Comparison of Clinical Features in Hematologic-Malignancy Patients and Tumor Patients Developing Pulmonary Embolism

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Abstract

Background: venous thromboembolism (VTE) is a common complication in patients with cancer. Pulmonary embolism (PE) is a form of VTE that is common and a major cause of morbidity and mortality in cancer patients. Patients with hematological malignancies (HM) constitute a particular subset of patients with significant differences that may require specific evidence for the management of pulmonary embolism (PE) prophylaxis and treatment.

Methods: a single-center retrospective analysis was conducted on HM and tumor patients developing PE from January 2015 to September 2020.

Results: in this study, 56% of the HM patients had malignancies derived from B-cells. Non-Hodgkin's lymphoma(NHL), especially diffuse large B-cell lymphoma, had the highest incidence rates. Seventy-six percent of HM patients occurred PE within 50 days from the date of diagnosis. But the onset time of PE in tumor patients had two peaks. Several factors, including developing pneumonia especially in male patient with a smoking history, catheter history and ongoing chemotherapy were more valuable in predicting PE occurrence in HM patients compared with caner patients. The D-dimer level was elevated in 84% of HM cases and 97.5% in tumor patients.The D-Dimer values in HM patients were significantly lower than those in tumor patients. There was no significant difference in embolus location between two groups. Patients with acute leukemia had a higher incidence of peripheral PE, whereas patients with NHL had a higher incidence of central PE. No treatment-related modality and major bleeding were observed in HM patients. PE-related mortality rate was similar to that in tumor patients.

Conclusions: this study identified several clinical differences between HM and tumor patients when PE occurred, which may be helpful for PE diagnosis, prevention and treatment of HM patients in the future.

Background

Cancer is an established cause of venous thromboembolic events (VTE). The reported incidence of VTE in patients with hematological malignancies (HM) is up to 10%, similar to the incidence observed in patients with solid tumors[1–3]. Pulmonary embolism (PE) is the most serious clinical presentation of VTE, leading to serious adverse events such as heart failure, respiratory failure, and sudden death[4–6]. The overall risk of PE is twenty-fold higher in patients with tumors than in the general population[7]. The prevalence of malignancy in patients with PE ranges between 4% and 20% [8, 9]. The majority of previous related studies have focused mainly on solid tumors, and the results cannot be readily extrapolated to patients with HM. Patients with HM constitute a particular subset of patients with significant differences, and evidence is needed to inform the management of PE prophylaxis and treatment in this population. Data available so far on PE do not distinguish among the different categories of HM [10, 11]. To date, little is known about the clinical characteristics and short-term prognosis in HM patients with PE. Therefore, we performed a single-center study to retrospectively analyze the clinical data of HM patients

and solid tumor patients with PE from January 2015 to September 2020, with the purpose of elucidated the distinctions between them.

Methods

This single-center, retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tongji Hospital. Available clinical records of patients with PE who had a diagnosis of HM or tumors from January 2015 to September 2020 in Tongji Hospital were analyzed. PE was diagnosed by computed tomography pulmonary angiography (CTPA). The diagnosis of PE prior to the onset of malignancy was exclusive. When PE was identified, the patient's basic demographic data (age, sex), medical history, disease-related information, platelet count, leukocyte count, and hemoglobin level at the date of PE were extracted. In addition, information on location, anticoagulant medication, and provoking factors for PE (for example, central venous catheters [CVCs] or peripherally inserted central catheters [PICCs]) were registered.

Statistical Analyses

The Statistical Package for Social Science software (version 18.0, SPSS Inc., Chicago, IL, USA) was used for all analyses. Continuous variables were assessed with regard to whether they violated the underlying assumption of a normal distribution. Normally distributed variables are expressed as the means and standard error of the means (SEMs) and other variables are represented by the median and associated interquartile range. Student's t-test was used to compare the means of continuous variables between the 2 groups, and the Pearson $\chi 2$ test or Fisher's exact test (the minimum expected cell size was 5) was performed for categorical variables. A p-value ≤ 0.05 indicated statistical significance.

Results

Patient characteristics

A total of 25 patients with HM and 79 patients with tumors were enrolled in this study. In the patients with HM, the mean age at the diagnosis of PE was 47.9 years (14–75 years). There were 17 males (68.0%) and 8 females (32%). A total of 9 patients (36%) had leukemia, including acute undifferentiated leukemia (AUL, n = 1) (4%), acute B-cell lymphoblastic leukemia (B-ALL, n = 2) (8%), acute myeloid leukemia (AML, n = 1) (4%), acute promyelocytic leukemia (APL, n = 2) (8%) and high-risk myelodysplastic syndrome (MDS, n = 3) (12%). A total of 14 patients had non-Hodgkin's lymphoma (NHL, 56%), including diffuse large B-cell lymphoma (DLBCL, n = 9) (36%), Burkitt lymphoma (n = 2) (8%), angioimmunoblastic T-cell lymphoma (AITL, n = 1) (4%), follicular lymphoma (FL, n = 1) (4%) and extranodal NK/T-cell lymphoma nasal type (NKTL, n = 1) (4%). Two patients had multiple myeloma (MM) (8%). One patient with MM had a previous history of VTE (deep vein thrombosis in the right lower limb). The remaining 24 patients had no previous history of VTE.

In patients with tumors, the mean age at diagnosis of PE was 58.5 years (19–82 years). There were 33 males (41.8 %) and 46 females (58.2%). A total of 41 patients (51.9%) had respiratory tumors, 23 patients (29.1%) had gynecological tumors, 8 patients (10.1%) had digestive system tumors, and 7 patients (8.9%) had other types of tumors. Table 1 showed the baseline characteristics of the enrolled PE patients.

Table 1
The baseline characteristics of enrolled PE patients

Characteristic	Hematological malignancies (n = 25)	Tumors (n = 79)	p value
Mean age, years	47.9 ± 3.892 (14–75)	58.5 ± 1.210 (19–82)	0.0007*
Male sex, No.(%)	17 (68.0)	33 (41.8)	0.008*
Cancer type, No.(%)			
AL	9 (36.0)		
NHL	14 (56.0)		
MM	2 (8.0)		
Respiratory system		41 (51.9)	
Digestive system		8 (10.1)	
Gynecological tumor		23 (29.1)	
other tumor types†		7(8.9)	
History of VTE, No.(%)	1 (4.0)	9 (11.4)	0.275
PE only, No.(%)	15 (60.0)	33 (41.8)	0.213
PE with DVT, No.(%)	10 (40.0)	46 (58.2)	0.213
Signs and symptoms, No.(%)			
Chest pain	0	1 (1.3)	
Dyspnea	20 (80.0)	57 (72.2)	
Swellig in the lower limb	2 (8.0)	4 (5.1)	
syncope	0	1 (1.3)	
back pain	0	2 (2.5)	
Aasymptomatic	0	4 (5.1)	
Multi-Symptom(≥2)	3 (12)	10 (12.7)	
Electrocardiograph changes, No.(%)			

Abbreviation: PE pulmonary embolism, DVT deep vein thrombosis, VTE venous thromboembolic events, AL acute leukemia, NHL non-Hodgkin's lymphoma, MM multiple myeloma

† Other tumor types referred to the tumor which only one case was included: prostate cancer, seminoma, breast cancer, osteosarcoma, melanoma, nasopharyngeal darcinoma, central nervous system tumor

Characteristic	Hematological malignancies (n = 25)	Tumors (n = 79)	p value
S1Q3T3 pattern	0	2 (2.5)	
Nodal tachycardia	6 (24.0)	18 (22.8)	
Atrial premature beats	1 (4.0)	2 (2.5)	
Paroxysmal ventricular tachycardia	1 (4.0)	2 (2.5)	
atrial fibrillation	0	2 (2.5)	
Normal	17 (68.0)	53 (67.1)	
Ongoing chemotherapy, No.(%)	17 (70.8)	15 (19.0)	< 0.0001*
Clinical outcomes, No.(%)			
PE-related death	4 (16.0)	17 (21.5)	0.49
Recurrence PE	0	2 (2.5)	
Embolus location, No.(%)			
Central PE	2 (8.0)	3 (3.8)	0.64
Peripheral PE	11(44.0)	41 (51.9)	
Both central and peripheral PE	12(48.0)	35 (44.3)	
Bilateral PE	10 (40.0)	36 (45.6)	0.625
Unilateral PE	15 (60.0)	43 (54.4)	
Laboratory tests			
Leukocyte count ($\times 10^9$/L)	11.75 ± 3.419	8.334 ± 0.5328	0.111
Hemoglobin (g/dL)	97.60 ± 5.481	113.9 ± 2.417	0.0025*
Platelet count ($\times 10^9$/L)	204.4 ± 26.16	230.7 ± 11.64	0.3017
Fibrinogen (g/L)	3.420 ± 0.2201	3.859 ± 0.1679	0.1759
D-Dimer (ug/ml FEU)	5.702 ± 3.141	14.64 ± 1.836	0.0171*
Clinical history, No.(%)			

Abbreviation: PE pulmonary embolism, DVT deep vein thrombosis, VTE venous thromboembolic events, AL acute leukemia, NHL non-Hodgkin's lymphoma, MM multiple myeloma

† Other tumor types referred to the tumor which only one case was included: prostate cancer, seminoma, breast cancer, osteosarcoma, melanoma, nasopharyngeal darcinoma, central nervous system tumor

Characteristic	Hematological malignancies (n = 25)	Tumors (n = 79)	p value
Smoking	9 (37.5)	18 (22.8)	
Diabetes	2 (8.3)	5 (6.3)	
Hypertension	4 (16.7)	16 (20.3)	
Pheumonia	16 (66.7)	22 (27.8)	0.001*
Bilateral	13 (54.2)	12 (15.2)	
Unilateral	3 (12.5)	10 (12.7)	
Pleurual effusion	14 (58.3)	51 (64.6)	0.68
Bilateral	11 (45.8)	27 (34.2)	
Unilateral	3 (12.5)	24 (30.4)	
Catheter	9 (37.5)	12 (15.2)	0.024*
cholecystolithiasis	1 (4.2)	11 (13.9)	
Fatty liver disease	2 (8.3)	2 (2.5)	
coronary artery disease	0	6 (7.6)	
Surgical history within 30 days	2 (8.0)	32 (40.5)	< 0.0001*
Treatment of patients with PE, No.(%)			
No anticoagulant treatment, No.(%)	5 (20.0)	14 (17.7)	
Anticoagulant treatment,No.(%)	20 (80)	65 (82.3)	
Abbreviation: PE pulmonary embolism, DVT deep vein thrombosis, VTE venous thromboembolic events, AL acute leukemia, NHL non-Hodgkin's lymphoma, MM multiple myeloma			
† Other tumor types referred to the tumor which only one case was included: prostate cancer, seminoma, breast cancer, osteosarcoma, melanoma, nasopharyngeal darcinoma, central nervous system tumor			

Incidence And Manifestations Of Pe

A total of 19 cases of PE (76.0%) in HM patients occurred within 50 days of the date of diagnosis of HM. Ten patients (10/19, 52.6%) were NHL patients and 36.8% (7/19) of them were AL patients. The onset time of PE in tumor patients showed two peaks: 44.3% of tumor patients developed PE within 2 weeks (n = 35), and 38.0% of tumor patients developed PE within 3 months of diagnosis (n = 30) (Fig. 1a)(Table 2). Patients with gynecological tumors had a tendency to develop PE within the first month after diagnosis,

and patients with digestive system tumors had a peak period of PE development from 3 to 12 months after diagnosis (Fig. 1b).

Table 2
The median time from diagnosis to the onset of PE

Median time from diagnosis, days	Hematological malignancies (n = 25)	Tumors (n = 79)
AL	21 (4-663)	
NHL	69 (5-1457)	
MM	-	
Respiratory system		51 (0-3257)
Digestive system		108 (1-1081)
Gynecological tumor		8 (0-764)

In HM patients, 15 patients (60.0%) had PE only. Ten patients (40.0%) had PE with deep vein thrombosis (DVT) and 8 of those 10 were NHL patients (32.0%). In tumor patients, 33 patients (41.8%) had PE only. Forty-six patients (58.2%) had PE with DVT, including 22 patients (27.8%) with respiratory system tumors and 17 patients (21.5%) with gynecological tumors. No significant differences were found between HM patients and tumor patients.

In HM patients, a unilateral embolus location was recorded in 15 patients (60.0%), and a bilateral embolus location was recorded in 10 patients (40.0%). Forty-three tumor patients(54.4%) had unilateral PE, and 36 patients (45.6%) had bilateral PE. Patients were further categorized according to the most proximal site of occlusion as having central PE (main trunk, left/right main pulmonary arteries and lobar branches) or peripheral PE (segmental and subsegmental branches). A total of 11 (44.0%) HM patients had peripheral PE, 2 (8.0%) patients had central PE, and 12 (48.0%) patients had multiple levels of PE. Peripheral PE was more likely to occur in leukemia patients (6/11, 54.5%), while NHL patients(8/12, 66.7%) were more likely to develop multiple levels of PE. In tumor patients, 41 (51.9%) patients had peripheral PE, 3 (3.8%) patients had central PE, and 35 (44.3%) patients had both. There was no significant difference in embolus location between HM and tumor patients.

Although the clinical manifestations of PE in tumor patients were more varied than those of HM patients, the main symptom was dyspnea in both groups (HM 80.0%, cancer 72.2%). ECG findings in most patients in both groups were normal (HM 68.0% vs. tumor 67.1%).

Risk Factors For Pe

Among HM patients in this study, NHL was the most common histology (56.0%), and the majority of them were in stages III and IV (n = 11, 44.0%). Patients with respiratory system tumors accounted for the majority of tumor patients (51.9%). In HM patients, a total of 17 (68.0%) patients developed PE during chemotherapy, whereas 8 (32.0%) developed PE occurring prior to chemotherapy, including 5 patients (4 DLBCL, 1 B-ALL) in whom PE and HM were diagnosed concurrently. Only 19% of tumor patients developed PE during chemotherapy, which was significantly lower than the proportion of HM patients ($p < 0.0001$). But, a total of 40.5% of the tumor patients had a history of surgery within 30 days, which was significantly higher than the proportion of HM patients (8%, $p < 0.0001$).

Sixteen (64.0%) HM patients had pneumonia when PE occurred, including 13 (54.2%) patients with bilateral pneumonia. Only 22 tumor patients (27.8%) had pneumonia, which was a significantly lower proportion in that of HM patients ($p = 0.001$). There was no significant difference in the incidence of pleural effusion between the two groups.

In total, 37.5% of HM patients had PICCs. Among these patients, PE occurred within 50 days after PICC catheterization in 6 patients (66.7%). Only 15.2% of tumor patients had history of PICCs. A significant difference was found between the 2 groups ($p = 0.024$).

Laboratory tests, including leukocyte count, hemoglobin value, platelet count, fibrinogen level and D-dimer level were further analyzed in both groups. Significant differences were found in hemoglobin and D-dimer levels between the two groups. The hemoglobin and D-dimer levels in HM patients were much lower than those in tumor patients ($p = 0.0025$, $p = 0.0171$). The D-dimer level was elevated in 84% of HM patients and 97.5% of tumor patients.

Impact Of Pe On Survival

The mean duration of treatment in the hospital with anticoagulant or thrombolytic therapy was 12.7 days (range 0–28 days) in this study. The 30-days PE-related mortality rates were 16% in HM patients and 22.8% in tumor patients. There was no significant difference between the two groups ($p = 0.49$) (Fig. 2). Prophylactic treatment with low-molecular-weight heparin (LMWH) was not administered to any patient in this study. After the development of PE, 80.0% of HM patients and 82.3% of tumor patients received anticoagulant or thrombolytic therapy in the hospital, including subcutaneous injections of the full therapeutic dose of LMWH (100 U/kg body weight every 12 h) and the administration of warfarin according to the therapeutic International Normalized Ratio (INR). The remaining patients were not treated because of contraindications, except for 2 HM patients and 5 tumor patients who died before treatment could be administered. As of the end of December 2020, treatment-related mortality had not been observed in either group. No treatment-related mortality or major bleeding was observed in HM patients. Unfortunately, because some patients were lost to follow-up, data on recurrent VTE were not obtained.

Discussion

VTE is a common complication in patients with cancer. PE is a form of VTE that is common and a major cause of morbidity and mortality in cancer patients. Patients with HM constitute a particular subset of cancer patients with significant differences. Thus far, little is known about the differences between HM and tumor patients in terms of the clinical characteristics at the time of the development of PE. PE can be classified into different subgroups based on the temporal pattern of presentation (acute, subacute, or chronic), the presence or absence of hemodynamic instability (massive PE, submassive PE, or low-risk PE), the anatomic location (saddle, lobar, segmental, or subsegmental), and the presence or absence of symptoms. The signs and symptoms of PE are often nonspecific, making the diagnosis particularly challenging. The clinical presentation ranges from mild dyspnea or chest pain to sustained hypotension or shock. Sometimes, PE may even be asymptomatic and consequently diagnosed only with imaging procedures performed for other purposes. According to the results of 904 tumor patients with PE in the MD Anderson Cancer Center emergency department (ED) [12], symptoms were observed in 20% of patients, and shortness of breath (17.3%) was the main symptom. VTE was discovered in 20.9% of the patients with PE as a concurrent incidental finding and was associated with poor overall survival. In a study reported by the People's Liberation Army (PLA) 307 Hospital with 52 Chinese tumor patients included [13], symptoms of PE were observed in 88% of the patients. A total of 53.1% of the patients complained of dyspnea without obvious causes. A total of 34.4% of the patients had DVT. The main tumor types in the ED were gastrointestinal system tumors (29.4%) and respiratory system tumors (46.2%) in Chinese patients, which might have caused a lower proportion of patients with dyspnea in the ED study and a higher proportion of patients with dyspnea in the PLA study. Despite the large number of cases included in both studies, only a small proportion were HM patients, 9.9% and 23.1% respectively, and data on HM patients were lacking. In this study, symptoms were observed in all HM patients and 94.9% of tumor patients. In addition, 80% of the HM patients and 72.2% of the tumor patients presented with dyspnea, indicating that *the majority of Chinese cancer patients with PE had clinical manifestations and that dyspnea might be the first sign in both Chinese HM and cancer patients*. This is different from the results reported in Western countries, which may be caused by different constitutions of cancer types and different physical qualities of patients.

In addition, 27.9% of the patients in the ED had central PE and 36.4% of the patients had multiple levels of PE at the same time. A unilateral embolus location was recorded in 71.8% of patients. At PLA 307 Hospital, 54.2% of the patients had central-type PE, and the number of patients with multiple levels of PE was not specified. However, in the present study, the incidences of central PE were significantly lower and the incidences of multiple levels of PE were much higher in HM and tumor patients than those reported by the ED. Significant differences were not found between HM and tumor patients with respect to the location of PE. Further multi-center analysis with a large sample size are needed. *But, it is worth noting that patients with acute leukemia had a higher incidence of peripheral PE, whereas patients with NHL had a higher incidence of central PE.* Most of the cases involved unilateral PE. These differences may be caused by the nature of the disease itself.

VTE is likely to be a symptom of occult malignancy, and PE is often the first manifestation in patients with tumors[14]. Natasha Kekre summarized the incidence of VTE in patients with HMs [15], reporting that the overall risk of VTE in patients with ALL and APL remained high at close to 10%. Patients with AML had a VTE incidence of 5–8%, and patients with aggressive lymphoma had a VTE incidence of 4.2%. In a single-center study of over 1000 patients [16], patients with high-grade lymphoma had almost twice the incidence of VTE compared with that in patients with low-grade lymphoma (10.6% vs. 5.8%). Besides, the latest study reported by Veli Bakalov[17] analyzed the risk factors for VTE in 4236 hospitalized patients with hematological malignancy in the US. The largest number of PE patients with hematological malignancy to date, that is, a total of 944 patients, was included. According to its results, the rate of VTE was highest in patients with AML (6.6%), followed by patients with ALL (6.1%) and NHL (6.0%), and the VTE rate was lowest in patients with MM (3.5%) and chronic lymphocytic leukemia (CLL) (3.3%). The top three incidences of PE among the hematological malignancies occurred in CLL (28.7%), NHL (26.8%) and ALL (25.3%). However, in this study, *more than half of the HM patients had malignancies derived from B-cells. NHL, especially DLBCL, had the highest incidence among the reported cases rather than AL or CLL.* None of the cases were CLL or chronic myelogenous leukemia (CML) in this study. The incidences of VTE were similar between HM and tumor patients. Combining all of the above data, PE was more common in NHL than in other types of HM. But the types of HM most prone to PE might be related to the population in different areas. What's more, *it showed that a high incidence of VTE does not necessarily mean a high incidence of PE in HM patients.*

Fifty percent of tumor patients had PE occurring in the 3 months before or after the tumor diagnosis[13]. The highest incidence of VTE occurred in the first 6 months from diagnosis in patients with ALL, AML and APL and within the first 12 months in patients with CLL and lymphoma [15].In this study, the onset time of PE in tumor patients had two peaks. The majority of tumor patients developed PE within 2 weeks or 3 months after the diagnosis of the cancer, which was basically consistent with the literature. Patients with gynecological tumors had a tendency to develop PE within the first month after diagnosis, which was much earlier than in patients with other types of tumors. And, *most HM patients developed PE within 50 days of the diagnosis of HM. This showed that PE in HM patients occurred much earlier than in patients with most other types of cancer. Patients with HM or gynecological tumors need to be alert to the risk of early PE when developing acute dyspnea.*

MM has a high rate of VTE associated with immunomodulatory therapies, with this rate ranging from 1–6%[18]. The use of thalidomide and lenalidomide has been associated with a marked increase in the risk of VTE[18]. The study reported that the highest incidence of VTE occurred in the first 16 months from diagnosis in patients with MM and in the first 3 months in patients treated with immunomodulatory drugs such as thalidomide or lenalidomide [15]. In this study, patients with MM had a PE incidence of 8.3%. Consistent with the VTE incidence in the above-reported investigations, all of the patients in the present study experienced PE in the first 3 months.

Tumor metastasis aggravates a high blood-coagulation state, which is a major cause of the increasing rate of PE in patients with advanced cancer [15]. The strongest risk factors for VTE other than cancer are

infectious complications, including sepsis, invasive candidiasis, pneumonia and IV line infections [17, 19]. In a study reported by Wang H[13], factors such as age, sex, smoking history and hypertension were not significantly different between tumor and nontumor patients with PE, but factors such as coronary heart disease, hyperlipidemia, chronic obstructive pulmonary disease and diabetes were significantly different between the two groups. In this study, the medical history of all patients with PE had no obvious similarities. However, 64% of HM patients had pneumonia when PE occurred and 40.5% of tumor patients had surgical history within 30 days. Among tumors patients who had a surgical history within 30 days, 46.9% developed pneumonia. In addition, 68% of HM patients in this study were male; moreover, all of the male patients with PE had a history of smoking, and 76.5% of the male patients had pneumonia. The results indicated that *developing pneumonia and a history of smoking in male patients were potential risk factors for PE occurrence in HM patients, especially in DLBCL patients. For patients with tumors, a surgical history within 30 days complicated with pneumonia might increase the risk of PE occurrence*.

Furthermore, chemotherapy was an important trigger for hospitalization secondary to VTE [20]. The odds ratios for the development of VTE were significantly higher in tumor patients receiving chemotherapy than in chemotherapy-naïve cancer patients [21]. The possible mechanism for this increased risk might be direct damage to endothelial cells caused by chemotherapy and surgery, induction of the coagulation pathway or activation of the coagulation system in vivo by the release of tissue factors. *This study showed that ongoing chemotherapy in HM patients was associated with a greater risk of PE than tumor patients*. In addition to chemotherapy, CVCs also constitute a very important clinical risk factor for VTE [22]. According to a study reported by the MD, CVC-PE events were responsible for 9.4% and 4.7% of cases in the ALL and AML groups, respectively [22]. In our center, a PICC line was usually placed once a patient was diagnosed with HM. *A total of 36% of the HM patients had PICCs and most of them developed PE within 50 days after the PICC line was placed*. However, it was difficult to identify the effects of malignancies and PICCs on PE occurrence.

In addition, several risk factors for VTE in cancer patients, such as thrombocytosis, leukocytosis, low hemoglobin levels, and elevated D-dimer levels, have been reported [23–26]. According to PE guidelines, a D-dimer level below 0.5 μg/mL is a PE exclusion criterion. The D-dimer level was found by Bai CM to be elevated in 90.9% of PE patients [27]. Similarly, *the D-dimer level was elevated in 84% of HM cases and 97.5% of tumor patients in the present study. However, the D-dimer values in HM patients were much lower than those in tumor patients.* Although the hemoglobin levels in HM patients were much lower than those in tumor patients, this finding might be related to the HM. To date, there are no clear data supporting the association of the abovementioned factors with PE in patients with HMs. Multicenter studies with a larger number of PE cases are needed for further analysis.

Treatment of PE in HM patients is more complex than that for PE in the setting of other kinds of cancer. Anticoagulation in patients with hematologic malignancy is challenging due to severe thrombocytopenia and a high risk of bleeding. Some studies have indicated that withholding anticoagulation when platelets drop below 50×10^9/L could avoid bleeding but is associated with higher VTE recurrence [28–31]. Limited data are available to guide decisions on the management of PE prophylaxis, and treatment in HM

patients. In this study, 80.0% of HM patients received anticoagulant or thrombolytic therapy in the hospital. No treatment-related mortality or major bleeding was observed. *The 30-days PE-related mortality rate was similar in HM and tumor patients, and no significant difference was found.*

Our investigation was limited because it was a retrospective and descriptive single-center study. The number of PE patients included was limited. In addition, because CTPA was not regularly performed in our center, some PE patients without clinical symptoms might have been missed. In addition, the long-term bleeding rates and incidence of recurrent VTE were not captured by this study because patients received outpatient medical treatment after discharge from the hospital leading to loss to follow-up in some of them. Therefore, a long-term clinical observational study should be performed in PE patients with HMs.

Conclusion

Patients with HMs constitute a particular subset of patients with significant differences, and evidence is needed to inform the management of PE prophylaxis and treatment in this population. *This study identified several clinical features of PE in HM patients that differ from those in tumor patient, which may be helpful for the diagnosis, prevention and treatment of PE in HM patients in the future*. However, because of several limitations described above, further investigations are needed.

List Of Abbreviations

AL acute leukemia

APL acute promyelocytic leukemia

AUL acute undifferentiated leukemia

AITL angioimmunoblastic T-cell lymphoma

B-ALL B-cell lymphoblastic leukemia

CML chronic myelogenous leukemia

CLL chronic lymphocytic leukemia

CTPA computed tomography pulmonary angiography

CVC central venous catheters

DVT deep vein thrombosis

DLBCL diffuse large B-cell lymphoma

FL follicular lymphoma

HM hematological malignancies

LMWH low-molecular-weight heparin

MDS myelodysplastic syndrome

MM multiple myeloma

NHL non-Hodgkin's lymphoma

PICCs peripherally inserted central catheters

PE pulmonary embolism,

VTE venous thromboembolic events

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tongji Hospital. Since this study does not involve the collection of human tissues, blood and other samples, only the original medical records would be collected for retrospective analysis, we obtained verbal informed consent from all participants or their family members (if the patients have passed away), and the ethics committee approved this procedure.

Consent for publication: Not applicable.

Availability of data and material The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Authors' Contributions: SM L and XW W collected the data, JY analyzed the data and wrote the manuscript. YC Z helped design the study. All authors have read and approved the manuscript.

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Figures

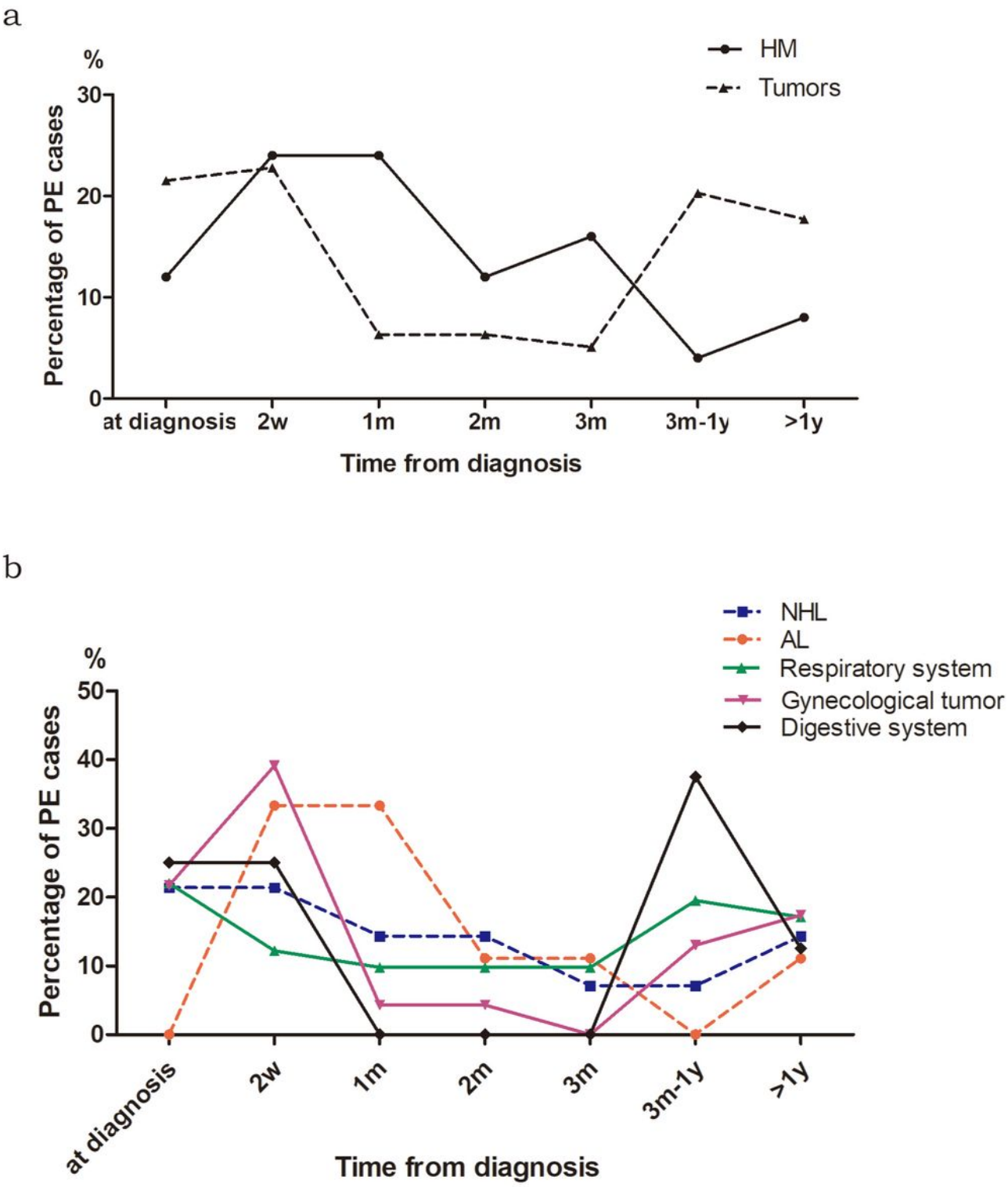

Figure 1

The time between the occurrence of pulmonary embolism and disease diagnosis. A total of 76.0% HM patients developed PE within 50 days of the date of diagnosis of HM. The onset time of PE in tumor patients had two peaks: 44.3% of tumor patients developed PE within 2 weeks and 38.0% developed PE within 3 months of diagnosis (Figure 1a). Further subgroup analyses are shown in Figure 1b.

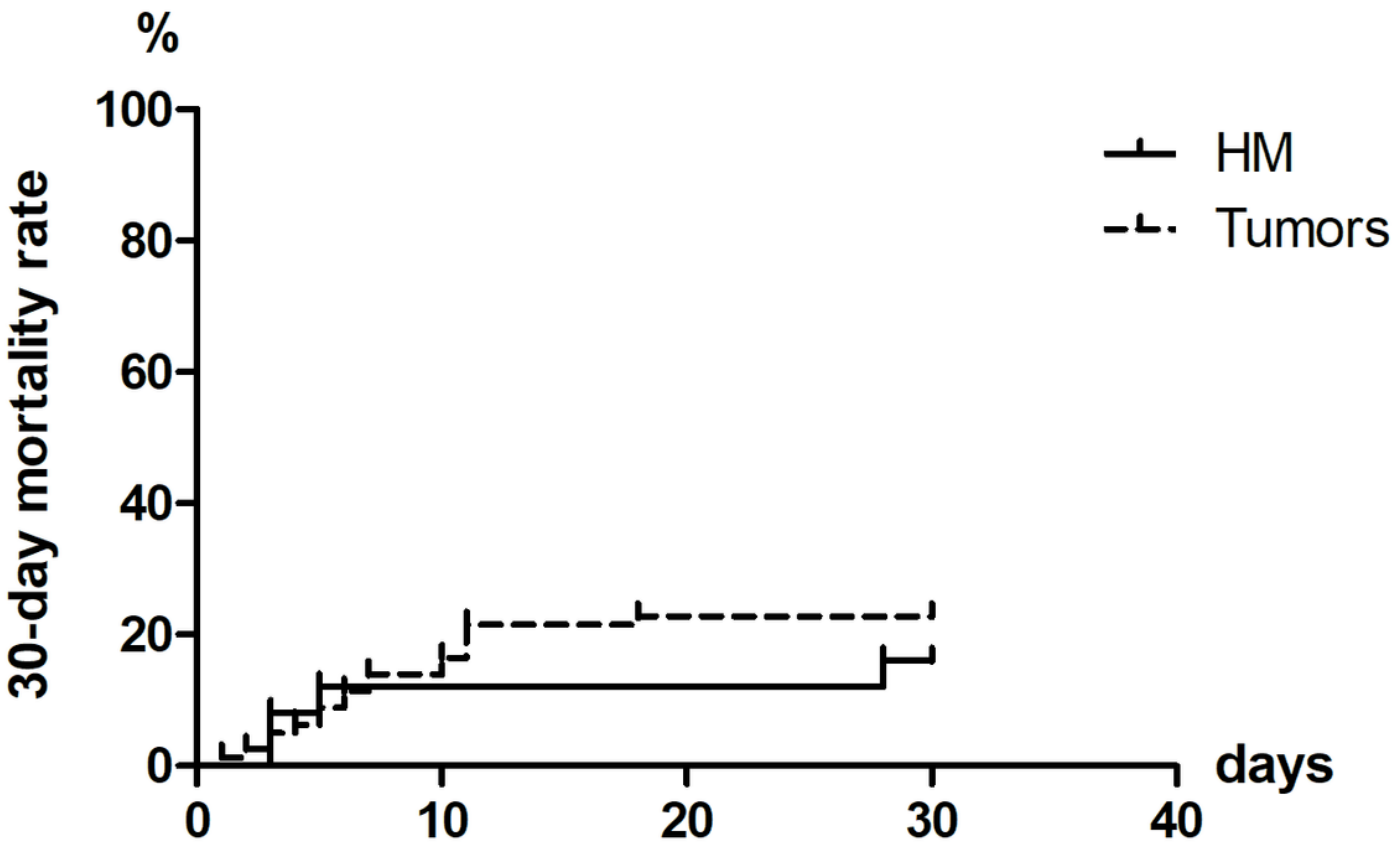

Figure 2

The 30-days PE-related mortality rates in HM and tumor patients.