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Mohammad Faizan Zahid
Aga Khan University

M Hassan Murad

Mark R. Litzow
Hogan

William J. Hogan

Mrinal S. Patnaik

See next page for additional authors

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Authors

Mohammad Faizan Zahid, M Hassan Murad, Mark R. Litzow, William J. Hogan, Mrinal S. Patnaik, Alok Khorana, Alex C. Spyropoulos, and Shahrukh K. Hashmi

Venous thromboembolism following hematopoietic stem cell transplantation—a systematic review and meta-analysis

Mohammad Faizan Zahid¹ · M. Hassan Murad^{2,3,4} · Mark R. Litzow⁵ · William J. Hogan⁵ · Mrinal S. Patnaik⁵ · Alok Khorana⁶ · Alex C. Spyropoulos⁷ · Shahrukh K. Hashmi⁵

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Abstract Venous thromboembolism (VTE) is a common complication of hematopoietic stem cell transplantation (HSCT). Graft-versus-host disease (GVHD) is another complication of HSCT that may modify the risk of VTE. Our objective was to explore the incidence of VTE (deep venous thrombosis and pulmonary embolism) following HSCT and to evaluate its association with GVHD. A comprehensive search of Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus was conducted to search for both retrospective and prospective HSCT studies which had reported VTE. Random-effects meta-analysis was used to pool incidence rates. We included 17 studies reporting on allogeneic- and 10 on autologous-HSCT; enrolling 6693 patients; of which 5 were randomized. The overall incidence of

VTE after HSCT was 5 % (4–7 %). Incidence in allogeneic-HSCT was 4 % (2–6 %) and in autologous-HSCT was 4 % (1–15 %). Eleven and nine studies reported data on acute and chronic GVHD, respectively. The incidence of VTE in chronic GVHD was 35 % (20–54 %), whereas in acute GVHD it was 47 % (32–62 %). Based on the results of this meta-analysis, VTE is a fairly common complication after HSCT, emphasizing the importance of assimilating guidelines for both treatment and prophylaxis in this patient population.

Keywords Venous thromboembolism · Deep venous thrombosis · Pulmonary embolism · Bone marrow transplantation · Hematopoietic stem cell transplantation · Complication

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✉ Shahrukh K. Hashmi
Hashmi.Shahrukh@mayo.edu

- ¹ Medical Graduate, Aga Khan University, Karachi, Pakistan
- ² Evidence-Based Practice Program, Mayo Clinic, Rochester, MN, USA
- ³ Center for the Science of Healthcare Delivery, Mayo Clinic, Rochester, MN, USA
- ⁴ Division of Preventive, Occupational, and Aerospace Medicine, Mayo Clinic, Rochester, MN, USA
- ⁵ Mayo Clinic Transplant Center, Blood and Marrow Transplant Program, Mayo Clinic, Rochester, MN, USA
- ⁶ Taussig Cancer Institute, Department of Hematology and Oncology, Cleveland Clinic, Cleveland, OH, USA
- ⁷ Hofstra-North Shore LIJ School of Medicine, Manhasset, NY, USA

Introduction

Hematopoietic stem cell transplantation (HSCT) is the standard of care in a variety of benign and malignant hematologic disorders and is being employed at an increasing frequency in the last two decades [1].

Recent studies have recognized that thromboembolic complications, such as venous thromboembolism (VTE), are a serious cause of morbidity and mortality in HSCT patients [2–5]. Recipients of HSCT are prone to develop VTE due to several risk factors. These include underlying cancer, indwelling central venous catheters, hospital admission leading to prolonged periods of immobility, cytotoxic chemotherapy or radiation therapy as preparative regimens, infections, and graft-versus-host disease (GVHD) [2, 3].

Hepatic sinusoidal obstruction syndrome (SOS) and thrombotic microangiopathy (TMA) are well-known thrombotic complications following HSCT [6, 7]. SOS is usually related to high-dose cytotoxic chemotherapy, as is used in

myeloablative conditioning regimens [8], while TMA can be associated with the use of calcineurin inhibitors, sirolimus, and rarely GVHD [9, 10]. However, the incidence and risk factors for VTE following HSCT are not well defined. HSCT patients are also at an increased risk of bleeding following transplant [1, 2], which has been associated with a shorter survival in such patients [11]. Consequently, clinicians face a difficult choice regarding VTE prophylaxis in HSCT patients and lack sufficient information to make informed decisions. There is little information regarding appropriate therapeutic and prophylactic approaches to VTE in this complex patient population. The incidence of VTE in HSCT has been reported with variable frequencies, ranging from 0.5 % to as high as 23.5 % [12, 13].

Given the increasing recognition of the endothelial form of GVHD resulting in an increase in cardiovascular complications, we hypothesized that VTE incidence would be heightened in patients suffering from GVHD [14].

Thus, we performed a systematic review and meta-analysis to assess the overall incidence of VTE following HSCT, including deep venous thrombosis (DVT) and pulmonary embolism (PE). We also assessed the likelihood of VTE following allogeneic-HSCT and autologous-HSCT, separately.

Materials and methods

This systematic review and meta-analysis is reported following criteria set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (<http://www.prisma-statement.org>) [15].

Eligibility criteria

Types of studies We searched literature databases for clinical trials as well as prospective and retrospective observational studies with patients receiving allogeneic- and/or autologous-HSCT. Studies reporting the outcome and complications in these patients (venous thrombosis alone or in addition to other complications of HSCT) were included.

Types of participants We included all patients receiving either allogeneic- or autologous-HSCT for treatment. There were no restrictions in regards to age, ethnicity, gender, or underlying disease for which HSCT was being performed.

Types of outcome measures The primary outcome was the development of thrombosis in the venous system after the infusion of hematopoietic stem cells following pre-transplant conditioning chemotherapy. This included upper and lower extremity DVT, PE, thrombosis in veins related to internal organs (e.g., hepatic vein, internal jugular vein, etc.), and

thrombosis associated with indwelling catheters used during the transplantation process.

Exclusion criteria The exclusion criteria are as follows: (1) case reports, case series and studies with patient population of <5 (to avoid statistical skewing of the results); (2) studies involving patients that do not represent typical HSCT patients (e.g., involving the use of erythropoiesis-stimulating agents, immunotherapy, or other interventions that are not typically used simultaneously with HSCT, immunotherapy with subcutaneous IL-2 after transplant, multiple myeloma patients who had relapsed disease after getting allogeneic-HSCT and were getting lenalidomide as salvage treatment, multiple myeloma patients getting thalidomide immediately after getting auto-transplant, etc.); (3) review articles and studies in which patients who developed VTE after HSCT were not quantifiable; (4) studies describing thrombotic complications other than VTE, e.g., SOS or arterial thrombosis; (5) autopsy studies reporting VTE in HSCT patients (to maintain uniformity); (6) studies reporting only catheter-related thrombosis; and (7) studies describing VTE in patients prior to HSCT or in non-HSCT patients.

Information sources and search strategy

A comprehensive search of several databases from each database's earliest inception to June 2014, in any language, was conducted. The databases included Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of VTE in bone marrow transplantation. The actual strategy is available in [Appendix](#).

Study selection and data collection

Two investigators (SKH and MFZ) independently screened all studies by reviewing titles and abstracts. Potentially relevant studies were retrieved as full text articles. All full text articles were screened again in duplicate following the same inclusion criteria. In case of any disagreement in regards to inclusion of a study, this was discussed with a third investigator (MSP). All studies were critically appraised in regards to relevance and validity for inclusion in this systematic review or for further exclusion. Data were collected for the variables described in data items below and recorded in an excel sheet.

The following data were extracted from each study: author, year of publication, total study population, indication for HSCT, type of HSCT (allogeneic vs. autologous), total incidence of VTE, and type of VTE (PE, DVT, catheter-related thrombosis, etc). Our primary outcome was the occurrence of

first VTE. We defined VTE as thrombosis involving the deep veins of any extremity detected by any standard radiologic means.

Study quality appraisal (risk of bias)

The Cochrane Collaboration's tool for assessing risk of bias was used for quality appraisal of randomized studies [16] (Table 1). We used the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies [21] (Table 2).

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis Version 2.0 (Englewood, NJ). We used the random-effects model to pool outcomes across studies due to anticipated heterogeneity. Outcome measure was evaluated as cumulative incidence (i.e., event rate). Subgroup analyses were undertaken based on (a) allogeneic vs. autologous transplants, (b) presence of GVHD, and (c) type of GVHD, i.e., acute vs. chronic.

Results

Electronic search yielded 755 articles (Fig. 1) out of which only 146 articles were relevant to the study question. Many studies reported patients that developed VTE after HSCT, but the incidence could not be quantified so they were excluded. Thrombotic complications other than VTE, e.g., SOS or arterial thrombosis ($n=13$), were excluded. However, if they had also reported VTE incidences, then the VTE numbers were included in the analysis. Studies reporting VTE in HSCT patients prior to stem cell infusion or in non-HSCT patients ($n=18$) were also excluded. Some studies ($n=4$) had reported postmortem finding of VTE and they were excluded. Only 23 studies fulfilled the strict inclusion criteria and were included in the statistical analysis. The randomized trials and the observational studies had moderate risk of bias, overall.

Twelve studies in allogeneic-HSCT yielded an incidence rate of 4 % (95 % CI 2–6 %) with significant heterogeneity ($I_2=80$). Six studies in autologous-HSCT yielded a similar incident rate of 4 % (95 % CI 1–15 %) with significant heterogeneity ($I_2=89$). Five studies with patients undergoing both autologous- and allogeneic-HSCT yielded an incident rate of 6 % (4–9 %) with significant heterogeneity ($I_2=93$). There was no significant difference in the incidence of VTE between allogeneic- and autologous-HSCT ($p=0.94$). Overall VTE incidence from 23 studies was 5 % (4–7 %).

When we analyzed the GVHD data with respect to VTE incidence, 11 studies reported data on acute GVHD in which the incidence of VTE was found to be very high at 47 % (95 % CI 32–62 %) with significant heterogeneity ($I_2=98$). The

incidence of VTE in chronic GVHD from nine studies was also found to be very high at 35 % (95 % CI 20–54 %) indicating a possibly strong association with GVHD.

Discussion

We conducted a systematic review and meta-analysis of studies evaluating VTE after HSCT. We found that VTE is fairly common with an overall incidence of 5 %. In patients with GVHD, the risk was much higher. The certainty in these estimates is limited due to the presence of heterogeneity that remained unexplained and likely reflects differences in outcome surveillance and ascertainment as well as heterogeneity in the population's other risk factors for VTE.

Clinically apparent VTE occurs in up to 10 % of patients with active cancer [33], and many algorithms exist which can predict the risk of cancer thrombosis among which the Khorana model is regarded as the gold standard [34]. No such model exists for HSCT patients due to the absence of data on the risks and outcomes of VTE in this population. Theoretically, HSCT survivors who do not have any relapses of cancer should not have an elevated risk of VTE unless other known risk factors are present or new factors are acquired. A well-known non-relapse risk factor of VTE in HSCT patients is the presence of central venous catheters which are inserted in majority of the patients undergoing HSCT [2, 3, 32]. Some studies have indicated HSCT-associated VTE incidences of 0.5 % [13], whereas other studies have indicated an incidence as high as 23.5 % [12] post-HSCT. To delineate the totality of evidence of VTE risks and outcomes in HSCT population, we undertook this meta-analysis.

Our meta-analysis of both observational studies and randomized clinical trials showed that the overall risk of VTE post-HSCT was similar to that described by Gerber et al. [2]. We found no significant difference between allogeneic- and autologous-HSCT for VTE occurrence. However, when we undertook the analysis of GVHD with VTE, a significantly high risk of VTE was observed both in acute and chronic GVHD of 47 and 35 %, respectively.

Besides being the first meta-analysis on the risk of VTE in HSCT patients, this analysis separates out the risk of provoked (line associated) vs. unprovoked VTE. We did a comprehensive qualitative assessment of the prospective randomized studies included in our meta-analysis using Cochrane Collaboration's tool for assessing risk of bias. Our strict selection criteria excluded VTE post-HSCT in the patients with pre-existing hypercoagulable states. We did the analysis based on both chronic and acute GVHD for VTE incidence to ascertain a possible association of GVHD with VTE.

In 1856, Virchow proposed a triad of causes for venous thrombosis, postulating that stasis, changes in the vessel wall, or changes in the blood could lead to thrombosis. GVHD can

Table 1 Randomized studies reporting venous thromboembolism after hematopoietic stem cell transplantation

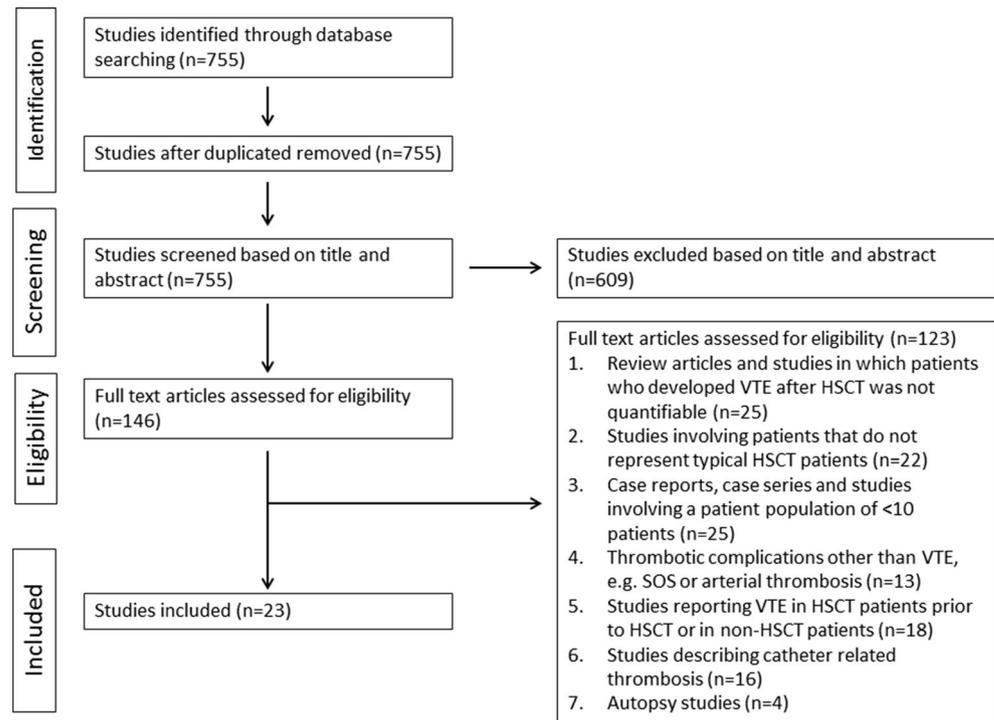
Year and authors	VTE patients/total patients (%)	Type of transplant	Underlying disease	Type of VTE	GVHD	Cochrane Collaboration's tool for assessing risk of bias					
						Sequence generation	Allocation concealment	Blinding	Incomplete data	Selective outcome reporting	Other sources of bias
[17] Johnston et al. (2011)	1/11 (9.1 %)	Allo-HSCT	AML, ALL, NHL, MDS	1 hepatic vein thrombosis	aGVHD = 54.5 %	High risk	High risk	High risk	Low risk	Unclear	High (closed to accrual, small number of patients) Low risk
[12] Barlogie et al. (2006)	153/651 (23.5 %)	Double auto-HSCT	MM	DVT and PE (not mentioned how many of each)	N/A	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
[18] Wadhwa et al. (2005)	1/101 (1 %)	Auto-HSCT	High risk or refractory/relapse NHL	1 PE	N/A	Unclear	Unclear	High risk	Low risk	Low risk	Low risk
[19] Lonial et al. (2010)	2/39 (5.1 %)	Auto-HSCT	MM	2 VTE (DVT and PE not specified)	N/A	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
[20] Krishnan et al. (2011)	21/625 (3.4 %)	All patients received auto-HSCT first then either allo- or second auto-HSCT.	MM	21 DVT	aGVHD = 35 % (grade II–IV = 26 %, grade III–IV = 9 %) cGVHD at 1 year was 47 and 54 % at 2 years	Unclear	Unclear	High risk	Low risk	Low risk	Low risk

AA aplastic anemia, *ALL* acute lymphoblastic leukemia, *Allo-HSCT* allogeneic- hematopoietic stem cell transplant, *AML* acute myeloid leukemia, *Auto-HSCT* autologous- hematopoietic stem cell transplant, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia, *DVT* deep venous thrombosis, *FL* follicular lymphoma, *GvHD* graft-versus-host disease, *aGvHD* acute GvHD, *cGvHD* chronic GvHD, *HD* Hodgkin's disease, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *MPD* myeloproliferative disorders, *MUD* matched unrelated donor, *NHL* non-Hodgkin's lymphoma, *PCT* pulmonary cytolytic thrombi, *PE* pulmonary embolism, *SCID* severe combined immunodeficiency, *VTE* venous thromboembolism

Table 2 Non-randomized studies reporting venous thromboembolism after hematopoietic stem cell transplantation

Year and authors	VTE patients/total patients (%)	Type of transplant	Underlying disease	Type of VTE	GVHD	The Newcastle-Ottawa scale for assessing the quality of non-randomized studies		
						Selection	Comparability	Exposure
[22] Chiusolo et al. (2000)	2/69 (2.9 %)	Auto-HSCT = 46 Allo-HSCT = 23	AML, ALL	1 DVT, 1 PE	Not reported	2	0	1
[23] Maris et al. (2006)	3/103 (2.9 %)	MUD allo-HSCT	AML, ALL, CML, MDS, CLL, HD, NHL, MM	3 DVT	aGVHD = 53 % (grade II = 39 %, grade III = 10 %, grade IV = 4 %) cGVHD = 49 % aGVHD = 17 % (grade II–IV = 14 %, grade III–IV = 3 %) cGVHD = 54 %	3	1	1
[13] Russell et al. (2008)	1/200 (0.5 %)	Sibling matched allo-HSCT	Various benign and malignant disorders	1 PE	aGVHD = 52 % (grade II–IV = 36 %, grade III–IV = 16 %) cGVHD was documented in 23 (34 %) of 68 eligible patients aGVHD = 12.8 % (grade II = 10.6 %, grade III = 2.1 %, grade IV = 0) cGVHD = 60 %	3	1	3
[24] de Lima et al. (2004)	1/94 (1.1 %)	Allo-HSCT	AML and high-risk MDS	1 PE	Not reported	3	0	2
[25] Khouri et al. (2008)	3/47 (6.4 %)	Allo-HSCT	Relapsed FL	3 DVT	Not reported	3	0	1
[26] Uderzo et al. (1993)	3/67 (4.5 %)	Allo-HSCT	Leukemia	3 PE	aGVHD = 16.6 % cGVHD = 50 %	3	0	1
[27] Chevret et al. (2011)	7/202 (3.5 %)	Allo-HSCT	AML, ALL, CML, MDS, CLL, MM, MPD, various lymphomas, AA, and others	7 VTE (DVT and PE not specified)	11 of these 13 patients had GVHD (aGVHD = 10 and cGVHD = 1) aGVHD = 56 % (grade II–IV = 40 %, grade III–IV = 16 %) cGVHD = 14.8 %	3	0	2
[28] Rini et al. (2002)	1/12 (8.3 %)	Allo-HSCT	Metastatic renal cell carcinoma	1 DVT	Not reported	2	0	1
[29] Woodard et al. (2000)	13/1228 (1.1 %)	Allo-HSCT	ALL, AML, CML, AA, SCID	13 PCT	Not reported	2	0	2
[30] Smith et al. (2011)	14/324 (4.3 %)	Allo-HSCT	ALL, AML, CML	14 PCT	Not reported	3	1	2
[1] Labrador et al. (2012)	26/431 (6.03 %)	Allo-HSCT	ALL, AML, CML, MDS, MM, NHL	11 DVT, 5 DVT with PE, 3 PE	Not reported	2	1	1
[31] Pihusch et al. (2004)	12/89 (13.5 %)	Allo-HSCT	AML, CML, ALL, NHL, MDS, AA, sickle cell anemia	7 catheter-related thrombosis, 7 catheter-related thrombosis	aGVHD = 71.9 % cGVHD = 34.8 %	2	0	1
[2] Gerber et al. (2008)	70/1514 (4.6 %)	Auto-HSCT = 928 Allo-HSCT = 586	AML, ALL, CML, CLL, NHL, HD, MDS, AA, MM, breast cancer, ovarian cancer, other solid tumors	5 VTE (including DVT and PE), 55 upper extremity DVT, 11 DVT, 9 PE	aGVHD and cGVHD total = 51.2 %	2	1	2
[32] Richters et al. (2014)	42/439 (9.6 %)	Auto-HSCT = 245 Allo-HSCT = 194	AML, ALL, MDS, NHL, MM, CML, CLL	42 patients had thrombosis, DVT, PE were not specified	Not reported	2	1	2
[4] Pihusch et al. (2002)	40/447 (8.9 %)	Auto-HSCT = 83 Allo-HSCT = 364	AML, ALL, CML, MDS, NHL, HD, AA	18 catheter-related thrombosis, 22 VTE (including DVT and PE)	aGVHD = 68.7 % cGVHD = 47.5 %	3	2	2

AA aplastic anemia, ALL acute lymphoblastic leukemia, Allo-HSCT allogeneic- hematopoietic stem cell transplant, AML acute myeloid leukemia, Auto-HSCT autologous- hematopoietic stem cell transplant, CLL chronic lymphocytic leukemia, CML chronic myeloid leukemia, DVT deep venous thrombosis, FL follicular lymphoma, GVHD graft-versus-host disease, aGVHD acute GVHD, cGVHD chronic GVHD, HD Hodgkin's disease, MDS myelodysplastic syndrome, MM multiple myeloma, MPD myeloproliferative disorders, MUD matched unrelated donor, NHL non-Hodgkin's lymphoma, PCT pulmonary cytolytic thrombi, PE pulmonary embolism, SCID severe combined immunodeficiency, VTE venous thromboembolism

Fig. 1 Search and inclusion of selected studies

cause significant endothelial injury which can result in a multitude of inflammatory cascades resulting in cytokine storm especially in the setting of acute GVHD [35, 36]. The role of donor T cells post-allogeneic-HSCT adhering to endothelium in the vasculature as the first potential extensive area of contact with new host antigens is well established [37, 38]. For chronic GVHD which exhibits a unique pathogenesis distinct from acute GVHD [39], current evidence indicates that, in addition to damage to targeted epithelia, changes to the microvascular endothelium play a role in the pathogenesis of chronic GVHD [40–42]. It is well known that long-term survivors after allogeneic-HSCT are at a high risk for premature arterial vascular disease [43–45]. The common endothelial syndromes that HSCT patients suffer from include TMA, SOS, engraftment syndrome, and capillary leak syndrome [6, 7, 46–48]. These early transplant-related endothelial damage syndromes result mainly due to direct cellular toxicity, a potent procoagulant condition, and heightened inflammatory responses manifested by cytokine storms post-HSCT. Thus, adequate mechanisms are well documented that provide a rationale for the biologic plausibility of a high thrombotic state in GVHD.

Since the incidence of VTE was reported as an adverse event in most of the studies and was not the primary outcome for most of the clinical trials, a definite causal link between GVHD and VTE cannot be established. Many other residual confounding factors may be present as the studies did not report all potential risk factors for GVHD.

Although we removed the studies (and/or patients in individualized studies) with catheter-related GVHD, it is possible

that some studies did not report presence or absence of central catheters since many patients at the time of HSCT and post-HSCT for few weeks or months still have catheters present, thus potentially confounding the association of VTE with acute GVHD. In chronic GVHD, although not reported in most studies, it is unlikely that majority of patients had central catheters, unless required for a treatment modality such as photopheresis. A VTE incidence of 35 % in chronic GVHD is alarming and suggests the need for further definitive studies to prove (or disprove) a causal link of GVHD with VTE. However, one must consider the possibility that these results may overestimate the incidence and link of VTE with GVHD. The details of GVHD were not available from each study; however, in all studies where the grades of GVHD were mentioned, they were compared. Incidental findings of VTE may also overestimate its incidence in HSCT patients, who usually undergo various investigations and extensive follow-up tests for various indications. The same incidence may not be true in patients with hematologic disorders being treated with non-transplant modalities. Another limitation in the present meta-analysis is that patient level (individual level) data was not available from each study. In addition, the included studies were inconsistent in reporting symptomatic VTE against asymptomatic VTE. While symptomatic VTE is a clear indication for therapeutic interventions, guidelines for the approach/treatment of asymptomatic VTE are not defined and open for discussion. Since incidental/asymptomatic VTE findings are common in HSCT patients considering the high rate of diagnostic procedures performed in this patient population, it is imperative to develop such protocols to guide

clinical practice. Exploring the incidence of symptomatic against asymptomatic VTE also represents a potential topic of future research interest.

It is evident from this meta-analysis that patients undergoing HSCT are at an elevated risk of both PE and DVT. Currently, the practice of DVT prophylaxis varies significantly between institutions as some transplant centers routinely provide anticoagulants post-HSCT for the prevention of SOS. Additionally, in autologous-HSCTs, a special consideration may be post-HSCT immuno-modulatory drug therapy which may be a risk factor for VTE post-HSCT. Lastly, the potential association of immobility due to severe chronic GVHD and VTE needs to be further evaluated in long-term studies. Definitive prospective trials are also needed to confirm the absolute and relative risks of VTE in HSCT patients and to prove the causal relationship between GVHD and VTE.

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Compliance with ethical standards

Conflict of interest None

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