7.

[21] T.H. Lu, R.N. Anderson, I. Kawachi, Trends in frequency of reporting improper diabetes-related cause-of-death statements on death certificates, 1985–2005: an algorithm to identify incorrect causal sequences, Am. J. Epidemiol. 171 (2010), https://doi.org/10.1093/aje/kwq057.

[22] C. Orsi, S. Navarra, L. Frova, E. Grande, S. Marchetti, M. Pappagallo, F. Grippo, Impact of the implementation of ICD-10 2016 version and Iris software on mortality statistics in Italy, Epidemiol. Prev. 43 (2019) 161–170.
[23] M.P. Fay, E.J. Feuer, Confidence intervals for directly standardized rates: a method based on the gamma distribution, Stat. Med. 16 (1997) 791–801.
[24] S. Barco, L. Valerio, W. Ageno, A.T. Cohen, S.Z. Goldhaber, B.J. Hunt, A. Iorio, D. Jimenez, F.A. Klok, N. Kucher, S.H. Mahmoudpour, S. Middeldorp, T. Münzel, V. Tagalakis, A.M. Wendelboe, S.v Konstantinides, Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000–18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database, Lancet Respir. Med. 9 (2021), https://doi.org/10.1016/S2213-2600(20)30417-3.
[25] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, N. Engl. J. Med. 384 (2021) 2092–2101, https://doi.org/10.1056/nejmoa2104840.
[26] N.H. Schultz, I.H. Sørvoll, A.E. Michelsen, L.A. Munthe, F. Lund-Johansen, M. T. Ahlen, M. Wiedmann, A.-H. Aamodt, T.H. Skattør, G.E. Tjønnfjord, P.A. Holme, Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. 384 (2021) 2124–2130, https://doi.org/10.1056/nejmoa2104882.
[27] S. Pavord, M. Scully, B.J. Hunt, W. Lester, C. Bagot, B. Craven, A. Rampotas, G. Ambler, M. Makris, Clinical features of vaccine-induced immune thrombocytopenia and thrombosis, N. Engl. J. Med. (2021), https://doi.org/10.1056/NEJMoa2109908.
[28] U. Fedeli, F. Avossa, E. Ferroni, A. de Paoli, F. Donato, M.C. Corti, Prevalence of chronic liver disease among young/middle-aged adults in Northern Italy: role of hepatitis B and hepatitis C virus infection by age, sex, ethnicity, Heliyon 5 (2019), e02114, https://doi.org/10.1016/j.heliyon.2019.e02114.
[29] Y.H. Yoon, C.M. Chen, M.E. Slater, M.K. Jung, A.M. White, Trends in premature deaths from alcoholic liver disease in the U.S., 1999–2018, Am. J. Prev. Med. 59 (2020) 469–480, https://doi.org/10.1016/j.amepre.2020.04.024.
[30] D. Caroli, E. Rosa-Rizzotto, C. Pilerci, S. Lobello, F. de Lazzari, M. Saia, Falling rates of hospital admissions for alcoholic liver disease in Northeast Italy: a retrospective study on a large database, Alcohol Alcohol. 54 (2019) 662–666, https://doi.org/10.1093/alcalc/agz070.
[31] C. Dong, Y.-H. Yoon, C.M. Chen, H.-Y. Yi, Heavy Alcohol Use and Premature Death From Hepatocellular Carcinoma in the United States, 1999-2006*, 2011. www.cdc.gov/nchs/data_access/Vitalstatsonline.htm.
[32] F. Thibaut, Alert out on tobacco and alcohol consumption in young European women, Eur. Arch. Psychiatry Clin. Neurosci. 268 (2018), https://doi.org/10.1007/s00406-018-0901-7.
[33] H.M. Haydon, P.L. Obst, I. Lewis, Examining women's alcohol consumption: the theory of planned behavior and self-identity 53 (2018), https://doi.org/10.1080/10826084.2017.1327972.
[34] K.K. Søgaard, K. Adelborg, B. Darvalics, E. Horváth-Puhó, J. Beyer-Westendorf, W. Ageno, H.T. Sørensen, Risk of bleeding and arterial cardiovascular events in patients with splanchnic vein thrombosis in Denmark: a population-based cohort study, Lancet Haematol. 5 (2018), https://doi.org/10.1016/S2352-3026(18)30133-9.