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Full Length Article

Identifying predictors for bleeding in hospitalized cancer patients: A cohort study

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ABSTRACT

Background: Bleeding and thrombosis are both major complications of hospitalization in cancer patients. Concern regarding bleeding risk may reduce compliance with thromboprophylaxis. We assessed incidence of major and clinically relevant non-major bleeding (MCRNMB) and identified risk factors associated with in-hospital bleeding risk in hospitalized cancer patients.

Methods: We conducted a retrospective cohort study of consecutive adults admitted to general oncology floor at Cleveland Clinic from 11/2012–12/2014 (n = 3525). Patients were excluded for bleeding on admission (n = 108), age < 18 (n = 1), non-malignant disease (n = 2) and incomplete data (n = 56). Data collected included demographics, body mass index (BMI), cancer type, length of stay (LOS), use of anticoagulants and baseline laboratory values (+ 48 h). Univariate risk factors were identified with logistic regression analysis. Multivariable risk factors were identified with stepwise logistic regression and confirmed with bootstrap analysis.

Results: The study population comprised 3358 patients of whom 69 (2.1%) developed MCRNMB. Median age was 62 (range, 19–98) years and 56% male. Median length of stay was 5 (range, 0–152) days. The majority of bleeding events were either gastrointestinal (GI) (N = 23, 33%) or retroperitoneal (N = 10, 14%). In multivariable analysis, anemia as the reason for admission (7.78, 95% CI 4.0–15.1, P < 0.001), GI cancer site (2.96, 95% CI 1.7–5.2 P < 0.001), BMI ≥ 40 (3.08, 95% CI 1.3–2.9, P = 0.008) and thrombocytopenia (1.7, 95% CI 1.0–2.9, P = 0.05) were predictive.

Conclusion: The incidence of MCRNMB in a population of hospitalized cancer patients was 2.1%. Risk factors at admission included type of cancer and morbid obesity. Improved prediction of bleeding risk can assist physicians in optimizing selection of thromboprophylaxis in this population that is also at increased risk of VTE.

1. Introduction

Venous thromboembolism (VTE) is a well-recognized and common complication in patients with cancer [1,2]. VTE has been identified as an important cause of mortality [3,4] second only to progression of the underlying cancer itself [5].

Amongst hospitalized patients the risk of VTE has been shown to be as high as 4.1% per hospitalization in cancer patients [6] which is considerably higher than the incidence (< 1%) reported in acutely ill medical patients without cancer in other studies [7,8]. Thromboprophylaxis has been shown to significantly reduce risk of VTE in hospitalized patients [9,10] and is universally recommended including inpatients with cancer [11,12]. However adherence with thromboprophylaxis amongst hospitalized cancer patients has been shown to be inconsistent and variable [13–15].

Along with an increased risk of VTE, cancer patients on therapeutic anticoagulation for VTE have also been shown to have an increased risk of bleeding as compared to patients that do not have cancer [16]. Bleeding in cancer patients can manifest in several ways, ranging from ecchymosis or low volume oozing to a catastrophic life threatening hemorrhage [17]. Hemorrhage can result from local processes such as local invasion to vessels to more systemic processes including disseminated intravascular coagulation or quantitative and/or qualitative platelet abnormalities. Both cancer and treatments for cancer including chemotherapy, radiation therapy, surgery and supportive care agents such as anticoagulants can be responsible for these processes [17].

Bleeding is a common feared feature of advanced cancer; in a post mortem study of 816 cancer patients over a three-year period,

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hemorrhage was the proximate cause of death in 7% [18,19]. Yet in a more recent study of a prospective cohort receiving outpatient chemotherapy that looked at causes of death, fatal bleeding was seen in 1.4% [20]. Concerns regarding bleeding are perceived to be a major barrier to thromboprophylaxis in this at risk population. In a prospective cross-sectional study of cancer inpatients, nearly one-third had a relative contraindication due to active bleeding (5.5%), severe thrombocytopenia (20.8%), history of bleeding (1.9%), or otherwise considered to have a high risk of bleeding (4.4%) [14]. However, data on the actual bleeding incidence, patterns and predictors of bleeding events in patients with active cancer hospitalized for acute medical illness are limited.

An increased understanding of the predictors of bleeding could help better assess risk and assist clinicians in optimizing the benefit of thromboprophylaxis in preventing VTE and its associated morbidity and mortality. We therefore aimed to assess the incidence of in-hospital major and clinically relevant bleeding and identify risk factors at admission associated with in-hospital bleeding risk in a cohort of hospitalized cancer patients.

2. Methods

The study comprised a cohort of 3525 consecutive adults admitted to hematology/oncology (identified by a diagnosis of malignancy and the admitting physician a hematologist/oncologist) at the Cleveland Clinic from November 2012–December 2014. For patients with multiple admissions only the first admission was included in the analysis. Approval from the institutional review board was obtained. Patients over the age of 18 with an active diagnosis of malignancy at the time of admission were included. Patients were excluded for bleeding on admission ($n = 108$), age < 18 ($n = 1$), non-malignant disease ($n = 2$) and incomplete data ($n = 56$) (Fig. 1).

Data were primarily collected using an electronic query system of the electronic health records (EHR). All admissions on the oncology service and admitting physician was an oncologist were pulled electronically and manually confirmed by chart review. Types of cancer were also extracted electronically and missing data ($< 2\%$) was filled in by chart review. Baseline data collected included patient demographics, BMI, cancer type, use of anticoagulants and antiplatelet agents on admission, laboratory values (up to 48 h from admission), and primary indication for admission. However data on anticoagulation prior to admission, dosage of anticoagulation (i.e. therapeutic or prophylactic) or prior history of bleeding was not available. In addition, reason for admission, care in an intensive care unit and surgery during index admission were also manually recorded for the study population. Bleeding was assessed using the International Society on Thrombosis Hemostasis definitions of major bleeding and clinically relevant non-major bleeding [21,22]. Bleeding events were identified from discharge summaries of admissions being studied. To obtain details of event, documentation including diagnostic tests (imaging and procedures) as well as clinical notes was used. All bleeding events were confirmed manually by two investigators (RP and AG, third year internal medicine residents at the time of study). When unclear, individual cases were cross-reviewed, discussed and included if both agreed. Of note no separate training was performed and no coding was used to extract bleeding information.

BMI was categorized into six groups using NIH criterion: underweight (BMI < 18.5), normal weight (18.5–24.9), overweight (25–29.9), obese/class I (30–34.9), obese/class II (35–39.9), obese/class III (≥ 40; extreme obesity).

Cancer site was categorized into five groups: Gastrointestinal (GI) tract cancers, genitourinary (GU) cancers, lung cancer, any other solid tumor, and hematologic malignancies. GI tract cancers included colon and rectum, pancreas, esophagus, stomach, peritoneum, and gallbladder. Genitourinary cancers included kidney, prostate, bladder, and testis cancers. Any other solid tumor included anything that was not GI, GU, or lung cancer. Hematologic malignancies included lymphoma, leukemia, myeloma, myelodysplastic syndrome, and myelofibrosis.

Based on individual chart review (including discharge summaries and admission history and physical documentation) by two investigators (RP and AG) the admissions were categorized into 9 categories including elective chemotherapy, infections, gastrointestinal symptoms (including vomiting, abdominal pain, bowel obstruction, jaundice, dysphagia, diarrhea and constipation but excluding bleeding), pain management, neurologic complaints (including delirium), cardiorespiratory symptoms/failure, renal (including acute kidney injury, electrolyte disturbances and tumor lysis syndrome) and anemia (without symptoms of bleeding at time of admission, based on the admission note). Patients admitted to the hospital for bleeding were also excluded.

Institutional normal ranges were used to categorize laboratory values as below normal, normal, or above normal. Institutional normal ranges are 13.0–17.0 g/dL for males and 11.5–15.5 for females for hemoglobin, 3.70–11.00 k/μL for white blood cell count, 150–450 k/μL for platelet count, and 0.70–1.40 mg/dL for serum creatinine.

Standard descriptive statistics were used to describe characteristics of study patients. Logistic regression analysis was used to identify risk factors for bleeding, with results summarized as odds ratio (OR) and 95% confidence interval (CI). A stepwise selection procedure with a variable entry criterion of $P \leq 0.10$ and a variable retention criterion of $P \leq 0.05$ was used to identify a multivariable model; this model was confirmed with bootstrap analysis. In brief, 1000 samples of size 3358 were randomly selected with replacement from the study data and stepwise logistic regression analysis was performed on these samples. Variables that occurred in $> 50\%$ of these 1000 models were considered to be significant. BMI, laboratory, and cancer site were analyzed in univariate analysis using all categories, described above. In multivariable analysis, it was not possible to include all categories of significant variables based on the limited number of bleeding events so categories were combined as needed for parsimony. Specifically, cancer site was GI tract versus all other sites, reason for admission was anemia versus all other reasons, BMI was obese/class III versus all others ($\geq$ All statistical tests were two-sided; $P \leq 0.05$ indicated statistical significance. Data were analyzed using SAS software, Version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Study population

The study population comprised 3358 patients (Table 1). Of these, 1868 (56%) were male, median age was 62 (range, 19–98) years and 5% ($n = 144$) had BMI ≥ 40. A total of 2198 (65%) had solid tumors and 1160 (35%) patients had a hematologic malignancy. The most common primary sites for solid tumors included gastrointestinal tract ($n = 654$; 19%, including 6% colorectal cancer), lung ($n = 471$; 14%), breast ($n = 229$; 7%) and head and neck ($n = 159$; 5%). The most common hematologic malignancies included lymphoma ($n = 436$; 13%), leukemia ($n = 411$, 12%) and myeloma ($n = 250$; 7%). Reasons for admission were grouped into nine categories of which infection ($n = 663$; 20%) elective chemotherapy ($n = 589$; 18%), and gastrointestinal symptoms; excluding bleeding (468; 14%) were the most frequent. Median length of stay (LOS) was five days with a range of 0–152 days (Patients in observation for less than two nights, were classified as 0 admission days). Use of anticoagulation and antiplatelet medications occurred on day of admission in 67% ($n = 2258$) and 14% ($n = 474$) of patients respectively and increased to 79% ($n = 2659$) and 19% ($n = 642$) when including use anytime during admission. Amongst the patients categorized for admission with anemia 67% ($n = 445$) received anticoagulants on admission and 80% ($n = 528$) were taking them at any time during the admission. There was no statistical difference in the proportion of patients admitted for anemia