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Risk of venous thromboembolism and major bleeding in the clinical course of osteosarcoma and Ewing sarcoma

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ABSTRACT

Background: Patients with osteosarcoma (OS) and Ewing sarcoma (ES) are considered to have a high venous thromboembolism (VTE) risk, although the exact incidence and prognostic impact are under-researched in general as well as in relevant age groups.
Aims: To study the impact of VTE and major bleeding (MB) in OS and ES patients, subdivided in children, Adolescents Young Adults (AYAs; aged 18–39) and older adults.
Methods: Retrospective single-center chart review in 519 OS and 165 ES patients treated between 1980 and 2018. Patients were followed from sarcoma diagnosis until an outcome of interest (VTE, MB) or death occurred. Cumulative incidences were estimated with death as competing risk. Cox models were used to determine prognostic impact.
Results: Five-year cumulative incidences of VTE were 12 % (95%CI 9.1–15) for OS and 6.7 % (95%CI 3.5–11) for ES patients, mostly happening in patients ≥18 years; the most frequent VTE presentation was catheter-related upper-extremity thrombosis (OS: 18/65, ES: 7/11). Five-year cumulative incidences for MB were 5.8 % (95% CI 4.0–8.1) in OS and 5.4 % (95%CI 2.5–9.8) in ES patients. 192 OS and 77 ES AYAs were included, who faced similar VTE and MB incidences as older adults. In OS, VTE and MB were both associated with mortality (adjusted HRs 2.0 [95%CI 1.4–2.9] and 2.4 [95%CI 1.4–4.0], respectively), whereas in ES this association was only present for MB (aHR 3.4 [95%CI 1.2–9.6]).
Conclusions: VTE is a frequent complication in adult OS and to a lesser extent in ES patients, while the rate of MB was comparably high in both sarcoma types.

1. Introduction

Bone sarcomas are rare and represent <1 % of all malignant tumors in adults. [1] Osteosarcoma and Ewing sarcoma are the most encountered types of primary bone cancer, with an incidence of 2.5 and 1.5 per million per year, respectively. [2] Venous thromboembolism (VTE) is a common complication in patients with a malignancy, although the VTE risk differs considerably between cancer types. [3,4] The exact incidence of VTE and its complications in osteosarcoma and Ewing sarcoma are largely unknown. Available studies show a wide range of results, varying from 1 % to 20 %, due to small cohorts and inconsistent outcome measures. [5–7] Better knowledge of the VTE incidence as well as

Abbreviations: (a)HR, (adjusted) hazard ratio; AYA, adolescents and young adults; CI, confidence interval; CVC, central venous catheter; DVT, deep-vein thrombosis; ES, Ewing sarcoma; IQR, interquartile range; KRS, Khorana risk score; LMWH, low-molecular-weight heparin; MB, major bleeding; OS, osteosarcoma; PE, pulmonary embolism; TF, tissue factor; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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insight into predictors and determinants of both VTE and bleeding is relevant to the management of osteosarcoma and Ewing sarcoma patients, for decision making regarding primary pharmacological thromboprophylaxis. The literature on bleeding has focused on the perioperative phase, but also spontaneous bleeding of soft tissue tumors or metastases are mentioned. [8–10]

The aim of our study was to provide reliable cumulative incidences of clinically relevant thrombotic and bleeding complications in a large practice-based cohort of osteosarcoma and Ewing sarcoma patients. Furthermore, possible clinical predictors for VTE and bleeding were explored, and the prognostic impact of thrombosis and bleeding was evaluated. Lastly, as osteo- and Ewing sarcoma often occur in AYAs (adolescents and young adults), who face unique challenges with respect to cancer care [11], this age group was studied separately.

2. Methods

2.1. Study design, patients and data collection

We performed a single-center retrospective cohort study of all consecutive patients diagnosed with osteosarcoma and Ewing sarcoma between January 1984 and December 2018 at the Leiden University Medical Center (LUMC, Leiden, The Netherlands), a dedicated referral center for treatment of primary bone sarcoma. Patients with a histologically proven osteosarcoma or Ewing sarcoma, and a minimal follow-up up to 1 year after diagnosis or death within this period, were included in the study.

Since the introduction of chemotherapy in the treatment of sarcomas in the 1980s, the standard of care for these patients has not relevantly changed. For osteosarcoma this consists of neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy (chemotherapy regimens usually containing doxorubicin, a platinum-based agent and high-dose methotrexate; Euramos-1 trial [NCT00134030] [12]). Radiotherapy was only given in specific cases, as osteosarcoma generally is insensitive for radiotherapy. Standard care for Ewing sarcoma is neoadjuvant chemotherapy, often with concurrent radiotherapy, followed by surgery and adjuvant chemotherapy (chemotherapy regimens usually contained vincristine, doxorubicin, etoposide, cyclophosphamide and ifosfamide in various combinations and schedules; Euro Ewing trials [13,14]). Palliative treatment for patients with irresectable tumors and/or metastatic disease was individualized. Exact chemotherapy regimens differed slightly throughout the years and were often conducted in trial setting. Patients received thromboprophylaxis according to the LUMC hospital protocol, with all patients ≥18 years old receiving prophylactic anticoagulation (vitamin K-antagonist [VKA] in the 1980s or low-molecular-weight heparin [LMWH] afterwards) during hospitalization and until week 6 post-surgery. In patients below 18 years of age, thromboprophylaxis was decided on an individual basis. No primary anticoagulant prophylaxis was prescribed in ambulatory patients.

Patients were followed between two weeks before histopathological sarcoma diagnosis until their last follow-up visit in the LUMC before the end of data collection, or until a thrombotic event or bleeding complication or death occurred (depending on the analysis), whichever came first. The two weeks before diagnosis were included because the usual timespan between suspicion of a sarcoma and histopathological confirmation is several days to weeks. The end of data collection was February 2019 for ES patients and February 2020 for OS patients, respectively.

Data collection was performed by scrutinizing patient charts for baseline characteristics (demographics, tumor characteristics and treatment details including the presence of a central venous catheter [CVC]) and outcomes of interest, using a standardized electronic case report form. The study was approved by the local Institutional Review Board (the Medical Research Ethics Committee Leiden-The Hague-Delft; MREC LDD) and the need for informed consent was waived (approval code: G18.065/SH/gk).

2.2. Outcomes

The main study outcomes were VTE and major bleeding (MB) during follow-up. The endpoints were adjudicated by two independent experts (AJV and FAK). VTE consisted of symptomatic or incidental pulmonary embolism (PE), deep vein thrombosis (DVT) of the upper or lower extremities, cerebral sinus vein thrombosis or splanchnic vein thrombosis, confirmed by computed tomography (CT), magnetic resonance (MR) or ultrasound imaging. [15,16] A VTE was considered catheter-related when a mural or occlusive upper-extremity DVT occurred within the vein cannulated with the central venous catheter or a contiguous vein, or within four weeks after removal of the catheter. The International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding was used, defining MB as 1) fatal bleeding, 2) symptomatic bleeding in a critical area or organ, or 3) bleeding causing a fall in hemoglobin level of ≥1.24 mmol/L, or leading to a transfusion of ≥2 units of blood. [17] Perioperative bleeding was defined as during surgery or within 14 days after surgery.

2.3. Statistical analysis

Patient characteristics were described using standard descriptive statistics. All analyses were performed separately for patients with osteosarcoma and Ewing sarcoma. Furthermore, additional to the analyses of the total cohort, patients <18 years old (referred to as "pediatric patients"), 18–39 years old (Adolescent Young Adults ["AYA"] age group)) and ≥ 40 years old ("older adults") at sarcoma diagnosis were analyzed separately. A sensitivity analysis was performed for the patients diagnosed after January 1st, 2010, as from that timepoint the current electronical patient record system was in use, leading to better accessible information. Also, this concerns a subgroup with a homogenous and up-to-date sarcoma and antithrombotic treatment.

Cumulative incidences were estimated using the cumulative incidence competing risk (CICR) method [18], to adjust for the competing risk of death, and are presented with 95 % confidence intervals (CI). Outcome predictors were determined with univariate Cox regression models (presented as hazard ratio [HR] with 95%CI). To assess the prognostic impact of the outcomes, cause-specific Cox regression analyses with time-dependent covariates were performed [19], with adjustment for age, sex and distant metastases (presented as adjusted hazard ratio [aHR] with 95%CI). [19,20] In multivariable analyses only complete cases were included. Statistical analyses were carried out in SPSS Statistics version 25.0 and RStudio version 1.3.1056.

3. Results

3.1. Patients

In total 519 osteosarcoma and 165 Ewing sarcoma patients were included in the study. Their baseline characteristics are presented in Table 1. The median age at OS diagnosis was 23 years old (range 3.5–84 years), whereas it was 19 years old (range 1.2–66 years) at ES diagnosis. The majority of patients was male (55 % in the OS cohort and 69 % in the ES cohort). The OS cohort contained 192 AYAs (37 %) and the ES cohort 77 (47 %). Most of the primary tumors were located in the extremities (OS $n = 366$ [71 %], ES $n = 91$ [55 %]). In 109 OS patients (21 %) and in 50 ES patients (30 %) distant metastases were present at time of diagnosis. The median follow-up time was 60 months (IQR 22–143) for OS and 42 months (IQR 19–124) for ES patients, respectively.

3.2. Venous thromboembolism

3.2.1. VTE events in osteosarcoma patients

In total, 65 patients (13 %) developed a VTE during follow-up. The median time to VTE was 5.4 months (IQR 1.7–30). A deep-vein thrombosis (DVT) of the upper extremities was the most common type of VTE

Table 1
Baseline characteristics.

	Osteosarcoma $N = 519$	Ewing sarcoma $N = 165$
Age at diagnosis in years (median, range)	22.8 (3.50–80.7)	19.4 (1.22–66.1)
Age groups (n, %)		
<18 years old	166 (32)	70 (42)
18–39 years old	192 (37)	77 (47)
≥40 years old	161 (31)	18 (11)
Male sex (n, %)	287 (55)	113 (69)
Location of sarcoma (n, %)		
Extremity	407 (78)	91 (55)
Pelvis	43 (8.3)	32 (19)
Other	108 (21)	42 (26)
Presence of distant metastases at diagnosis (n, %)	109 (21)	50 (30)
Tumor resection (n, %)	458 (88)	105 (64)
No postoperative thromboprophylaxis	36 (7.9)	20 (19)
Chemotherapy during follow-up (n, %)	388 (75)	n/a
CVC placement during follow-up (n, %)	394 (76)	152 (92)
Radiotherapy during follow-up (n, %)	73 (14)	106 (64)
Patients died (n, %)	256 (49)	82 (50)
Due to sarcoma	215	78
Pulmonary embolism	0	0
Major bleeding	5	3
Total follow-up in months (median, IQR)	60 (22–143)	42 (19–124)

Note: SD: standard deviation; n: number; IQR: interquartile range; n/a: not available, CVC: central venous catheter.

(n = 20; 31 %), of which 18 had a catheter-associated thrombosis. Seventeen patients (26 %) developed a lower extremity DVT, 16 patients (25 %) a pulmonary embolism (PE; none was fatal), and 3 patients a concurrent DVT and PE. Nine patients had other sites of thrombosis (splanchnic veins, intracardiac thrombus or sinus thrombosis). The majority of VTEs was symptomatic (n = 44; 77 %). Ten patients (15 %) developed a VTE within 6 weeks after surgery, and half of the VTEs occurred during chemotherapy (n = 32; 49 %). At time of the VTE diagnosis, 11 patients used anticoagulation, of whom 3 (5 %) in a therapeutic and 8 (12 %) in a prophylactic dose. The majority of patients started treatment for the VTE (n = 55; 85 %). Two PEs remained untreated, as one incidental PE and one symptomatic subsegmental were considered not clinically relevant by the treating physician. One incidental portal vein thrombosis and three DVTs were left untreated. In four patients, the VTE the treatment was unknown.

Eleven pediatric patients developed a VTE, of whom four were under 16 years old. One pediatric VTE patient was using oral contraceptives.

3.2.2. VTE events in Ewing sarcoma patients

Eleven patients (6.7 %) were diagnosed with VTE during follow-up, none of them fatal, with a median time to VTE of 8.5 months (IQR 3.5–11), and all VTEs occurring within the first 2 years. An upper extremity DVT was the most common VTE type (n = 7; 64 %), which were all catheter-associated. Three patients developed PE (27 %) and one patient (9.1 %) a DVT of the leg. Most VTEs were symptomatic (n = 8; 72 %). One VTE occurred postoperatively, and 9 patients (82 %) had a VTE during chemotherapy treatment. Only one patient used anticoagulation (prophylactic dose) at time of the VTE diagnosis. Nine patients started anticoagulation for their VTE (6 LMWH, 3 VKA), and of 2 patients the treatment was unknown.

There were two VTEs in pediatric patients, both above 16 years old. One VTE was catheter-related, the other patient used oral contraceptives.

3.2.3. Cumulative incidences and associations

The adjusted cumulative VTE incidences are presented in Table 2 and Fig. 1. The 5-year cumulative incidence was 12 % (95%CI 9.1–15) in OS patients, and 6.7 % (95%CI 3.5–11) in ES patients, respectively. In the OS cohort the incidence rate was 8.8 per 100 patient years (95%CI 6.6–12) in the first year and 0.64 (95%CI 0.43–0.97) for the subsequent period. In the ES cohort this was 6.1 (95%CI 3.3–11) and 0.12 (95%CI 0.021–0.68) per 100 patient years, respectively. When looking separately at the different age groups at sarcoma diagnosis, for pediatric, AYA and older adult OS patients the 5-year cumulative incidence was 6.1 % (95%CI 3.1–10), 17 % (95%CI 12–23) and 11 % (95%CI 7–17), respectively. In the ES cohort the respective 5-year cumulative incidences were 2.8 % (95%CI 0.53–8.9), 7.8 % (95%CI 3.2–15) and 18 % (95%CI 4.0–39) (Table 3). Older age (HR 1.01, 95%CI 1.00–1.03) and CVC placement (HR 4.0, 95%CI 1.7–9.6) were predictive for a VTE event in OS patients, whereas no predictors were identified in the ES cohort (Table 4).

Table 2
Adjusted cumulative incidences.

	Osteosarcoma	Ewing sarcoma
	Cumulative incidences[a]	Cumulative incidences[a]
	n% (95 % CI)	n% (95 % CI)
VTE		
3 months	5.2 (3.5–7.4)	1.8 (0.50–4.8)
6 months	6.7 (4.8–9.1)	1.8 (0.50–4.8)
1 year	8.3 (6.1–11)	6.1 (3.1–10)
2 years	8.9 (6.6–9.1)	6.7 (3.5–11)
5 years	12 (9.1–15)	6.7 (3.5–11)
MB		
3 months	1.2 (0.48–2.4)	0
6 months	2.3 (1.3–3.9)	0.61 (0.06–3.1)
1 year	3.3 (2.0–5.1)	1.2 (0.24–4.0)
2 years	4.0 (2.6–6.0)	2.5 (0.81–5.8)
5 years	5.8 (4.0–8.1)	5.4 (2.5–9.8)

Note: n: number, CI: confidence interval, VTE: venous thromboembolism, MB: major bleeding.
[a] Cumulative incidence adjusted for the competing risk of death.

In the sensitivity analysis, a higher 5-year cumulative incidence was found (16 %, 95%CI 11–23) in OS patients diagnosed after 2010 (Supplementary Table 3). In the ES patients the results of the sensitivity analysis were comparable to the total cohort (Supplementary Table 3).

3.3. Major bleeding

3.3.1. MB events in osteosarcoma patients

Thirty-one patients (6.0 %) developed a major bleeding (MB) during follow-up. Fourteen MBs (45 %) were perioperative (i.e., related to resection of either the primary tumor or metastases, or other surgical procedures). The resection site of the primary tumor (n = 10; 32 %) was the most common bleeding location, followed by intrathoracic bleeding (n = 9; 29 %), the latter all associated with (surgery for) pulmonary or pleural metastases. The median time to MB was 10 months (IQR 4.2–27). Five MBs were fatal (3 spontaneous and 3 perioperative bleedings). Twelve patients used anticoagulation at time of the MB diagnosis, of whom 5 (16 %) in prophylactic and 7 (23 %) in therapeutic dose. Of the latter, 2 patients used anticoagulation for a previous VTE.

3.3.2. MB events in Ewing sarcoma patients

Nine patients (5.5 %) had a major bleeding during follow-up, of which 3 (33 %) were located intracranially and 2 (22 %) in the region of the primary tumor. The other bleeding sites were gastrointestinal, ovarian, retinal and thoracic. The median time to MB was 27 months (IQR 12–48). One patient was known to use (prophylactically dosed) anticoagulation at time of the MB diagnosis. Two MBs were postoperatively, and 3 MBs were fatal (2 intracerebral, 1 gastrointestinal).

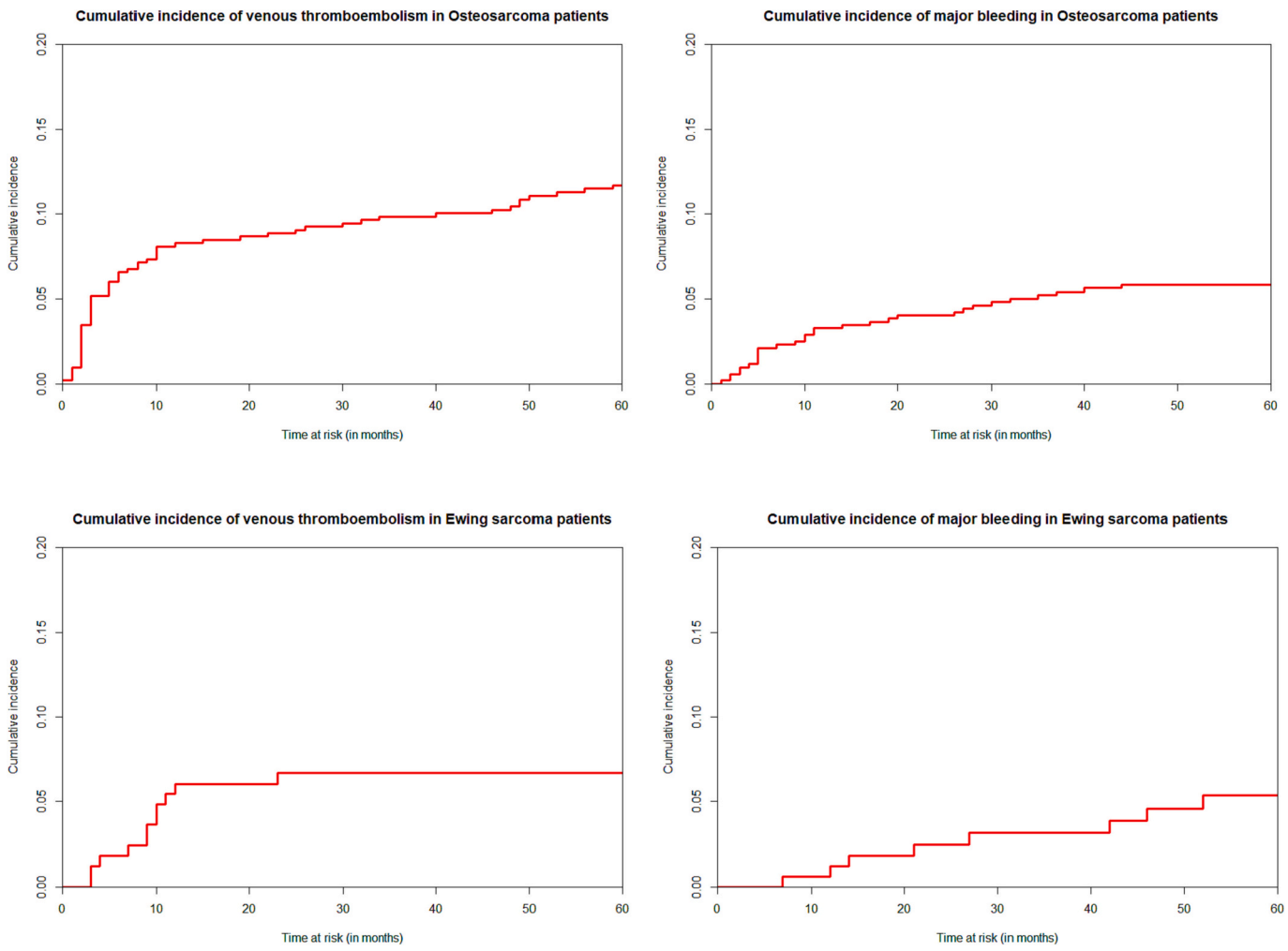

Fig. 1. Adjusted cumulative incidences of venous thromboembolism and major bleeding in osteosarcoma and Ewing sarcoma patients.

Table 3
Adjusted cumulative incidences in different age groups of osteosarcoma and Ewing sarcoma patients.

	Osteosarcoma			Ewing sarcoma		
	Pediatric patients	AYAs	Older adults	Pediatric patients	AYAs	Older adults
	N = 166	*N* = 192	*N* = 161	*N* = 70	*N* = 77	*N* = 18
	Cumulative incidences[a] n% (95 % CI)					
VTE						
3 months	2.4 (0.79–5.7)	6.3 (3.4–10)	6.8 (3.6–11)	0	3.9 (1.0–10)	0
6 months	3.6 (1.5–7.3)	8.3 (5.0–13)	8.1 (4.5–13)	0	3.9 (1.0–10)	0
1 year	4.2 (1.9–8.1)	10 (6.6–15)	9.9 (5.9–15)	2.8 (0.53–8.9)	7.8 (3.2–15)	11 (1.7–30)
2 years	5.4 (2.7–9.6)	11 (7.0–16)	9.9 (5.9–15)	2.8 (0.53–8.9)	7.8 (3.2–15)	18 (4.0–39)
5 years	6.1 (3.1–10)	17 (12–23)	11 (7.0–17)	2.8 (0.53–8.9)	7.8 (3.2–15)	18 (4.0–39)
MB						
3 months	0	1.0 (0.21–3.4)	2.5 (0.82–5.8)	0	0	0
6 months	0.60 (0.006–3.1)	2.1 (0.69–4.9)	4.3 (1.9–8.3)	0	1.3 (0.11–6.3)	0
1 year	1.8 (0.49–4.8)	3.1 (1.3–6.3)	5.0 (2.3–9.1)	0	2.6 (0.49–8.2)	0
2 years	1.8 (0.49–4.8)	4.2 (2.0–7.7)	6.2 (3.2–11)	1.5 (0.12–7.0)	3.9 (1.0–10)	0
5 years	4.3 (1.9–8.2)	6.3 (3.5–10)	6.8 (3.6–11)	2.2 (0.57–9.8)	7.2 (2.6–15)	6.4 (0.35–26)

Note: n: number, CI: confidence interval, VTE: venous thromboembolism, MB: major bleeding, AYA: adolescent and young adult.
[a] Cumulative incidence adjusted for the competing risk of death.

3.3.3. *Cumulative incidences and associations*

Table 3 and Fig. 1 show the adjusted cumulative incidences of MB in both cohorts. The adjusted 5-year cumulative incidence was 5.8 % (95% CI 4.0–8.1) in the OS cohort and 5.4 % (95%CI 2.5–9.8) in the ES cohort. The incident rate was 3.4 (95%CI 2.1–5.3) per 100 patient years in the first year and 0.39 (95%CI 0.23–0.66) in the subsequent years for OS patients, whereas this was 1.2 (95%CI 0.33–4.2) and 0.80 (95%CI 0.39–1.6) for ES patients, respectively. In the pediatric OS patients, the

Table 4
Association between clinical variables and outcomes of interest in osteosarcoma and Ewing sarcoma patients.

Osteosarcoma			
Variable	VTE (HR, 95% CI)	MB (HR, 95% CI)	Mortality (HR, 95%CI)
Age (years)	1.01 (1.00–1.03)	1.02 (0.99–1.03)	1.01 (1.00–1.02)
AYA			
vs. children	2.8 (1.4–5.5)	1.7 (0.66–4.1)	1.1 (0.82–1.6)
vs. older adults	1.2 (0.68–2.0)	0.86 (0.39–1.9)	0.83 (0.06–1.1)
Sex (female vs. male)	1.2 (0.72–1.9)	0.97 (0.48–2.0)	0.82 (0.63–1.1)
Tumor location (axial vs. non-axial)	1.2 (0.47–3.0)	1.5 (0.46–5.0)	1.3 (0.79–2.2)
Metastases at diagnosis (yes vs. no)	1.1 (0.56–2.1)	2.0 (0.89–4.5)	4.8 (3.6–6.3)
CVC placement (yes vs. no)	3.0 (1.3–6.9)	1.2 (0.50–3.0)	0.90 (0.66–1.2)

Ewing sarcoma			
Variable	VTE (HR, 95%CI)	MB (HR, 95%CI)	Mortality (HR, 95%CI)
Age (years)	1.03 (0.99–1.07)	1.03 (0.98–1.08)	1.02 (0.99–1.03)
AYA			
vs. children	3.0 (0.60–15)	1.9 (0.45–8.0)	1.8 (1.1–2.8)
vs. older adults	0.47 (0.12–1.9)	1.3 (0.15–11)	1.3 (0.61–2.6)
Sex (female vs. male)	0.79 (0.21–3.0)	2.5 (0.65–9.4)	0.70 (0.43–1.2)
Tumor location (axial vs. non-axial)	2.5 (0.77–8.2)	0.81 (0.17–3.9)	0.99 (0.60–1.7)
Metastases at diagnosis (yes vs. no)	0.87 (0.23–3.3)	2.0 (0.53–7.3)	0.99 (0.61–1.6)
CVC placement (yes vs. no)	n/a	n/a	n/a

Note: HR: hazard ratio; CI: confidence interval; n: number; VTE: venous thromboembolism; MB: major bleeding; CVC: central venous catheter; n/a: not applicable (i.e., cannot be calculated due to insufficient number of events within groups).

5-year cumulative was 4.3 % (95%CI 1.9–8.2), whereas it was 6.3 % (95%CI 3.5–10) for AYAs and 6.8 % (95%CI 3.6–11) for older adults. In the ES patients, the 5-year cumulative incidence was 2.2 % (95%CI 0.57–9.8) for pediatric patients, 7.2 % (95%CI 2.6–15) for AYAs and 6.4 % (95%CI 0.35–26) for older adults.

No predictors for major bleeding were identified in either of the total cohorts (Tables 4 and 5). In the OS cohort, distant metastases at OS diagnosis were associated with more MBs (HR 16, 95%CI 3.0–83) in pediatric patients, whereas a VTE during follow-up was a predictor for MB (aHR 5.7, 95%CI 1.6–20) in the AYA group (Supplementary Table 1 and 2).

In the sensitivity analyses, the cumulative incidences and regression analysis showed similar results for patients diagnosed after 2010 (Supplementary Table 3).

3.4. Survival

Half of the OS and 49 % of the ES patients died during follow-up, the majority of whom due to sarcoma (Table 1). Older age (HR 1.01, 95%CI 1.00–1.02), metastases present at diagnosis (aHR 4.8, 95%CI 3.7–6.4), VTE (aHR 2.0, 95%CI 1.3–2.9) and MB (aHR 2.3, 95%CI 1.4–3.9) during follow-up were all associated with increased mortality in OS patients (Tables 4 and 5). When VTE was categorized in CVC- and non-CVC-related VTE, only the latter was predictive for mortality (aHR 0.90, 95%CI 0.40–2.0, vs. aHR 2.7, 95%CI 1.8–4.2, respectively). The only predictor for mortality identified in the ES cohort was major bleeding (aHR 3.4, 95%CI 1.2–9.6). The sensitivity analyses with patients diagnosed after 2010 showed comparable results (Supplementary Table 3).

Table 5
Prognostic impact of thrombotic and bleeding events in osteosarcoma and Ewing sarcoma patients.

Osteosarcoma				
	MB (HR, 95%CI)		Mortality (HR, 95%CI)	
	Crude[a]	Adjusted[a]	Crude[a]	Adjusted[a]
VTE (yes vs. no)	2.2 (0.76–6.3)	2.0 (0.68–5.7)	2.1 (1.4–3.0)	2.0 (1.4–2.9)
MB (yes vs. no)	–	–	2.7 (1.6–4.6)	2.4 (1.4–4.0)

Ewing sarcoma				
	MB (HR, 95%CI)		Mortality (HR, 95%CI)	
	Crude[a]	Adjusted[a]	Crude[a]	Adjusted[a]
VTE (yes vs. no)	1.8 (0.22–14)	1.6 (0.17–15)	0.75 (0.27–2.1)	0.68 (0.24–1.9)
MB (yes vs. no)	–	–	3.0 (1.1–8.4)	3.4 (1.2–9.6)

Note: HR: hazard ratio; CI: confidence interval; VTE: venous thromboembolism; MB: major bleeding.
[a] Crude HR derived from univariable Cox regression analysis with a time-dependent covariate. Adjusted HR derived from time-dependent multivariable Cox regression, with adjustment for age, sex and metastases at diagnosis.

4. Discussion

Our results show that venous thromboembolism is a frequent complication in osteosarcoma and Ewing sarcoma patients, especially in the first year after diagnosis, and is associated with a worse prognosis. We observed important differences between the two sarcoma types and age classes, which have potential implications for the discussion concerning the use of (primary) thromboprophylaxis in these patients.

We observed higher cumulative incidences of VTE in osteosarcoma than in Ewing sarcoma patients, which was not evident in previous studies with smaller cohorts. [6,7,21] Patients with OS and ES have often shared VTE risk factors as immobility, (orthopedic) surgery, invasion of the tumor into vascular tissue, or other treatment interventions as systemic therapy and vascular catheters. [22] However, it has been described that osteosarcoma cells express abundant levels of tissue factor (TF), which contributes to metastatic dissemination. [23] As TF is one of the primary initiators of coagulation, this could explain the higher VTE incidence in osteosarcoma patients. Ewing sarcoma has a different tumor biology, but specific literature on TF overexpression is lacking. Furthermore, unlike for ES, chemotherapy regimens in OS treatment usually contain cisplatin, which is linked to a higher VTE risk. [24]

In our study VTE mainly occurred in AYAs and older adult sarcoma patients, and was very rare in children. This is in line with previous studies and supports current practice to not routinely prescribe thromboprophylaxis in pediatric patients with cancer in general, or with OS or ES specifically. [25–27] The sensitivity analysis in patients diagnosed with osteosarcoma after 2010 showed a higher VTE incidence than in the total cohort (1-year adjusted cumulative incidence of 13 % [95%CI 8.3–19] vs. 8.3 % [95%CI 6.1–11], respectively), which is probably explained primarily by the older age of this cohort (median age 40 [range 5.2–79] vs. 23 years [range 3.5–84]). This was the result of centralization of pediatric oncology in the Netherlands in the past decade, which meant that children were no longer treated in the LUMC.

When comparing the VTE risks in our study with those of the cohorts used for developing/validating the Khorana Risk Score (KRS; the most renowned risk assessment score for thromboprophylaxis in ambulatory cancer patients starting chemotherapy), OS patients would be classified as 'high-risk' patients (6-month VTE cumulative incidence of 6.7 %, corresponding to KRS ≥3), whereas the risk in ES patients corresponds

to the 'intermediate risk' group (1.8 %, in line with KRS 1–2). [4] These incidences might justify thromboprophylaxis according to current guidelines [28], especially in the setting of OS. However, the background bleeding incidence in the OS cohort was higher than in the placebo groups of the clinical trials focusing on thromboprophylaxis in ambulatory cancer patients with intermediate-high risk tumors (6-month MB incidence of 2.3 % vs. 1 %). [29,30] Furthermore, no fatal VTEs occurred in our cohort, while there were several fatal MBs, although usually not related to anticoagulation.

In addition, the most encountered type of VTE in both OS and ES cohorts was catheter-associated upper extremity DVT. The use of a CVC is very common in sarcoma patients (e.g., 80 % of our total cohort received a CVC at one point during their treatment) and reported incidences of catheter-related DVT vary widely due to inconsistency among studies. Our findings are in line with recent literature, with symptomatic events occurring in 0–5 % of patients with a CVC. [31,32] Catheter-related DVT may impede cancer treatment and may be complicated by post-thrombotic syndrome or recurrent VTE, but severe complications as (fatal) pulmonary embolism seem rare. [31,33] In the absence of conclusive evidence, international guidelines suggest against standard use of (LMWH) thromboprophylaxis in patients with a CVC. [28,34] Treatment of a CVC-related DVT with anticoagulation is usually recommended for a duration of 3 months, irrespective of active cancer. The large proportion of catheter-associated thrombosis in our cohort might explain the absence of an evident association between advanced/metastatic disease and VTE, or between VTE and subsequent bleeding (or mortality in Ewing sarcoma patients), in contrast to similar observational studies focusing on VTE in other malignancies. [35,36]

Altogether these findings provide arguments against initiating routine thromboprophylaxis in OS and especially ES patients. Even so, a subgroup analysis of the AVERT-trial (primary prophylaxis with apixaban 2.5 mg BD vs. placebo in patients with KRS $\geq$2) regarding patients with a CVC indicated that primary pharmacological prophylaxis might be effective and safe. [37] Also, the emerging drug class of factor XI inhibitors are very promising, as they primarily inhibit contact pathway activation and theoretically do not increase bleeding risk, though this should be proven in currently ongoing outcome studies. [38,39] If over time accumulating evidence would confirm the effectiveness and excellent safety of these newer agents, the balance could be shifted in favor of primary thromboprophylaxis.

AYAs are increasingly recognized as a distinct population within the oncology, as they may have different cancer risk factors [40], and encounter unique psychosocial challenges typical for their stage of life. The results of our study indicate that AYAs with OS and ES face similar thrombosis and bleeding risks as older adults, possibly indicating that the same strategies for preventing and treating VTE would be applicable to both groups. Even so, dedicated studies focusing on AYA preferences on prevention and treatment of VTE are lacking, an unmet clinical need that should be incorporated in current research priorities.

To our knowledge, we described the largest cohort of osteo- and Ewing sarcoma subtypes followed specifically for the occurrence of clinically relevant VTE and major bleeding. Limitations of our study include that the Ewing sarcoma cohort was relatively small, leading to large confidence intervals in the subgroup analyses. The earliest cases in our cohort had largely non-digital patient charts, associated with a higher probability of incomplete information. Even so, as discharge letters and radiology reports were virtually all digitally accessible, this does not apply heavily to our primary study outcomes. Notably, we did not have information on the type of CVCs in our cohort, possibly carrying different VTE risks. We did not have data on the timing of all surgeries and chemotherapy treatments that occurred during the observation period; hence we could not assess the association with VTE. Further, we did not have an accurate overview of the treatment of comorbidities at baseline, for which we were unable to estimate the overall bleeding risk associated with the use of anticoagulation during the study period.

In conclusion, this study confirms that VTE is a relevant problem in osteosarcoma patients, especially in the first year after diagnosis, but to a clear lesser extent in Ewing sarcoma patients. AYAs with OS and ES face similar VTE and bleeding risks as older adults, while children have much lower risk. Routine thromboprophylaxis in ambulatory patients appears not indicated in ES patients, and although the VTE risk in OS is higher, considering the large proportion of catheter-associated DVTs and the high bleeding incidence in these patients, it seems not justified in OS either.

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Declaration of competing interest

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Appendix A. Supplementary data

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