SSC Subcommittee Project Template

Subcommittee Name: Subcommittee on Hemostasis and Malignancy

Project Name: Isolated and Unusual Abdominal Venous Thrombosis in Cancer Patients – A Multicenter Study

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Template Form Date: 4/29/2024

Project Description/Abstract:

State the project's broad, long-term objectives and specific aims, making reference to the proposed health/scientific impact as a result of the project. Suggested length is 2-3 paragraphs.

Cancer associated thrombosis (CAT) is a major cause of increased morbidity and mortality in cancer patients. In previous studies, up to 11% of CAT were unusual abdominal venous thrombosis, mostly splanchnic vein thrombosis (SpVT). Currently, the optimal management of cancer-associated SpVT (CA-SpVT) remains unclear and major society guidelines provide little guidance due to lack of high-quality evidence. SpVT has been most well studied in patients without cancer. Those studies have suggested that anticoagulation improves rates of recanalization, complications such as portal hypertension, and mortality, without increased risk of bleeding. However, it is unclear whether these findings are generalizable to cancer patients as a whole, or varying cancer types and histologies. Cancer patients are not only diverse in their propensity for thrombosis and bleeding, but also may form tumor SpVT from malignant venous invasion, which may be distinct from bland SpVT. There are no randomized control trials on management of CA-SpVT, and existing retrospective studies have been mostly limited to single institutional experiences. Thus, these studies are often limited by small cohort size, relative lack of diversity of population demographics, and predominant institutional practice in treatment of SpVT affecting ability to adequately compare management strategies.

Our study aims to describe the natural history of CA-SpVT by cancer type and thrombus composition, and to compare the rates of usual-site venous thromboembolism (VTE), major and clinically relevant nonmajor bleeding (MB/CRNMB), recanalization/progression of SpVT, and mortality within 1 year of diagnosis between patients with anticoagulation (AC) practices vs. no AC. This project will impact the understanding of the prognosis of patients with CA-SpVT, and the association of patient-related and thrombus-related factors on clinical outcomes. Additionally, the analysis will shed light on the association between anticoagulation strategies and the aforementioned outcomes. This will help inform clinicians in their treatment decisions in patients with CA-SpVT.

Project Design and Methodology:

List the data expected to collect, sample size and statistical analysis. Concisely describe the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

Data will be collected through retrospective data extraction and manual chart review when necessary. Outcomes will be collected up to 12 months following the index date (defined as the first ever SpVT diagnosis date meeting inclusion/exclusion criteria). Analysis will report pre-specified outcome assessment at 6 months after index date. Patients will be censored for loss to follow-up (defined as the last continuous face-to-face clinical encounter within 6 months), end of data availability, or death.

Outcomes will include:

- Usual-site VTE
  - PE
  - Lower extremity (LE) DVT
  - Upper extremity (UE) DVT
- Bleeding:
  - MB by ISTH criteria
  - CRNMB by ISTH criteria
- Recanalization:
  - Only assessed in patients with available repeat contrast CT, MRI, or Doppler US 3 to 12 months after initial SpVT diagnosis
  - Partial recanalization: reduction in thrombus size
  - Complete recanalization: complete resolution of thrombus
- Progression
  - Increase in thrombus size, extension to contiguous veins, or new non-contiguous SpVT
- All-cause mortality

Baseline variables that will be collected at time of SpVT diagnosis include:

- Demographics
  - Age
  - Sex
  - NIH race
  - NIH ethnicity
  - Insurance status
- SpVT-specific:
  - Venous location: portal, mesenteric, splenic, hepatic, IVC (isolated without LE-DVT), renal, gonadal/ovarian
  - Thrombus composition: bland, tumor, mixed, unknown
  - Acute vs. chronic
  - Symptomatic vs. incidental
  - AC vs. no AC:
    - Inpatient diagnosis: AC defined as new weight-based therapeutic AC initiated within 4 weeks after SpVT diagnosis with a duration >72 hours

and an intention to continue upon hospital discharge (e.g. not true in hospice patients)
        - Outpatient diagnosis: AC defined as new weight-based therapeutic AC initiated within 4 weeks after SpVT diagnosis (prescription)
        - AC date may be different than SpVT diagnosis date
- Cancer-specific:
    - Cancer histology
    - Cancer stage
    - Cancer treatment
    - Time from cancer diagnosis to SpVT diagnosis
- Patient-specific:
    - NCI-comorbidity index (NCI-CI; modified Charlson)
        - Myocardial infarction
        - Congestive heart failure
        - Peripheral vascular disease
        - Cerebrovascular disease
        - Chronic pulmonary disease
        - Hemiplegia or paraplegia
        - Diabetes
        - Renal disease
        - Liver disease
        - Rheumatic disease
        - AIDS/HIV
    - ECOG performance status (PS)
    - Body mass index (BMI)
    - VTE history (not on active AC – see exclusion above)
    - White blood cell count
    - Hemoglobin
    - Platelet count

Statistical analysis will include a descriptive analysis of baseline characteristics (Table 1), including incidence of SpVT by cancer histology, by thrombus composition (bland vs. tumor), and by AC status (AC vs. no AC). An unadjusted analysis will be performed to assess the association between AC and SpVT. Outcomes assessed will include usual-site VTE and MB/CRNMB at 6 months after index date using a competing risk method with death as competing risk. Mortality will be assessed at 6 months after the index date using the Kaplan-Meier method. Venous patency will be assessed in the subset of patients with available repeat imaging 3-12 months after index date (if multiple imaging, we will use the first one after at least 3 months). Proportions will be calculated as the number of patients with recanalization or progression on repeat imaging divided by total number of patients with repeat imaging. Differences will be compared using 2-sided Fisher's exact test.

An adjusted analysis for association between AC and SpVT will be done using a propensity score weighted analysis for AC vs. no AC. Variables to be tested include SpVT composition, SpVT location, SpVT acuity, SpVT symptomatic, cancer histology, cancer stage, age, sex, race, ECOG PS, NCI-CI, and VTE history.

Study Population:

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List the inclusion and exclusion criteria, eligibility, patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number:
Suggested length 2-3 paragraphs

Adult patients with cancer diagnosis 2011-2022 and new SpVT diagnosis concurrently with or up to 36 months after the cancer diagnosis will be included. Thrombus can be bland, tumor or mixed; symptomatic or incidental; acute or chronic as long as this is the first ever radiologic diagnosis. Locations can involve portal, mesenteric, splenic, hepatic, IVC (isolated without LE-DVT), renal, gonadal/ovarian veins. Patients will be screened by using the International Classification of Disease (ICD) code for “non-specific venous thromboembolism” or through natural language processing (NLP) algorithm for SpVT keywords from radiology reports or clinical documentation.

Exlusion criteria include: known myeloproliferative neoplasms, known history of SpVT diagnosis before cancer diagnosis (not cancer associated), delayed SpVT diagnosis >36 months after cancer diagnosis (not cancer associated), concurrent PE/DVT diagnosis (not isolated SpVT), baseline AC for any reason on or before SpVT diagnosis, and inadequate follow up to assess outcomes (defined as <3 months after SpVT diagnosis, unless death has occurred).

Institutions involved for data collection include Baylor College of Medicine/ Harris Health System, Beth Israel Deaconess Medical Center, and others via ISTH SSC Subcommittee on Hemostasis and Malignancy. For a statistical power of 0.80, at a significance level of 0.05, to detect an effect size of the incidence of each outcome of 5% vs 10% in the AC vs no AC groups, assuming an even distribution between AC and no AC, a minimum number of 868 patients would be included. These approximations of incidence were based on prior data on incidence of complications of SpVT in the general population (Candeloro et al.) as well as data already collected in patients with CA-SpVT for the purposes of this study. Current sample size is about 500 from BIDMC and 300 from BCM from data preliminarily collected. We expect a total number of participants of over 1,000 patients through SSC collaboration.

Infrastructure:
Description of project set-up, management, operational requirements and resources.

A Redcap collection instrument has already been designed to be used at participating institutions. It is already being set up between Baylor and BIDMC. A DUA has been established to allow for sharing of de-identified data between Baylor and BIDMC. We will will set up additional DUA for deidentified datasets between other participating institutions.

The project will be discussed during monthly steering committee meetings and ISTH SSC meetings. The project will be presented in person at the ISTH SSC meeting during ISTH Congress 2025.

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Timeline and Milestones:

Project stage/set up: June-August, 2024
Launch: August, 2024
Duration: 9 months to allow for data collection
Finalization/analysis: Analysis and finalization to occur May-June, 2025.
Reporting (annual at minimum): The project will be discussed during monthly steering committee meetings and ISTH SSC meetings.
Publication: June, 2025

Expected Outcomes:

Describe potential for future collaboration, funded research grant, publication (specify type – SSC Communications, Guidance Document, Original Article, etc.):

We anticipate presentation at the ISTH SSC meeting during ISTH Congress 2025 and publication as an original research article.

Possible References:

1. Shang H, Jiang JY, Guffey D, et al. Natural history of cancer-associated splanchnic vein thrombosis. *J Thromb Haemost*. Feb 1 2024;doi:10.1016/j.jtha.2024.01.019
2. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. *Blood*. Dec 11 2014;124(25):3685-91. doi:10.1182/blood-2014-07-551515
3. Ageno W, Riva N, Schulman S, et al. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. *JAMA Intern Med*. Sep 2015;175(9):1474-80. doi:10.1001/jamainternmed.2015.3184
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5. Wang TF, Billett HH, Connors JM, Soff GA. Approach to Cancer-Associated Thrombosis: Challenging Situations and Knowledge Gaps. *Oncologist*. Jan 2021;26(1):e17-e23. doi:10.1002/onco.13570
6. Valeriani E, Di Nisio M, Riva N, et al. Clinical history of cancer-associated splanchnic vein thrombosis. *J Thromb Haemost*. Apr 2021;19(4):983-991. doi:10.1111/jth.15214
7. Candeloro M, Valeriani E, Monreal M, et al. Anticoagulant therapy for splanchnic vein thrombosis: an individual patient data meta-analysis. *Blood Adv*. Aug 9 2022;6(15):4516-4523. doi:10.1182/bloodadvances.2022007961
8. García-Villa A, Criado-Álvarez JJ, Carnevali M, Aramberri M, Font C, Díaz-Pedroche C. Cancer-associated splanchnic vein thrombosis: Clinical features upon diagnosis and short-term outcomes. *Thromb Res*. Nov 2023;231:84-90. doi:10.1016/j.thromres.2023.10.002
9. Riva N, Ageno W, Schulman S, et al. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. *Lancet Haematol*. Jun 2016;3(6):e267-75. doi:10.1016/s2352-3026(16)30020-5
10. Afzal A, Suhong L, Gage BF, et al. Splanchnic vein thrombosis predicts worse survival in patients with advanced pancreatic cancer. *Thromb Res*. Jan 2020;185:125-131. doi:10.1016/j.thromres.2019.11.023

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