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Review Article

Laboratory biomarkers for venous thromboembolism risk in patients with hematologic malignancies: A review

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ABSTRACT

Introduction: Despite high rates of venous thromboembolism (VTE) among patients with hematologic malignancies, few tools exist to assist providers in identifying those patients at highest risk for this potentially fatal complication. Laboratory biomarkers, such as d-dimer, have demonstrated utility in some clinical settings to distinguish patients at increased risk.

Materials and methods: We performed a systematic review of the literature utilizing search terms including "biomarker", "venous thromboembolism", "hematologic malignancy", "lymphoma", "myeloma" and "leukemia" in the Medline database. A total of 25 studies investigating laboratory biomarkers of increased thrombotic risk in the setting of hematologic malignancy were identified and included in this review.

Results and conclusions: The most studied biomarkers, d-dimer and fibrinogen, demonstrated some degree of efficacy in identifying high-risk patients at levels > 4.0 mg/L or < 1.0 g/L respectively. Additional markers which demonstrated promise included thrombin generation, mean platelet volume, soluble VEGF, soluble P-selectin and extracellular vesicles. Other biomarkers reviewed, which did not consistently demonstrate significant associations with VTE included prothrombin fragments F1 + 2, factor VIII, protein C, protein S, von Willebrand antigen and activity, antithrombin, thrombin antithrombin complex, antiphospholipid antibody, plasminogen activator inhibitor, tissue factor pathway inhibitor and several variants associated with known hypercoagulable states (factor V Leiden, prothrombin gene variant, methylenetetrahydrofolate reductase variant). Data to support any of the biomarkers discussed here in routine clinical decision-making are currently lacking, but additional investigation in clinical studies, ideally in combination with clinical factors known to be associated with increased thrombotic risk, is warranted.

1. Introduction

Venous thromboembolism (VTE) is a common complication of the treatment of hematologic malignancy. Approximately 5% of adult patients with acute leukemia will experience VTE within 2 years of diagnosis [1]. A similar percentage of patients undergoing hematopoietic stem cell transplant (HSCT) will experience VTE within 180 days of transplant [2]. Despite these high rates, and the availability of potential interventions, such as low molecular weight heparin (LMWH) prophylaxis, we have few tools to predict which patients are at highest risk and might most benefit from such interventions. Furthermore, despite the associations between many therapies for hematologic malignancy (including asparaginase and immunomodulatory drugs (IMIDs) for myeloma) and VTE, tools to identify such risks in early stage trials are lacking. Clinical risk prediction models such as the Khorana score demonstrate utility in identifying patients in a general cancer population at elevated risk [3] but have not yet proven adequate to identify patients for whom there is a clear, beneficial intervention [4,5]. Furthermore this score is highly dependent on factors, such as leukocyte, hematocrit and platelet counts, which are uniquely affected and variable in this population.

A 2013 review of the use of laboratory biomarkers to predict VTE among patients with malignancy concluded that d-dimer and soluble P-selectin both demonstrated association with risk of VTE among patients

Abbreviations: VTE, venous thromboembolism; HSCT, hematopoietic stem cell transplant; LMWH, low molecular weight heparin; IMIDs, immunomodulatory drugs; AML, acute myeloid leukemia; IQR, interquartile range; TAT, thrombin antithrombin; FVII, factor VII; FVIII, factor VIII; CVC, central venous catheter; TFPI, tissue factor pathway inhibitor; VEGF, vascular endothelial growth factor; MPV, mean platelet volume; PAI, plasminogen activator inhibitor; MTHFR, methyletetrahydrofolate reductase; APL, acute promyelocytic leukemia; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; DVT, deep venous thrombosis

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with various malignancies and therefore might be useful for risk prediction [6]. Additional biomarkers, such as prothrombin fragments F1 + 2 [7], thrombin generation [8] and tissue factor microparticles [9] have also shown promise but have significant limitations, including variable sensitivity and specificity depending on tumor subtype [6]. Relatively few patients suffering from hematologic rather than solid tumor malignancy were included in such studies however and treatments for and outcomes in these diseases remain fundamentally different than those of solid tumors.

Hematologic malignancy patients experience a number of unique risk factors for both VTE and hemorrhage, including prolonged periods of thrombocytopenia, extended use of central venous access devices and the use of previously mentioned, unique chemotherapeutic or targeted agents associated with high risk of VTE. Additionally, hematologic malignancies have higher rates of association with abnormal states of coagulation, such as disseminated intravascular coagulation (DIC), suggesting that biomarkers of coagulation may perform differently in these patients [10]. Here we report the results of a systematic review of the literature for studies evaluating the use of laboratory biomarkers for prediction of risk of VTE specifically in patients with hematologic malignancy.

2. Methods

We searched Medline (inception to September 2017) for relevant articles. See Supplemental Materials for the full search strategy which included "venous thromboembolism", "biomarker", "hematologic neoplasm", "leukemia", "lymphoma", "multiple myeloma." Inclusion criteria were (1) research studies including patients with hematologic malignancy, (2) inclusion of at least one laboratory-based biomarker used prospectively for prediction of VTE. Articles were excluded if outcomes specific to hematologic malignancy patients were not reported or otherwise distinguished from solid tumor or non-cancer patients. Additional exclusion criteria included (1) case reports or series including < 5 patients, (2) non-English language (3) not in humans (including in vitro or animal model studies).

A total of 76 studies were identified with the initial search strategy. Sixty-three articles were excluded by abstract alone, 13 underwent full text review and six were included (Fig. 1). Reasons for exclusion included: review/guidelines only (13), in vitro/animal or other not in human study (2), hematologic malignancy patients not included/addressed separately (19), no VTE reported (1), case report/series only (14), biomarker measurements not used prospectively (18), non-English language (1) study retraction (1).

Following review of all included studies, separate searches of Medline were performed using the previous search criteria but replacing the term "biomarker" with specific terms for each biomarker identified on initial review. These terms included "d-dimer", "fibrinogen", "antithrombin", "F1", "Factor VII", "Factor VIII", "von Willebrand", "thrombin generation", "tissue factor plasminogen", "plasminogen activator inhibitor", "antiplasmin", "p-selectin", "VEGF", "platelet volume" and "extracellular vesicles". Nineteen additional studies which met criteria were identified by this method.

3. Results

We identified 18 potential groups of biomarkers addressed in 25 separate publications during literature review. The results of all 25 studies are included by study in Table 1. Here we discuss evidence by biomarker group.

3.1. D-dimer

Six identified studies reported VTE events in association with d-dimer levels. Four studies measured d-dimer at a baseline and evaluated for VTE at subsequent points during therapy. The largest study, performed by Libourel et al., included 404 patients with acute myeloid leukemia (AML). Hazard ratio (HR) for VTE among patients with d-dimer 0.5–4.0 mg/L and > 4.0 mg/L vs ≤ 0.5 mg/L were 5.58 (95% CI 0.62–49.97) and 32.05 (95% CI 3.58–286.83) ($p = 0.002$) respectively [11]. The second largest study utilized a subset of 111 patients from the Vienna Cancer and Thrombosis Study (CATS) with hematologic malignancies (lymphoma and multiple myeloma), including 8 patients who experienced VTE. Elevated d-dimer levels (> 1.4 mg/L, the 75th percentile) were found to be positively associated with an increased risk of VTE (HR 1.8, IQR 1.0–3.2) among all patients enrolled in this study. While results were not reported separately for patients with hematologic vs other malignancies, the findings did not change on multivariate analysis controlling for malignancy type (HR 1.8, IQR 1.0–3.2) [12].

A slightly smaller study, performed by Negaard et al., reported no association between d-dimer prior to treatment and VTE among a cohort of 93 patients with AML, chronic lymphocytic leukemia (CLL),

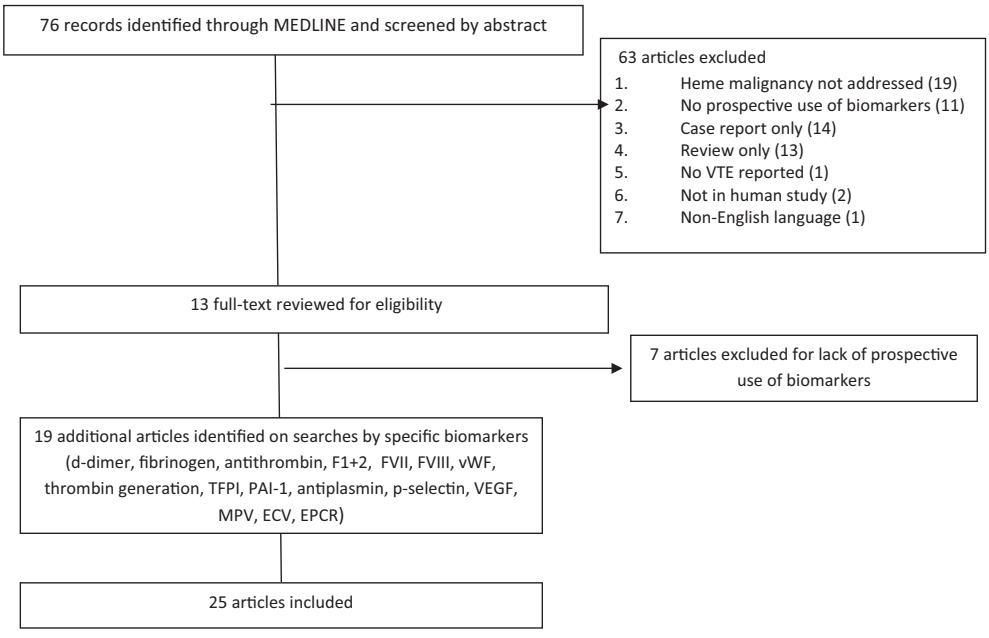

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of included and excluded studies.