



OPEN Clinical analysis of bleeding and thrombotic events in haematological-oncology patients with severe thrombocytopenia and a high risk of thrombosis

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Background: Haematological patients with severe thrombocytopenia and high thrombotic risk face challenges related to balancing bleeding and thrombosis risks. This study investigated factors associated with bleeding and thrombosis in high-risk haematological oncology patients with severe thrombocytopenia not receiving anticoagulant therapy and characterized their clinical features when both events occurred. **Methods:** A total of 446 haematological oncology patients with Caprini scores ≥ 5 were included from July 2022 to June 2023 at Mianyang City Central Hospital. Those not receiving prophylactic anticoagulants due to an admission platelet count $< 50 \times 10^9/L$ were studied. Patients were categorized into bleeding/nonbleeding and thrombotic/nonthrombotic groups on the basis of hospital course. Relevant clinical data were collected, and univariate/multivariate logistic regression was used to analyse the influencing factors. The platelet count at admission was assessed via ROC curves for thrombosis prediction. **Results:** In the bleeding group, higher proportions of patients with leukaemia, myeloid tumours, lung infections, and a central venous catheter (CVC) with two lumens were observed, along with shorter catheter durations, lower initial and minimum platelet counts during hospitalization, and prolonged plasminogen times (all $P < 0.05$). The thrombotic group had a greater thrombosis history, initial platelet count, use of two venous catheter lumens, parenteral nutrition, sedation, and autologous haematopoietic stem cell transplantation (Auto-HSCT), with a lower leukaemia proportion ($P < 0.05$). Logistic regression identified lymphoma type and minimum platelet count as bleeding protective factors and the Charlson Comorbidity Index (CCI) score as an independent risk factor. Thrombosis history, two venous catheter lumens, and sedation were risk factors for thrombosis. The median platelet count was lower at bleeding and thrombosis than at admission ($P = 0.007$). The platelet count at admission had predictive value for thrombosis, especially severe thrombocytopenia, with an AUC of 0.735 (95% CI 0.613–0.858, $P = 0.003$) and a cut-off value of $42.5 \times 10^9/L$. **Conclusions:** For haematological neoplasm patients with a high risk of venous thromboembolism (VTE), severe thrombocytopenia and high CCI scores, risk prevention and control of bleeding take precedence over thrombosis prophylaxis. Prophylactic anticoagulation is still recommended for patients with lymphoma assessed at high risk for VTE and with platelet counts of at least $42.5 \times 10^9/L$.

Keywords Haematological Neoplasms, Thrombosis, Bleeding, Thrombocytopenia, Risk factors, Thrombohemorrhagic syndrome (TSH)

Abbreviations

CVC Central venous catheter
Auto-HSCT Autologous haematopoietic stem cell transplantation

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VTE	Venous thromboembolism
BMI	Body mass index
CCI	Charlson comorbidity index
EPO	Erythropoietin
GFR	Glomerular filtration rate
CCr	Endogenous creatinine clearance rate
PICC	Peripherally inserted central catheter
NEUT	Neutrophil granulocyte count
NVUGIB	N0n-variceal upper gastrointestinal bleeding
OAC	Oral anticoagulants
TSH	Thrombohemorrhagic syndrome
CAT	Cancer-associated thrombosis
TP	Thrombocytopenia
EHA	European Hematology Association
NCICTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ISTH	International Society on Thrombosis and Haemostasis
NCCN	National Comprehensive Cancer Network
ITAC	International Initiative on Thrombosis and Cancer

Thrombosis is a common complication faced by all patients with malignant diseases^{1,2}. The incidence of venous thromboembolism (VTE) in patients with haematological malignancies has been reported to range from 2.5–9.3%³. This is comparable to that of solid tumours. The incidence of bleeding in haematological malignant tumours can reach 20–51.3%⁴ because of the disease itself, therapeutic factors, abnormalities in coagulation and thrombocytopenia^{5,6}. Therefore, patients with haematological malignancies are often challenged by the dual risks of bleeding and thrombosis at the same time. Especially when thrombocytopenia is known to be severe, thrombosis prophylaxis and treatment must be attempted to avoid and reduce the occurrence of bleeding events. This becomes a difficult clinical issue. Most existing guidelines support neutral and noninterventional strategies in the case of severe thrombocytopenia^{7–10}, both in terms of thromboprophylaxis and interventional therapy when thrombosis occurs. Whether such treatment principles can effectively reduce the risk of bleeding and thrombosis has rarely been studied. There are also few clinical studies on the coexistence of thrombotic and bleeding events in haematological oncology patients. Therefore, how to balance the risks of thrombosis and bleeding in haematological oncology patients with high thrombotic risk and severe thrombocytopenia needs to be further explored. The aim of this study was to investigate the risk factors associated with the occurrence of bleeding and thrombosis in haematological oncology patients at high risk of thrombosis with severe thrombocytopenia in the absence of prophylactic anticoagulation. This study also examined the clinical features when bleeding and thrombosis coexisted. This study aimed to provide a basis and solutions for balancing, preventing and managing thrombosis and bleeding in such contradictory and challenging settings.

Methods

Study population

This study included 446 patients consecutively admitted to the Department of Hematology at Mianyang Central Hospital (Mianyang, China) from July 2022 to June 2023. These patients had a Caprini score of ≥ 5 and were not treated with prophylactic anticoagulant therapy because their minimum platelet count was $< 50 \times 10^9/L$ at the time of admission. The following are the inclusion criteria: (1) aged ≥ 15 years, (2) diagnosed with haematological malignancies, (3) a Caprini score ≥ 5 , (4) a minimal platelet count $< 50 \times 10^9/L$, (5) not prophylactically anticoagulated, (6) able to read and communicate normally, and (7) willing to participate. The following are the exclusion criteria: (1) mental illness or cognitive impairment, (2) poor compliance, (3) other malignant diseases, (4) those who reported missing important data or were unavailable, (5) those who opted to forgo treatment, and (6) those with a hospital stay of less than 24 h. A flow chart of patient screening (Fig. 1).

Clinical information

Basic clinical information and relevant factors relevant to thrombosis and bleeding reported in the literature were collected for all patients, including physical characteristics (gender, age, height, weight, body mass index (BMI)), health history (smoking, alcohol consumption, diabetes mellitus, hypertension, coronary artery disease, hyperlipidaemia, history of thrombosis), disease characteristics (types of haematological malignancies, cellular origin, lower limb oedema, septicaemia, lymph node mediastinal involvement, extranodal disease, coexisting pulmonary infection, Charlson Comorbidity Index (CCI) score, Caprini score), laboratory tests, diagnostic status (bedridden for > 72 h, intravenous catheter placement, erythropoietin (EPO), parenteral nutrition, steroids, immunomodulators, sedation, chemotherapy, Autologous Haematopoietic Stem Cell Transplantation (Auto-HSCT)), and patient survival outcomes^{3,4,11–18}. The patients were divided into bleeding and nonbleeding groups according to whether bleeding occurred during hospitalization. The patients were divided into thrombotic and nonthrombotic groups according to whether thrombosis occurred.

Definitions

Severe thrombocytopenia was defined as a platelet count $< 50 \times 10^9/L$ ¹⁹.

Bleeding events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 3.0 criteria, with grades 1–5.

A Caprini score of ≥ 5 was x bleeding symptoms but previous treatment with short-term tertiary or greater thrombocytopenia after medium- and high-dose chemotherapy.

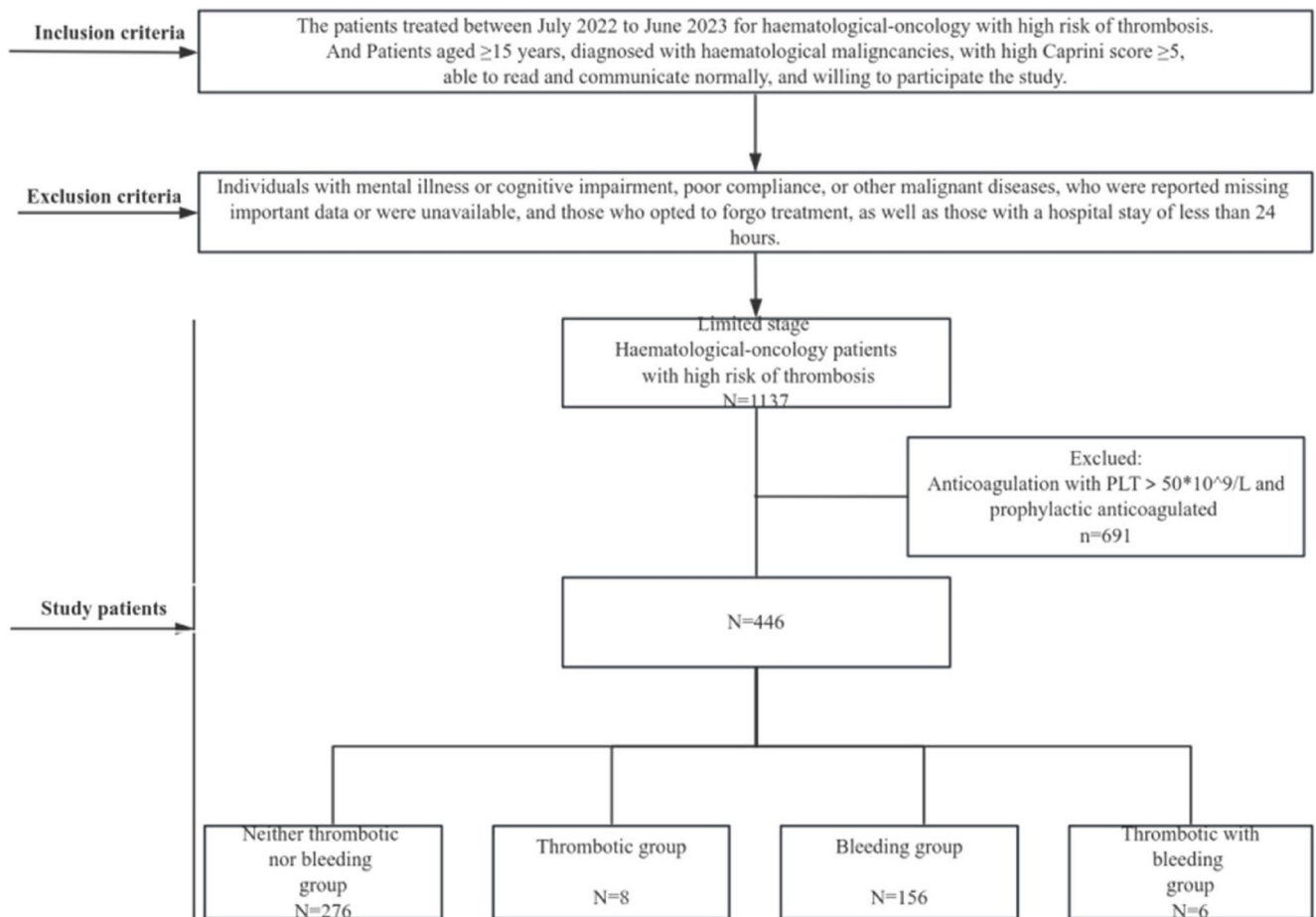


Figure 1. Flow chart of patient screening.

Statistical methods

This study used SPSS 27.0 statistical software for statistical analysis. For one-way statistical analyses between the two groups, the normality of the sample data was first determined via the Kolmogorov–Smirnov normality test for continuous (quantitative) data. If the data were normally distributed, the independent samples t test was applied, and the mean \pm standard deviation was used. If the data were not normally distributed, the Wilcoxon test was applied, and the median (interquartile spacing) was used. For categorical (qualitative) data, the χ^2 test or Fisher’s exact test was applied, and frequencies (%) were used. Multiple analyses were performed by setting the variables with p values < 0.05 from the results of the univariate analyses in each group separately as independent variables and performing binary logistic regression analyses via the input method.

For descriptive statistical analysis, the normality of the sample data was determined via the Shapiro–Wilk normality test for continuous (quantitative) data. The mean \pm standard deviation was used if the data were normally distributed, and the median (IQR) was used if the data were not normally distributed. For categorical (qualitative) data, frequency (%) was used for statistical description. For the analyses of the three groups, for continuous (quantitative) data, the normality of the sample data was first determined via the Shapiro–Wilk normality test. If the data conformed to a normal distribution, one-way ANOVA was applied, and the results are expressed as the means \pm standard deviations. If the data were not normally distributed, the Kruskal–Wallis H test was applied, and the median (quartiles) was used. For two-by-two comparisons, the independent samples Kruskal–Wallis test was applied.

The ability of the platelet count at admission to predict thrombosis was evaluated by plotting an ROC curve. Differences were considered statistically significant when the two-sided p value was < 0.05 .

Results

Clinical characterization of haematological oncology patients with a high risk of thrombosis suffering thrombosis and bleeding simultaneously or sequentially during the same hospital stay

Among the 1137 patients, 11 had thrombosis combined with haemorrhagic events. Most of the patients were male (63.74%), the median age was 52.09 ± 20.04 years, and the median BMI was 22.67 kg/m^2 . In terms of health history, 27.27% of the patients had a history of thrombosis, 72.73% had no smoking habit, and 91.91% had no history of alcohol consumption or diabetes. All personnel had no history of hypertension, coronary

heart disease, or hyperlipidaemia. In terms of disease characteristics, 54.55% of the patients had myeloid leukaemia, 90.91% had no lower limb oedema, 63.64% had no sepsis, 81.82% had no mediastinal involvement of the lymph nodes, and all had no extranodal disease; however, 72.73% had a combined lung infection. In this group, the median CCI score was 4, the median Caprini score was 6, and the ISTH DIC score was 5.33 ± 1.58 . For the initial laboratory tests, the serum ALB concentration was 35.78 ± 4.90 g/L, the glomerular filtration rate (GFR) was 69.54 ± 32.67 mL/min, the median creatinine concentration was 70.50 μ mol/L, and the median endogenous creatinine clearance rate (CCr) was 87.80 mL/min. The median platelet count during hospitalization was a minimum of 25×10^9 /L. In terms of treatment status, 45.45% of patients were bedridden for more than 72 consecutive hours, 90.91% received EPO and immunomodulators, 63.64% were treated with parenteral nutrition and steroids, 72.73% received chemotherapy, 18.18% received sedation and Auto-HSCT, and 72.73% of the patients had an intravenous catheter placed, with the majority of the types of catheters being single lumen (62.50%) and a peripherally inserted central catheter (PICC) (75.00%), and the length of intravenous catheter retention was 105.88 ± 91.00 days. A total of 90.91% of the patients survived. With respect to the timing of bleeding and thrombus occurrence, thrombus occurred first in 45.45% (5/11) of patients, bleeding occurred first in 36.36% (4/11) of patients, and thrombus and bleeding occurred simultaneously in 18.18% (2/11) of patients (Table 1).

Laboratory findings at three different stages (admission, bleeding and thrombosis) were subjected to one-way ANOVA or the Kruskal-Wallis H test. The results showed that the median platelet count was lower at the time of bleeding and thrombosis than at admission (23 vs. 26 vs. 161×10^9 /L, $H=9.845$, $P=0.007$). A two-by-two comparison revealed that platelet counts were significantly lower during bleeding than at admission ($Z=12.455$, $P=0.008$) and during thrombosis than at admission ($Z=9.227$, $P=0.075$). There was no statistically significant difference in platelet counts during bleeding versus thrombosis (23 vs. 26×10^9 /L, $Z=-3.227$, $P=1.000$). The

Variables	Thrombosis with bleeding	Variables	Thrombosis with bleeding
Physical characteristics of patients		Laboratory tests	
Gender, n (%)		Liver and kidney function at admission	
Male	7 (63.64)	Albumin (g/L)	35.78 ± 4.90
Female	4 (36.36)	Creatinine (μ mol/L)	70.50 (58.90-85.55)
Age (years)	52.09 ± 20.04	GFR(mL/min)	69.54 ± 32.67
Weight (kg)	62.27 ± 14.19	CCr (mL/min)	87.80 (40.30-119.80)
Height (cm)	162.82 ± 9.06	Minimum platelet count ($\times 10^9$ /L)	25(5-58)
BMI, kg/m ²	22.67 (19.63-24.22)	Diagnostic and treatment status	
Patient health history		Bedridden > 72 h, n (%)	5 (45.45)
Smoking history, n (%)	3 (27.27)	Intravenous catheter placement, n (%)	8 (72.73)
History of alcohol consumption, n (%)	1 (9.09)	Types of intravenous catheter, n (%)	
History of diabetes, n (%)	1 (9.09)	PICC	6 (75.00)
History of hypertension, n (%)	0 (0.00)	CVC	2 (25.00)
History of coronary heart disease, n (%)	0 (0.00)	Number of intravenous catheter lumens, n (%)	
History of hyperlipidaemia, n (%)	0 (0.00)	One	5 (62.50)
History of thrombosis, n (%)	3 (27.27)	Two	3 (37.50)
Characteristics of the disease		Length of time the intravenous catheter (day)	105.88 ± 91.00
Type of haematological malignancies, n (%)		Erythropoietin, n (%)	1 (9.09)
Leukaemia	6 (54.55)	Parenteral nutrition, n (%)	7 (63.64)
Lymphomas	3 (27.27)	Steroids, n (%)	7 (63.64)
Plasma cell tumour	2 (18.18)	Immunomodulators, n (%)	1 (9.09)
Cell source of malignancies, n (%)		Sedatives, n (%)	2 (18.18)
Myeloid	6 (54.55)	Chemotherapy, n (%)	8 (72.73)
B-lineage	5 (45.45)	Auto-HSCT, n (%)	2 (18.18)
Lower limb oedema, n (%)	1 (9.09)	Patient outcomes	
Septicaemia, n (%)	4 (36.36)	Survival outcome, n (%)	
Mediastinal involvement of lymph nodes, n (%)	2 (18.18)	Survive	10 (90.91)
Extranodal diseases, n (%)	0 (0.00)	Dead	1 (9.09)
Lung infection, n (%)	8 (72.73)	Bleeding-thrombosis sequence, n (%)	
CCI score	4(3-5)	Thrombus priority	5 (45.45)
Caprini score	6(6-7)	Bleeding priority	4 (36.36)
ISTH DIC score	5.33 ± 1.58	Bleeding-thrombosis at the same time	2 (18.18)

Table 1. Clinical characteristics of 11 patients with thrombosis combined with bleeding out of the 1137 patients at high risk for thrombosis. BMI, body mass index; CCI, Charlson Comorbidity Index; PICC, peripherally inserted central catheter; CVC, central venous catheter; GFR, glomerular filtration rate; CCr, endogenous creatinine clearance rate; Auto-HSCT, autologous haematopoietic stem cell transplantation.

Variables	Admission	Bleeding	Thrombosis	Statistic	P value
Routine blood tests					
WBC ($\times 10^9$ /L)	10.52 (2.89–13.67)	1.48 (0.13–13.67)	3.54 (1.50–9.80)	H = 3.416	0.181
NEUT ($\times 10^9$ /L)	8.71 (2.10–12.85)	1.07 (0.00–12.85)	2.15 (0.28–9.18)	H = 4.065	0.131
Haemoglobin (g/L)	83 (68–118)	83 (72–110)	72 (69–105)	H = 0.405	0.817
Platelet ($\times 10^9$ /L)	161 (58–205)	23(5–58)	26 (13–100)	H = 9.845	0.007*
Coagulation					
Fibrinogen (g/L)	3.53 \pm 1.63	3.86 \pm 1.71	4.28 \pm 2.68	F = 0.346	0.710
PT (s)	12.80 (10.70–14.30)	12.50 (11.00–14.60)	11.90 (11.15–13.28)	H = 0.108	0.947
APTT(s)	26.20 (22.80–29.70)	24.20 (22.80–28.50)	25.90 (24.70–27.75)	H = 0.799	0.671
D-dimer (μ g/L)	3.20 (0.60–15.77)	1.40 (0.70–12.50)	3.68 (1.22–6.09)	H = 0.129	0.938

Table 2. Comparison of laboratory findings at three time points in 11 patients with bleeding combined with thrombosis out of the 1137 patients at high risk of thrombosis. WBC, white blood cell count; NEUT, neutrophil granulocyte count; PT, prothrombin time; APTT, activated partial thromboplastin time. *Statistically significant.

Groups	Z	S	P value
Bleeding - Thrombosis	-3.227	4.120	1.000
Bleeding - Admission	12.455	4.120	0.008*
Thrombosis - Admission	9.227	4.120	0.075

Table 3. Intergroup comparisons of platelet counts. *Statistically significant.

median white blood cell count was lower during bleeding than during thrombosis and at baseline, but the difference was not statistically significant (1.48 vs. 3.54 vs. 10.52×10^9 /L, H = 3.416; $P = 0.181$). The median neutrophil granulocyte count (NEUT) was lower during bleeding than during thrombosis and at baseline, but the difference was not statistically significant (1.07 vs. 2.15 vs. 8.71×10^9 /L, H = 4.065; $P = 0.131$). D-dimer was significantly lower during bleeding than during thrombosis and baseline (1.40 vs. 3.68 vs. 3.20μ g/L, H = 0.129, $P = 0.938$) (Tables 2 and 3).

Comparison of the clinical characteristics of haemato-oncology patients with bleeding (bleeding group) and without bleeding (nonbleeding group) among those with high Caprini scores and those who were not treated with prophylactic anticoagulant agents due to severe thrombocytopenia

Among the 446 patients included, 284 did not experience bleeding, and 162 (36.32%) did. The bleeding group had a higher percentage of leukaemia (80.25% vs. 63.03%, $P < 0.001$), higher percentage of myeloid tumours (77.16% vs. 65.49%, $P = 0.025$), higher rate of lung infections (64.81% vs. 50.70%, $P = 0.004$), higher percentage of indwelling intravenous catheters central venous catheter (CVC) (18.09% vs. 5.52%, $P = 0.001$), higher proportion of 2 intravenous catheter lumens (23.80% vs. 12.88%, $P = 0.030$), shorter length of time with the intravenous catheter (60 vs. 89 days, $P = 0.015$), lower initial platelet and minimum platelet counts during hospitalization (20 vs. 39.5×10^9 /L, 6 vs. 14×10^9 /L, $P < 0.001$), longer prothrombin time (PT) (12 vs. 11.7, $P = 0.031$), and significant difference in the CCI score ($Z = -3.266$, $P = 0.001$). The other variables were not statistically significant (Table 4).

Comparison of the clinical characteristics of haemato-oncology patients with thrombosis (thrombotic group) and without thrombosis (nonthrombotic group) and those with high Caprini scores who were not treated with prophylactic anticoagulant agents due to severe thrombocytopenia

Among the 446 patients included, 432 did not have thrombosis, and 14 (3.14%) had thrombosis. The thrombotic group had a greater proportion of patients with a history of thrombosis (35.71% vs. 3.24%, $P < 0.001$), a greater initial platelet count (76 vs. 31×10^9 /L, $P = 0.003$), and a greater proportion of patients with 2 venous catheter lumens (70.00% vs. 14.57%, $P < 0.001$). More patients in the thrombotic group were treated with parental nutrition (57.14% vs. 22.22%, $P = 0.007$), sedation (14.29% vs. 0.69%, $P = 0.009$), and Auto-HSCT (28.57% vs. 3.01%, $P = 0.004$). There were fewer leukaemia patients in the thrombotic group (35.71% vs. 70.37%, $P = 0.006$), and the remaining patients were not significantly different (Table 4).

Variables	Non-Bleeding group (n = 284)	Bleeding group (n = 162)	Statistic	P value	Non Thrombotic group (n = 432)	Thrombotic group (n = 14)	Statistic	P value
Physical characteristics of patients								
Gender, n (%)			0292	0.589			0.560	0.454
Male	152 (53.52)	91 (56.17)			234 (54.17)	9 (64.29)		
Female	132 (46.48)	71 (43.83)			198 (45.83)	5 (35.71)		
Age (years)	60 (52–69)	59 (46.75–69.00)	-1.436	0.151	60 (51–69)	60.5 (47.50–72.50)	-0.253	0.800
Weight (kg)	60 (51–66)	60 (51.88–67.63)	-0.594	0.553	60 (51–66)	63 (58.75–68.50)	-1.696	0.090
Height (cm)	160 (155–167)	160 (157–168)	-1.230	0.219	160 (156–167)	162 (158–168.50)	-1.179	0.238
BMI, kg/m ²	22.84 ± 3.40	22.69 ± 3.39	0.474	0.636	22.74 ± 3.39	24.22 ± 3.31	-1.605	0.109
Patient health history								
Smoking history, n (%)	41 (14.44)	24 (14.81)	0.012	0.913	61 (14.12)	4 (28.57)	1.262	0.261
History of alcohol consumption, n (%)	34 (11.97)	18 (11.11)	0.074	0.785	49 (11.34)	3 (21.43)	0.539	0.463
History of diabetes, n (%)	34 (11.97)	23 (14.20)	0.458	0.498	55 (12.73)	2 (14.29)	0.000	1.000
History of hypertension, n (%)	43 (15.14)	25 (15.43)	0.007	0.934	66 (15.28)	2 (14.29)	0.000	1.000
History of coronary heart disease, n (%)	11 (3.87)	1 (0.62)	3.026	0.082	11 (2.55)	1 (7.14)	0.043	0.836
History of hyperlipidaemia, n (%)	13 (4.58)	4 (2.47)	1.251	0.263	16 (3.70)	1 (7.14)	0.000	1.000
History of thrombosis, n (%)	13 (4.58)	6 (3.70)	0.193	0.660	14 (3.24)	5 (35.71)	27.551	<0.001*
Characteristics of the disease								
Type of haematological malignancies, n (%)			18.912	<0.001*			11.362	0.006*
Leukaemia	179 (63.03)	130 (80.25)			304 (70.37)	5 (35.71)		
Lymphomas	64 (22.54)	13 (8.02)			73 (16.90)	4 (28.57)		
Plasma cell diseases	26 (9.15)	15 (9.26)			36 (8.33)	5 (35.71)		
Others tumours	15 (5.28)	4 (2.47)			19 (4.40)	0 (0.00)		
Cell source of malignancies, n (%)			7.374	0.025*			5.465	0.057
Myeloid	186 (65.49)	125 (77.16)			305 (70.60)	6 (42.86)		
B-lineage	75 (26.41)	31 (19.14)			99 (22.92)	7 (50.00)		
T/NK-lineage	23 (8.10)	6 (3.70)			28 (6.48)	1 (7.14)		
Lower limb oedema, n (%)	4 (1.41)	3 (1.85)	NA	0.708	6 (1.39)	1 (7.14)	0.375	0.540
Septicaemia, n (%)	64 (22.54)	32 (19.75)	0.473	0.492	92 (21.30)	4 (28.57)	0.103	0.748
Mediastinal involvement of lymph nodes, n (%)	17 (5.99)	13 (8.02)	0.683	0.408	28 (6.48)	2 (14.29)	0.366	0.545
Extranodal diseases, n (%)	3 (1.06)	2 (1.23)	NA	1.000	5 (1.16)	0 (0.00)	NA	1.000
Lung infection, n (%)	144 (50.70)	105 (64.81)	8.329	0.004*	240 (55.56)	9 (64.29)	0.419	0.517
CCI score	3 (2–4)	3 (2–4)	-3.266	0.001*	3 (2–4)	3 (3–4)	-1.198	0.231
Caprini score	6 (6–7)	6 (6–7)	-0.747	0.455	6 (6.00–7.00)	7 (6.00–7.25)	-1.079	0.281
Initial laboratory tests								
Routine blood tests								
WBC (×10 ⁹ /L)	3.72 (1.60–6.95)	3.15 (1.40–11.67)	-0.152	0.879	3.56 (1.54–8.37)	4.63 (2.49–11.12)	-0.860	0.390
NEUT (×10 ⁹ /L)	1.60 (0.48–2.99)	1.18 (0.29–3.37)	-0.965	0.335	1.42 (0.39–3.04)	2.28 (1.27–7.43)	-1.799	0.072
Haemoglobin (g/L)	77 (63.00–99.00)	78.50 (63.75–99.25)	-0.157	0.875	78.00 (63.00–99.00)	87.50 (67.00–129.25)	-1.440	0.150
Platelet (×10 ⁹ /L)	39.5 (19.25–90.75)	20 (6.00–46.50)	-5.338	<0.001*	31 (14.00–75.75)	76 (46.75–200.00)	-3.002	0.003*
Coagulation								
Fibrinogen (g/L)	3.38 (2.57–4.56)	3.32 (2.55–4.32)	-0.623	0.533	3.34 (2.57–4.49)	3.58 (2.61–4.67)	-0.144	0.885
PT (s)	11.70 (10.90–12.90)	12 (11.10–13.25)	-2.153	0.031*	11.80 (11.00–13.20)	11.60 (10.73–12.58)	-0.763	0.446
APTT (s)	25.95 (24.20–28.80)	26.65 (24.20–29.90)	-1.669	0.095	26.20 (24.20–29.18)	25.85 (24.08–28.88)	-0.412	0.680
D-dimer (µg/L)	1.33 (0.34–3.77)	1.39 (0.57–7.26)	-0.904	0.366	1.39 (0.48–3.80)	1.29 (0.26–5.00)	-0.622	0.534
Liver and kidney functions								
Albumin (g/L)	38.27 ± 7.81	37.48 ± 7.05	1.073	0.284	37.99 ± 7.51	37.78 ± 8.86	0.104	0.917
Creatinine (µmol/L)	66.85 (54.43–83.70)	65.3 (55.00–83.20)	-0.102	0.918	65.45 (54.42–83.68)	70.65 (57.18–96.60)	-0.912	0.362
GFR (mL/min)	68.57 ± 20.80	69.37 ± 23.09	-0.372	0.710	68.81 ± 21.30	70.40 ± 31.46	-0.187	0.854
CCr (mL/min)	82.26 (59.03–102.03)	85.33 (60.22–112.61)	-1.238	0.216	83.04 (59.39–107.45)	87.85 (49.64–101.30)	-0.021	0.983
Continued								

Variables	Non-Bleeding group (n = 284)	Bleeding group (n = 162)	Statistic	P value	Non Thrombotic group (n = 432)	Thrombotic group (n = 14)	Statistic	P value
Minimum platelet count ($\times 10^9/L$)	14 (6–27)	6 (3–14)	-7.187	<0.001*	10 (4–20)	15.50 (7.50–36.00)	-1.581	0.114
Diagnostic and treatment status								
Bedridden > 72 h, n (%)	25 (8.80)	16 (9.88)	0.142	0.706	39 (9.03)	2 (14.29)	0.040	0.841
Intravenous catheter placement, n (%)	163 (57.39)	94 (58.02)	0.017	0.897	247 (57.18)	10 (71.43)	1.128	0.288
Types of intravenous catheter			10.349	0.001*			2.535	0.111
PICC	154 (94.48)	77 (81.91)			224 (90.68)	7 (70.00)		
CVC	9 (5.52)	17 (18.09)			23 (9.31)	3 (30.00)		
Number of intravenous catheters lumens, n (%)			4.737	0.030*			17.400	<0.001*
One	142 (87.12)	72 (76.60)			211 (85.43)	3 (30.00)		
Two	21 (12.88)	22 (23.40)			36 (14.57)	7 (70.00)		
Length of time the intravenous catheter (day)	89 (26–178)	60 (20–126)	-2.429	0.015*	79 (24–156)	42(21–175)	-0.490	0.624
Erythropoietin, n (%)	16 (5.63)	9 (5.56)	0.001	0.972	25 (5.79)	0 (0.00)	0.113	0.737
Parenteral nutrition, n (%)	60 (21.13)	44 (27.16)	2.100	0.147	96 (22.22)	8 (57.14)	7.398	0.007*
Steroids, n (%)	180 (63.38)	104 (64.20)	0.030	0.863	273 (63.19)	11 (78.57)	1.386	0.239
Immunomodulators, n (%)	18 (6.34)	6 (3.70)	1.406	0.236	23 (5.32)	1 (7.14)	0.000	1.000
Sedatives, n (%)	1 (0.35)	4 (2.47)	NA	0.061	3 (0.69)	2 (14.29)	NA	0.009*
Chemotherapy, n (%)	196 (69.01)	97 (59.88)	3.822	0.051	283 (65.51)	10 (71.43)	0.030	0.863
Auto-HSCT, n (%)	10 (3.52)	7 (4.32)	0.180	0.671	13 (3.01)	4 (28.57)	17.699	<0.001*
Patient outcomes								
Survival outcome, n (%)			0.155	0.694			0.000	1.000
Survive	269 (94.72)	152 (93.83)			408 (94.44)	13 (92.86)		
Dead	15 (5.28)	10 (6.17)			24 (5.56)	1 (7.14)		
Thrombosis, n (%)	8 (2.82)	6 (3.70)	0.267	0.605				
Thrombus type			NA	1.000				
DVT	5 (62.50)	4 (66.67)						
Intubation-associated thrombosis	3 (37.50)	2 (33.33)						
Thrombosis time			NA	1.000				
Within 1 year of diagnosis	7 (87.50)	5 (83.33)						
More than 1 year since diagnosis	1 (12.50)	1 (16.67)						
Bleeding, n (%)					156 (36.11)	6 (42.86)	0.267	0.605
Bleeding level, n (%)							0.000	1.000
1–2					147 (94.23)	6 (100.00)		
3–5					9 (5.77)	0 (0.00)		

Table 4. Comparison of clinical baseline characteristics: nonbleeding vs. bleeding and nonthrombotic vs. thrombotic groups. BMI, body mass index; CCI, Charlson comorbidity index; PICC, peripherally inserted central catheter; CVC, central venous catheter; DVT, deep venous thrombosis; WBC, white blood cell count; NEUT, neutrophil granulocyte count; GFR, glomerular filtration rate; CCr, endogenous creatinine clearance rate; PT, prothrombin time; APTT, activated partial thromboplastin time; Auto-HSCT, autologous haematopoietic stem cell transplantation; NA, not available; *Statistically significant.

Multifactorial analysis of risk factors associated with the occurrence of bleeding and thrombotic events in haemato-oncology patients with high Caprini scores who were not treated with prophylactic anticoagulant agents due to severe thrombocytopenia

Univariate analysis revealed that haematological malignancy type, cellular origin, coinfection of the lungs, CCI score, initial platelet count, initial PT, minimum platelet count, types of intravenous catheter, lumen numbers of the intravenous catheter, and length of time the intravenous catheter was left in place may be risk factors for bleeding. These variables were set as independent variables and analysed via binary logistic regression via the input method with the inclusion criterion $P < 0.05$ and exclusion criterion $P > 0.1$. The results revealed that lymphoma type (OR = 0.122, 95% CI 0.029–0.524, $P = 0.005$) and the minimum platelet count (OR = 0.925, 95% CI 0.893–0.959, $P < 0.001$) were protective factors against bleeding. The CCI score (OR = 1.331, 95% CI 1.049–1.687, $P = 0.018$) was an independent risk factor for bleeding.

Univariate analysis revealed that thrombosis history, haematological malignancy type, initial platelet count, number of venous catheter lumens, parenteral nutrition, sedation, and Auto-HSCT may be risk factors for thrombosis. They were set as independent variables and analysed via binary logistic regression via the input method with the inclusion criterion $P < 0.05$ and the exclusion criterion $P > 0.1$. The results revealed that

thrombosis history (OR=17.284, 95% CI 1.666–179.291, $P=0.017$), 2 venous catheter lumens (OR=7.852, 95% CI 1.025–60.169, $P=0.047$), and sedation treatment (OR=34.969, 95% CI 1.582–772.771, $P=0.024$) were independent risk factors for thrombosis (Table 5).

Predictive efficacy of platelet count on admission in patients with high Caprini scores who are not treated with prophylactic anticoagulant agents due to severe thrombocytopenia

An ROC curve was constructed for platelet counts on admission in 446 included patients with high Caprini scores who were not treated with prophylactic anticoagulant agents because of thrombocytopenia.

ROC curves were used to analyse and evaluate the predictive value of the platelet count on admission for thrombosis events in this group of patients. The area under the ROC curve (AUC) was 0.735 (95% CI 0.613–0.858, $P=0.003$), the sensitivity was 85.7%, the specificity was 60.6%, and the cut-off value was $42.5 \times 10^9/L$. The platelet count on admission has good value for predicting thrombosis in patients with high Caprini scores who are not treated with prophylactic anticoagulant agents due to severe thrombocytopenia (Fig. 2).

Discussion

Bleeding and thrombosis are two adverse events that patients with haematological malignancies often experience. Previous studies on thrombosis in haematological tumours have focused mainly on the mechanisms of thrombosis, prevention, treatment strategies for recurrence, risk factors and risk prediction models. Most clinical studies^{8,20,21} excluded patients with platelet counts $<50 \times 10^9/L$. These patients, especially those with haematological malignancies, are often at high risk of both bleeding and thrombosis, making it difficult to make clinical decisions, and may face very serious consequences. The 446 patients accounted for 39.23% of the haemato-oncology patients admitted with a high risk of thrombosis during the same hospitalization. This suggests that a significant proportion of haematological oncology patients may face such a dilemma where present guidelines and a consensus cannot provide specific treatment recommendations.

For the 446 patients with haematological neoplasms included in this study, the analysis of risk factors associated with bleeding and thrombosis revealed that prolonged prothrombin time and disease types such as leukaemia may be risk factors for bleeding. This finding is consistent with those of Ting Liang, Woodruff and Bonlokke et al.^{5,22,23}. In terms of risk factors for thrombotic events, the findings of the present study differ from those of several studies^{3,24–26}. This study did not suggest that age and chemotherapy were related to thrombotic events. The reason may be the heterogeneity of the included subjects, ethnicity, and chemotherapy regimens for different diseases. Univariate analysis revealed that different haematological tumour types, initial platelet counts, and indwelling 2-lumen intravenous catheters were common risk factors for bleeding and thrombosis. Multiple analyses revealed that among haematological neoplasms, lymphoma and the lowest platelet count during hospitalization were protective factors for bleeding, and the CCI score was an independent risk factor for bleeding. Thrombosis history, indwelling 2-lumen intravenous catheters, and sedation treatment were independent risk factors for thrombosis. The predictive effects of thrombosis history, indwelling 2-lumen intravenous catheters, and sedation treatment on thrombotic events have been demonstrated in several clinical studies^{4,11,14,27,28}. Multiple analyses suggest that lymphoma is a protective factor against bleeding among different diseases. Compared with lymphoma, leukaemia and myeloma are more prone to bleeding events. In this group of patients, 54.55% of patients with coexisting bleeding and thrombosis had myeloid tumours. This is related to the fact that patients with acute leukaemia or myelodysplastic syndrome tend to have thrombocytopenia and are more likely to have an abnormal coagulation function. However, patients with multiple myeloma may suffer severe bleeding due to increased blood viscosity or impaired antibody-mediated coagulation factors⁵. In a study

Dependent variable	variables	B	Standard error	Wald coefficient	OR	95% CI	P value
Bleeding events	Type of haematological malignancies			9.158			0.027
	Lymphomas	-2.102	0.743	8.016	0.122	0.029–0.524	0.005
	Plasma cell diseases	-0.355	0.753	0.222	0.701	0.160–3.069	0.637
	CCI score	0.286	0.121	5.560	1.331	1.049–1.687	0.018
	Minimum platelet count	-0.078	0.018	18.175	0.925	0.893–0.959	<0.001
Thrombosis events	History of thrombosis	2.850	1.194	5.701	17.284	1.666–179.291	0.017
	2 intravenous catheter lumens	2.061	1.039	3.934	7.852	1.025–60.169	0.047
	Sedatives	3.554	1.579	5.065	34.969	1.582–772.771	0.024

Table 5. Multifactorial analysis: risk of bleeding and thrombosis in Haemato-Oncology. Bleeding events: haematological malignancy type, cellular origin, coinfection of the lungs, CCI score, initial platelet count, initial PT, minimum platelet count, type of intravenous catheter, number of intravenous catheter lumens, and length of time the intravenous catheter was left in place, may be risk factors for bleeding. They were set as independent variables and analysed via binary logistic regression via the input method with the inclusion criterion $P<0.05$ and the exclusion criterion $P>0.1$. Thrombosis events: history of thrombosis, type of haematological malignancy, initial platelet count, number of venous catheter lumens, parenteral nutrition, sedation, and Auto-HSCT may be risk factors for thrombosis. They were set as independent variables and analysed via binary logistic regression via the input method with the inclusion criterion $P<0.05$ and the exclusion criterion $P>0.1$. CCI, Charlson Comorbidity Index.

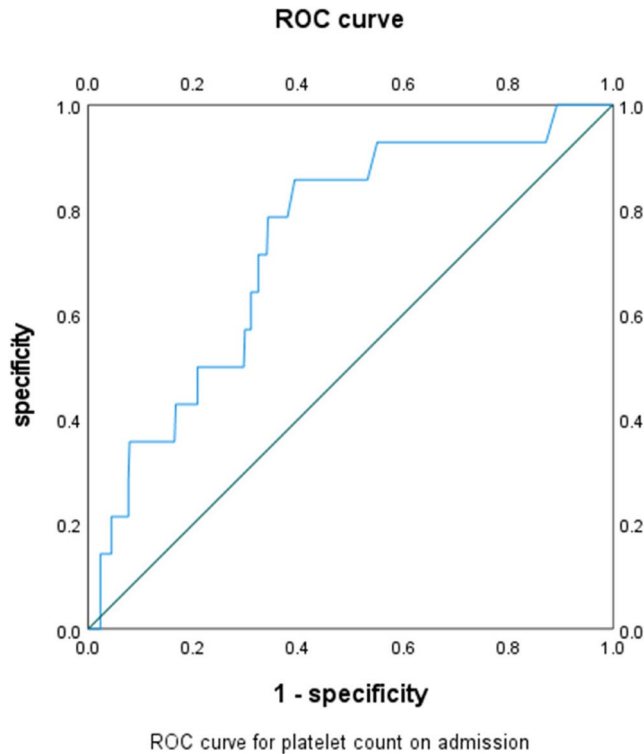


Figure 2. ROC curve for platelet count on admission.

on a population with nonvariceal upper gastrointestinal bleeding (NVUGIB) occurring during treatment with oral anticoagulants (OACs), Kim et al.²⁹ noted that the CCI was a significant risk factor for the development of rebleeding in upper gastrointestinal bleeding patients. This finding is similar to the findings of this study, suggesting that the CCI is an independent risk factor for bleeding in patients with high-risk Caprini scores and those who are unanticoagulated due to severe thrombocytopenia. Our analysis revealed that the most common complication among the 162 patients with bleeding was infection, which occurred in 82.72% of the patients. Among these patients, 64.81% had a combined grade 3 or higher lung infection, implying that infection may be an important risk factor for bleeding in unanticoagulated patients with high risk Caprini scores because of thrombocytopenia.

The coexistence of thrombosis and bleeding is known as thrombohemorrhagic syndrome (TSH)^{30,31}. As reported in the literature, the incidence of TSH in cancer patients is as high as 14.3%, with a mortality rate of 4.4%³². No relevant clinical reports of TSH in haematological tumours have been published to date. This study is the first to present the clinical characteristics of high Caprini score, high-risk haematological oncology patients who developed thrombosis and bleeding during the same hospitalization. The incidence of thrombosis and bleeding syndrome in this group of haematological neoplasms was 9.67%, and the mortality rate was 0.88%. Compared with other haematological neoplasms, leukaemia is more prone to TSH. This is related to the fact that leukaemia is associated with thrombocytopenia and high thrombotic risk due to oncological disease¹⁶. In addition, 72.73% of the patients in this cohort had a combination of grade 3 or higher lung infection and indwelling venous catheters. These findings are related to high risk factors for both bleeding and thrombosis and are in line with the literature^{3,11,33}. In this group of patients, the median platelet count at the time of thrombosis and bleeding was $< 30 \times 10^9/L$. This finding suggests that a reduction in platelet count does not imply a reduction in thrombotic risk, which is consistent with the findings of several other studies^{9,34–36}. Bleeding and thrombosis are influenced by multiple factors. On the one hand, thrombocytopenia suggests an increased risk of bleeding; on the other hand, thrombotic events may still occur during severe thrombocytopenia.

There have been several guidelines for the management of cancer-associated thrombosis (CAT)^{9,20,37–39} in recent years, but the management of thromboprophylaxis in oncology patients with thrombocytopenia (TP) is somewhat divergent. The European Haematology Association (EHA)⁴⁰ recommends graded management strategies on a case-by-case basis and, by degrees of thrombocytopenia, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). For grade 3 thrombocytopenia ($PLT < 50$ to $25 \times 10^9/L$), the International Society on Thrombosis and Haemostasis (ISTH) and National Comprehensive Cancer Network (NCCN) guidelines^{9,41} recommend a 50% reduction in anticoagulation agents. The International Initiative on Thrombosis and Cancer (ITAC) guidelines³⁹ recommend individualized treatment. Multiple guidelines^{9,37,39–41} agree that anticoagulation should be discontinued in patients with grade 4 thrombocytopenia ($PLT < 25 \times 10^9/L$). The Hokusai test, the Caravaggio test and the SELECT-D test suggested that different anticoagulants should be used only when the platelet count is $> 50 \times 10^9/L$, $75 \times 10^9/L$ and $100 \times 10^9/L$, respectively⁴². Although the study by Houghton et al.¹⁹ concluded that anticoagulation should be discontinued during periods of severe

thrombocytopenia ($<50 \times 10^9/L$) in haematological oncology patients to reduce adverse events, the NCCN guidelines⁴¹ also state that prophylactic anticoagulation is unsafe in patients with AML who have platelet counts $<50 \times 10^9/L$.

However, our study revealed that when haematological oncology patients with high Caprini scores are admitted to the hospital, there is still a high risk of thrombosis even if the platelet count reaches $42.5 \times 10^9/L$ or higher; therefore, prophylactic anticoagulation should still be considered. Compared with patients with other haematological tumours, patients with lymphoma may have a greater thrombotic risk when they are at dual risk of both thrombosis and bleeding. Presumably, whether this threshold can be further lowered for lymphoma patients deserves further exploration.

This study has several limitations. On the one hand, the study was a retrospective, single-centre analysis. Factors such as biomarkers, chemotherapy regimens, and other potentially relevant factors reported in the literature were not analysed in this study because of sample size limitations and some missing information. We also did not stratify the studies for factors such as haematological tumour type, degree of thrombocytopenia or bleeding. To explore these issues further, subsequent studies could be stratified by expanding the sample size. On the other hand, this study was initiated on the basis of the current state of the clinical environment. Under the VTE prevention system intervention, certain basic or physical prophylactic measures have been routinely taken in this group of medical records. Moreover, the diagnosis of thrombosis is based on imaging, which may miss some asymptomatic venous thromboembolism patients, which may have some impact on thrombosis judgement and prevention. To further validate these effects, future studies could be explored in prospective cohort studies.

Conclusions

In conclusion, in those with haematological malignancies other than lymphoma and a high risk for VTE combined with severe thrombocytopenia, especially those with a high CCI score, bleeding risk prevention and control takes precedence over thrombosis prophylaxis. Prophylactic anticoagulation should be recommended for lymphoma patients, especially those with a high risk of VTE and platelet counts of at least $42.5 \times 10^9/L$. In conclusion, for haematological oncology patients assessed as having a high risk for VTE in combination with a reduced platelet count, how to balance thrombosis and bleeding risk is not an uncommon and tricky clinical dilemma that deserves more in-depth discussion.

Data availability

The data generated or analyzed during this study are all included in this published article. For any further inquiries, please feel free to contact the corresponding author.

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Author contributions

JW and FX collaborated on the development of the study. MG was involved in topic selection and design, BC coordinated the resources and supervised the implementation. MG, SW, QS, QL, JY, LZ, MY, JT, DY, YX obtained data and cleared up the datasets. JW completed the data analyses and drafted the manuscript, which was guided and revised by FX. All authors approved the final manuscript.

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Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Mianyang Central Hospital (Mianyang, China; approval no. S-2024-0208-01). The patients/participants provided written informed consent to participate in this study. All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki.

Consent for publication

All authors consent to publication.

Competing interests

The authors declare no competing interests.

Additional information

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