Venous thromboembolism and mortality in patients with hematological malignancies

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ABSTRACT

Mortality and venous thromboembolism (VTE) are major risks for patients with hematological malignancies. However, they are commonly underrepresented in major clinical trials of VTE. Treatment decisions are further complicated by the unique characteristics they frequently exhibit, such as thrombocytopenia. In addition to discussing treatment challenges, knowledge gaps, and future directions, our goal in this narrative review is to provide an overview of the epidemiology and risk factors of mortality in patients with hematological malignancies and VTE.

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Introduction

Malignancy is a known strong risk factor for venous thromboembolism (VTE). Hematological malignancies (HM) include a variety of distinct types, such as acute or chronic leukemia, lymphoma, multiple myeloma (MM), and myeloproliferative neoplasms (MPNs). HM frequently carry special characteristics such as thrombocytopenia that can complicate treatment decisions of VTE and increase rates of treatment-related adverse events (*e.g.*, anticoagulant-related major bleeding).

With advances in anticancer and supportive care therapies, survival in patients with HM is rising.[1,2] In some HM (*e.g.*, lymphoma), non-cancer causes of death are surpassing those of cancer-related deaths.[3] Of secondary causes of death in cancer patients in one study, thromboembolism was noted to be the leading cause accounting for 9.2% of all deaths.[4] Thus, the interplay between VTE and mortality in this high-risk population is worth exploring. In this narrative review as an accompanying paper of the 12th International Conference on Thrombosis and Hemostasis Issues in Cancer Congress 2024, we intend to summarize some of the available literature on VTE and mortality in patients with hematological malignancy, highlight the knowledge gaps and future research directions. As MPNs have distinct characteristics including thromboembolism as a hallmark of the disease, directly related to the associated pathological mutation (*i.e.*, JAK2 V617F mutation), which affects disease management strategies and likely mortality, we elected to exclude MPNs in the current review as it deserves its own discussion.

Mortality and venous thromboembolism in hematological malignancies

Numerous studies have demonstrated an increased risk of mortality in patients with cancer and VTE *vs*. those with cancer without VTE. The association with mortality is higher when VTE is diagnosed concurrently with cancer diagnosis (as compared to VTE diagnosed after cancer). In a population cohort study using the Danish healthcare registry, the 1-year mortality rate was high

at 68% in patients with VTE diagnosed at the time of cancer diagnosis, 4-fold higher compared to a matched cohort of newly diagnosed cancer without VTE [38%, mortality rate ratio (MRR) 4.34, 95% confidence interval (CI): 3.95-4.78].[5] VTE diagnosed after cancer was also associated with a 3-fold higher risk of mortality (45% *vs*. 17%, MRR 3.48, 95% CI: 3.37-3.60).

Whilst much data shows the risk of death is higher in patients with cancer and VTE, the direct causation of VTE with mortality in these patients remains debated. Historically, progression of the underlying malignancy has been demonstrated to be the leading cause of death in patients with cancer. In a prospective, observational study by Khorana *et al.*, progression of the underlying cancer was the leading cause of death (70.9%) in ambulatory cancer patients receiving chemotherapy, followed by thromboembolism (9.2% total; arterial 5.6%, venous 3.5%) and infection (9.2%).[4] A more recent systematic review and meta-analysis including data from 29 studies (N=8000 patients) showed a combined all-cause mortality of 28.8%, with cancer progression accounting for 82.9% of all deaths.[6] With death from cancer as the leading cause of death for most cancers, VTE occurrence may be a surrogate for more aggressive cancer and the mortality may be related to such.

A higher association between aggressive cancer histology and VTE has been demonstrated and is significant in patients with HM. In a recent cohort study of more than 400,000 United States (US) veterans diagnosed with cancer between 2006 and 2021, 10% of the cohort (n=40,010) had a diagnosis of HM.[7] The cancer type with the highest 12-month cumulative incidence of VTE in the cohort was acute lymphoblastic leukemia (ALL) (18.6%). Overall, the aggressive-type HM had higher 12-month cumulative incidences of VTE [*i.e.*, ALL 18.6%, aggressive non-Hodgkin's lymphoma (NHL) 11%, Hodgkin's lymphoma (HL) 9.5%, MM 7.7%, and acute myelogenous leukemia (AML) 7.3%] when compared to more indolent HM types [*i.e.*, indolent NHL 4.5%, myelodysplastic syndrome (MDS) 2.7%, chronic myelogenous leukemia (CML) 2.1%, and chronic lymphocytic leukemia (CLL) 2.0%]. In multivariable analysis adjusting for baseline demographics, VTE risk factors, cancer type (reference = prostate cancer), anticoagulant or antiplatelet therapy, cancer stage, and cancer therapy, the hazard of VTE remained increased for the aggressive HM: ALL [hazard ratio (HR) 4.98, 95% CI: 3.71-6.68], aggressive NHL (HR 2.65, 95% CI: 2.43-2.89), AML (HR 2.10, 95% CI: 1.82-2.41), HL (HR 2.00, 95% CI: 1.68-2.38), MM (HR 1.72, 95% CI: 1.57-1.87) and was lower for more indolent HM: indolent NHL (HR 1.38, 95% CI: 1.26-1.51). Patients with CLL, MDS, and CML had a reduced hazard of VTE (compared to prostate cancer), with HR of 0.77, 0.76, and 0.57, respectively. These findings provide support for the relation between aggressive HM histology and VTE with mortality and call for continued attention to thromboembolism in HM and understanding of the role of VTE in death in this patient population.

In the aforementioned Danish cohort study, less than 10% of patients included had a diagnosis of HM; however, when focusing on patients with HM, the 1-year MRR increased beyond that of the full cohort (MRR 11.37-38.02 in patients with lymphoma and leukemia who presented with VTE concurrently with cancer diagnosis compared to 4.34 in the cohort at large).[5] Given the higher rate of mortality in patients with HM and VTE and the association of aggressive HM histology with VTE, histology-specific studies are needed to determine the exact role of VTE in mortality in these patients. We highlighted the pertinent data specific to cancer types below focusing on multiple myeloma, lymphoma, and acute leukemia given the higher incidence of VTE in these HMs (Table 1). Given the lower risk of VTE in some HM (*e.g.*, CLL, MDS, and CML), there is a paucity of data on the associated morbidity and mortality and future studies are needed. Finally, as monoclonal gammopathy of undetermined significance is a precursor state, it was not included in this narrative review.

Table 1. Incidence of venous thromboembolism and mortality in patients with hematologic malignancy and venous thromboembolism.

Type of malignancy/reference	12-month Cumulative incidence of VTE after cancer diagnosis, N, % (95% CI) 12-month		Hazard/risk of death in patients with VTE *vs.* no VTE, risk, (95% CI)
Leukemia*[45]	N=14,841	1.7 (1.5-2.0)	aHR 1.41 (1.01, 1.98)*
ALL[7,17]	N=193	18.6 (NR)	aHR 0.87 (0.83-0.91)*
AML[7,16,17]	N=2,657	7.3 (NR)	aHR 1.42 (1.13, 1.80)*
CLL[7]	N=6,486	2.0 (NR)	
CML[7]	N=3,840	2.1 (NR)	
HL[7,45]	N=1,129	9.5 (NR)	
	N=2,459	3.8 (3.1-4.6)	
NHL[12,45]	N=18,473	3.2 (3.0-3.5)	
Indolent NHL[7]	N=8,987	4.5 (NR)	HR 1.7 (1.5-1.9)#
Aggressive NHL[7]	N=5,351	11.0 (NR)	
MDS[7]	N=4,897	2.7 (NR)	
MM[7,45]	N=6,470	7.7 (NR)	aHR 1.66 (1.19-2.33)^
	N=6,693	3.8 (3.4-4.3)	aHR 2.9 (2.4-3.5)^
			HR 2.27 (1.26-4.08)^

*Not specified; #6-month risk; ^12-month risk. VTE, venous thromboembolism; CI, confidence interval; aHR, adjusted hazard ratio; HR, hazard ratio; NR, not reported; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoblastic lymphoma; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma.

Multiple myeloma

The available data on patients with MM is controversial. In a large retrospective cohort study of US veterans with newly diagnosed MM between 2006 and 2014, diagnosis of VTE was associated with a 2-fold increased risk of death at 6-months [adjusted hazard ratio (aHR) 2.31, 95% CI: 1.52-3.51] with risk persisting at 12-months (aHR 1.66, 95% CI: 1.19-2.33).[8] Findings were similar in the Swedish Cancer Registry where patients with MM and VTE had a 3-fold increase in risk of death at 12 months compared to those without VTE (aHR 2.9, 95% CI: 2.4-3.5).[9] However, for patients eligible for and treated in the randomized control (RCT) myeloma IX and XI trials, there was no association between the development of VTE and the risk of death.[10] It is unclear if this discrepancy between real-world data and that of the RCT is related to additional patient- or disease-related factors (*e.g.*, medical comorbidities, therapeutic intensity, *etc.*), or follow-up durations. In a systematic review and meta-analysis which included these 3 studies in addition to 6 others for a total of 38,047 patients, VTE was associated with a 2-fold increased risk of early mortality (HR 2.27, 95% CI: 1.26-4.08) in 3 studies and decreased overall survival in 3 studies (HR 0.79, 95% CI: 0.64-0.98) (a fourth study was excluded for heterogeneity).[11]

Lymphoma

In a retrospective study of 16,755 patients with NHL, acute VTE was associated with a 70% increase in the risk of death at 6 months (HR 1.7, 95% CI: 1.5-1.9) after adjusting for stage, comorbidities, age, and histopathology (*i.e.*, intermediate- or aggressive lymphoma).[12] Similarly, in HL, the presence of VTE was associated with increased mortality (32.3% *vs*. 5.9%, P<0.001); however, on examination of the causation of death in patients with VTE, all deaths were attributed to either infectious etiologies due to treatment or progression of the underlying lymphoma.[13] In primary central nervous system lymphoma, the 12-month cumulative incidence of VTE and major bleeding were high, 13.6% and 12.4%, respectively.[14] Pulmonary embolism (PE) [+/- deep vein thrombosis (DVT)] and major bleeding were both associated with significantly increased risks of mortality (HR 1.61 and HR 2.36, respectively).

Acute leukemia

Most studies focused on acute leukemia did not find an increased risk of mortality in patients with VTE and acute leukemia compared to those without VTE. In a cohort of 1088 patients with ALL from SEER-Medicare data, risk factors for VTE included kidney disease, heart failure, use of central venous catheters, and chemotherapy. Diagnosis of VTE was not associated with an increased hazard of death in the overall cohort, or when separating patients by ALL treatment status. Conversely, VTE appeared protective against the hazard of death in patients with ALL on chemotherapy-sparing treatment (*i.e.*, tyrosine kinase inhibitors) in adjusted analysis.[15] Findings for patients with AML within the SEER-Medicare data were similar to those with ALL with no increase in the hazard of death in patients with VTE. In adjusted analysis that accounted for AML treatment, VTE was associated with a 13% decreased risk of all-cause mortality.[16] The high mortality rate from acute leukemia itself could contribute to these findings (*i.e.*, the competing risk of death from acute leukemia prior to the development of VTE). However, another population-based cohort study that focused on VTE in acute leukemia did find an association between VTE and an increased hazard of mortality.[17] In this study, the outcome of interest focused on leukemia-specific mortality while censoring patients at the time of death for non-leukemia-related causes of death. In the adjusted analysis for AML (N=3252), both upper extremity (UE) DVT and PE +/- lower extremity DVT were associated with an increased risk of AML-specific death (aHR 1.42 for both, P 0.001 and P 0.003, respectively). Similar results were noted in the cohort of patients with ALL (N=1820). UE DVT was associated with an 80% increase in risk of ALL-specific death (aHR 1.80, P=0.0003), and PE +/- lower extremity DVT was associated with a 41% increase in risk of ALL-specific death (aHR 1.41, P=0.04).

Mortality associated with non-cancer causes

While available histology-specific studies provide mixed results, contemporary results may be changing. Some data shows that as survival for cancer increases, secondary causes of death (*i.e.*, non-cancer-related deaths) are rising and may replace cancer as the leading cause of death. In a study assessing trends in death from index cancer *vs*. secondary causes for patients diagnosed with cancer between 1973 to 2012, patients with lymphoma (NHL or HL) had significant declines in death from their index cancer.[3] Death due to index cancer decreased from >60% at study start to ≤40% in 2012. Accordingly, deaths from secondary causes outnumbered deaths from index cancer by 2012. Declines in death from MM were also noted in the study, however, death from MM remained the leading cause of death in these patients. In a similar study assessing causes of death in a combined cohort of solid and hematological cancers over a 40-year period, secondary (non-cancer) causes of death increased from 20% for persons diagnosed with cancer between 1975 and 1979 to 26% for those diagnosed between 2010 and 2014.[18] Of the secondary causes of death, "diseases of heart" was most common, with this category including PE. Ongoing research is needed to determine the contemporary mortality burden of VTE and VTE treatment in patients with HM.

Mortality associated with types of venous thromboembolism

Many studies assessing the association between VTE and mortality in HM combine VTE subtypes into a single category including all events within the definition of VTE (*e.g.*, UE DVT, lower extremity DVT, and PE), with some studies also including splanchnic vein thromboses in the definition of VTE. However, the risk of death with location of VTE may differ, especially for UE DVT where the risk of PE is known to be less than that of lower extremity DVT.[19] When focusing on VTE subtypes in the Danish cohort, patients diagnosed with PE had worse survival compared to those diagnosed with extremity DVT, with higher 1-year mortality rates and MRRs, regardless if PE was diagnosed concurrently with cancer or after.[5] For example, patients with PE diagnosed concurrently with cancer had a 1-year mortality rate as high as 73% (matched control 39.3%), as compared to 60.9% in those with DVT (matched control 37.3%). This indicates that at least in some patients, VTE (*i.e.*, PE) directly contributed to the poor outcome, which could be related to the PE itself, the need

for hospitalization for VTE and/or interruption of anticancer therapies, or complications related to treatment (*i.e.*, anticoagulant-related major bleeding). The high risk of death attributable to PE was demonstrated in the RIETE registry where PE-related death was a leading cause of 3-month mortality, second only to death from cancer itself in a cohort of 1,605 patients with cancer.[20]

Up to 50% of VTE events in patients with HM are due to UE thromboses, often due to the frequent use of central venous catheters in this patient population.[7] Despite the common occurrence, management of catheter-associated VTE in patients with cancer remains controversial as this patient population is largely excluded from the pivotal RCTs.[21] Therefore, high-quality evidence to guide the optimal management of catheter-related UE DVT, including the type and duration of anticoagulant therapy variable, is lacking.[22,23] Fortunately, as noted above, risks of PE are less with UE DVT (compared to lower extremity DVT) and mortality is rarely reported or noted to be directly related to catheter-related UE DVT alone. Accordingly, in the aforementioned study of UE DVT and acute leukemia, the presence of UE DVT (all patients were presumed to have central venous catheters) was associated with an increase in leukemia-specific mortality in both ALL (aHR 1.80; 95% CI: 1.31-2.47, P=0.0003) as well as AML (aHR 1.42; 95% CI: 1.16-1.73, P=0.001) patients after adjusting for the presence of confounders including PE.[17] However, the investigators were unable to quantify deaths directly attributable to VTE and/or VTE-directed treatment. In fact, the presence of a UE DVT was associated with an increased risk of subsequent bleeding for both patient populations ALL (aHR 1.62; 95% CI: 1.02-2.57, P=0.04) and AML (aHR 2.07; 95% CI: 1.60-2.68, P=<0.0001). Future well-designed studies are needed for catheter-related VTE therapy in patients with cancer.

Mortality associated with treatment of venous thromboembolism

Mortality during treatment of cancer-associated VTE can be related to recurrent VTE or anticoagulation-related bleeding. Patients with cancer have a 3- to 7-fold increased risk of recurrent VTE despite anticoagulant therapy compared to non-cancer counterparts.[24] In addition, cancer patients have a 2-fold increased risk of major hemorrhage on anticoagulant therapy compared to non-cancer patients.[25] Analysis of the RIETE registry showed that within the first 12 months of diagnosis of cancer-associated VTE, fatal PE was the second leading cause of death while major bleeding was the 4th most common.[26] In the CATCH trial, a RCT comparing low molecular weight heparin (LMWH) *vs*. vitamin K antagonist in patients with active cancer, most deaths were related to the progression of cancer (69%) as previously discussed.[27] However, of the remaining 31% causes of death, almost half were related to treatment of or recurrence of VTE (12.5% and 2.1% were caused by fatal recurrent PE and anticoagulant-related bleeding, respectively).[27] Similarly, a systemic review and meta-analysis of patients with cancer-associated VTE found that the case fatality rate of recurrent VTE in the oncology population was high at 14.8%, while the case fatality rate of anticoagulant-related major bleeding events was 8.9%.[6] Given the high case-fatality rates of recurrent VTE and anticoagulant-related bleeding, optimal management of VTE in cancer remains an active area of need.

While the focus of this review is not on thrombocytopenia in HM, this topic warrants discussion as thrombocytopenia is a major risk factor for anticoagulant-related bleeding (and thus, bleeding-related death) and may significantly contribute to mortality in patients with HM and VTE. Compared to solid tumors, the prevalence of thrombocytopenia in HM is also higher, with longer durations and severity of thrombocytopenia. This likely results from the disease-based marrow involvement and as toxicity from cancer-directed therapy (*e.g.*, high-dose chemotherapy). In a retrospective cohort study of 3,549 patients with active cancer and newly diagnosed VTE, thrombocytopenia (defined as platelet count $<100´10^9$/L) was present in 47% of patients with HM (n=647), as compared to 22% of patients with solid cancers (n=2,902).[28] Furthermore, 30% of patients with HM had a platelet count $<50´10^9$/L compared to only 7% of those with solid cancers. The presence of thrombocytopenia complicates VTE treatment decisions. In a prospective observational study (TROVE study) of 121 patients with active cancer with newly diagnosed VTE and thrombocytopenia (platelet count $<100´10^9$/L), 70% of enrolled patients had an underlying HM.[29] Patients treated with full-dose anticoagulant therapy had a higher risk of major bleed compared to those treated with modified-dose anticoagulant therapy (12.8% *vs*. 6.6%, Fine and Gray HR 2.18, 95% CI: 1.21-3.93), including one fatal hemorrhagic event *vs*. zero fatal events, respectively. Another prospective cohort study (CAVEaT study) included 105 patients with HM, new VTE, and platelet count $<50´10^9$/L).[30] Within 28 days, the mortality rate was high at 15%, while 8% of patients experienced VTE recurrence or progression, and 7% had major bleeding.

These studies provide a rationale for high-quality data from prospective RCTs to provide better guidance for the treatment of cancer-associated VTE in the setting of concurrent thrombocytopenia. A pilot RCT – START (STrategies for Anticoagulation in patients with thRombocytopenia and cancer-associated Thrombosis) (NCT05255003) – is currently underway to evaluate the feasibility of conducting such a trial, as well as the efficacy and safety of different management strategies in this setting. Based on the limited evidence currently available, the International Society on Thrombosis and Haemostasis and the European Hematology Association proposed guidance for the management of VTE in patients with cancer and thrombocytopenia, including those with HM (Figure 1).[31,32] In general, full-dose LMWH is recommended for patients with platelet counts of $\geq$40-$50´10^9$/L while anticoagulation dose modifications are recommended for platelet counts of 25 to 40-$50´10^9$/L, depending on the acuity and severity of VTE. The adoption of these or similar treatment strategies within clinical practice has resulted in variable VTE-related outcomes.[33]

With the case fatality rate of recurrent VTE being higher than that of anticoagulant-related bleeding in patients with cancer,[6] optimal anticoagulant strategies have been studied in large RCTs. To date, six randomized studies have been published assessing the treatment of cancer-associated VTE with direct oral anticoagulation (DOAC) *vs*. LMWH.[34-39] Meta-analysis of these studies found that treatment of cancer-associated VTE with DOAC is associated with a decrease in risk of recurrent VTE [risk ratio (RR) 0.67, 95% CI: 0.52-0.85].[40] However, the use of DOAC is associated with a significant increase in the risk of clinically relevant non-major bleeding (RR 1.66, 95% CI: 1.31-2.09) and a trend towards increased risk of major bleeding (RR 1.17, 95% CI: 0.82-1.67). While findings from these studies guide current practice, insight into the significance for patients with HM is lacking. Of the 3,703

patients enrolled in these trials, less than 10% (n=315, 8.5%) had a HM as their qualifying cancer. In addition, most of the trials did not report HM-specific outcomes (Table 2). Accordingly, treatment of cancer-associated VTE in HM relies on extrapolating findings from these trials that were predominately focused on patients with solid tumors.[41-43] Given the sparse data and unique treatment considerations (*i.e.*, thrombocytopenia) in patients with HM, and the potential implications on mortality, studies are urgently needed to improve outcomes and reduce VTE-associated mortality in this growing patient population.

Table 2. Representation of hematologic malignancies in randomized control trials comparing direct oral anticoagulants to low molecular weight heparin for acute venous thromboembolism in cancer (Table modified from Wang *et al.*, 2022).[44]

Randomized trials	Hokusai VTE cancer*	Select-D	ADAM VTE	Caravaggio	CASTA-DIVA	CANVAS
N, total participants	1046	406	300	1155	158	638^
N, HM (%)	111 (10.6%)	31 (7.6%)	28 (9.3%)	85 (7.4%)	13 (8.2%)	47 (7.4%)
Recurrent VTE (DOAC *vs.* LMWH)	2/56 (3.6%) *vs.* 4/55 (7.2%) Risk difference: 3.7%, 95% CI: -13.9% to 6.5%	N/A	NR	2/33 (6.1%) *vs.* 2/52 (3.8%)	NR	NR/24 *vs.* NR/23 Risk difference: -4.3%, 95% CI: -12.6% to 4.0%
Major bleeding (DOAC *vs.* LMWH)	1/56 (1.8%) *vs.* 2/55 (3.6%) Risk difference: 1.9%,95% CI: -9.7% to 6.0%	0/14 *vs.* 0/17	NR	0/33 *vs.* 0/52	NR	NR
CRNMB (DOAC *vs.* LMWH)	NR	2/14 (14.3%) *vs.* 0/17	NR	NR	NR	NR

*Hokusai reported on 12 months follow-up while the remaining studies report on 6 months follow-up; ^Randomized cohort data presented. VTE, venous thromboembolism; HM, hematological malignancies; DOAC, direct oral anticoagulants; CI, confidence interval; LMWH, low molecular weight heparin; NR: not reported; CRNMB, clinically relevant non-major bleeding.

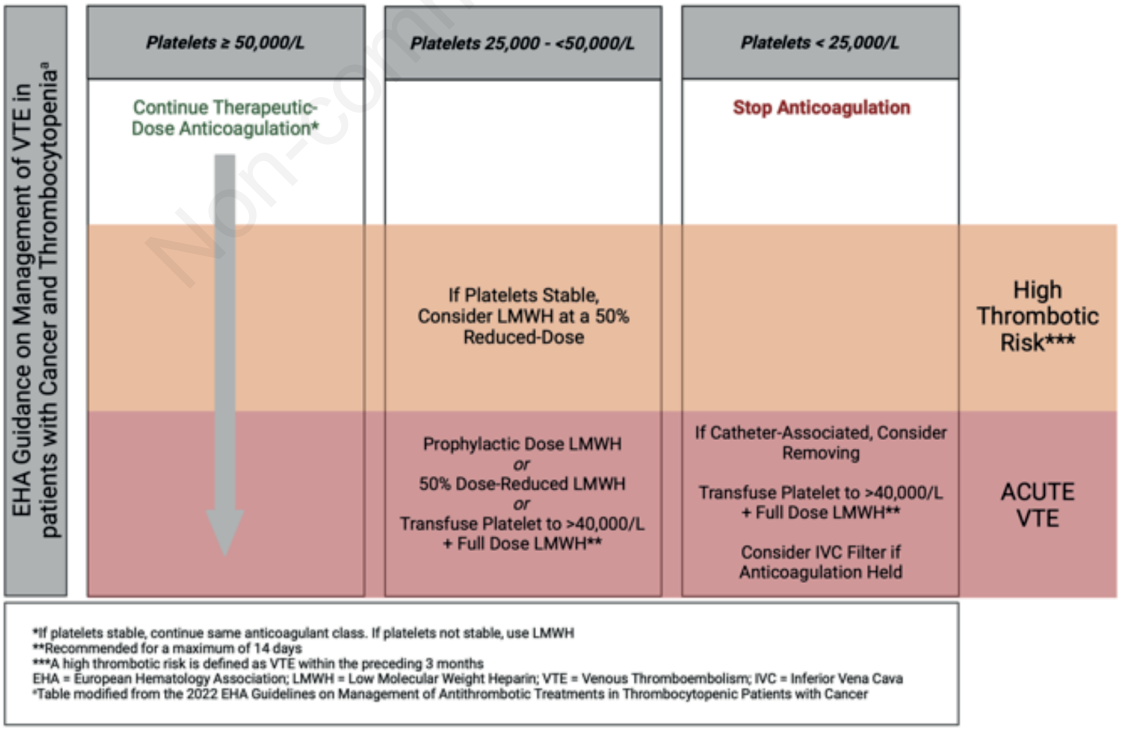

Figure 1. European Hematology Association guidance on management of venous thromboembolism in patients with cancer and thrombocytopenia.[31] Created with BioRender.com.

Conclusions

Patients with HM have unique characteristics and challenges that can contribute to their risks of VTE, VTE-related treatment complications (*i.e.*, recurrent cancer-associated VTE and anticoagulant-related bleeding), and mortality. However, these patients are commonly under-represented in cohort studies and clinical trials assessing outcomes. Future studies focusing on this high-risk population are needed.

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