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Original Article HEMATOLOGY

Incidence of and risk factors for venous thrombosis in hospitalized patients with hematologic malignancies: A single-center, prospective cohort study

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ABSTRACT

OBJECTIVE: Incidence of venous thromboembolism (VTE) is higher than the expected in patients with hematologic malignancies and duration of hospitalization period increases the risk of thrombosis. The objective of this study was to investigate the incidence of and risk factors for venous thrombosis in hospitalized patients with hematologic malignancies.

METHODS: We designed a prospective cohort study and enrolled patients with hematologic malignancies, who had been hospitalized between 2020 and 2021. Thromboprophylaxis was given to all patients, other than those under a high risk of hemorrhage.

RESULTS: 94 patients were enrolled. The incidence of superficial vein thrombosis was 11.7% and the incidence of deep vein thrombosis (including pulmonary embolism and catheter thrombosis) was 7.4%. Patients, who developed thrombosis, had statistically significantly longer hospital stays (21 vs. 11.5 days, p=0.023) and a higher number of hospitalizations (1 vs. 3, p=0.015) compared to those, who did not develop thrombosis. Patients, who had 3 or more risk factors for thrombosis, were found to be under the highest risk. (p=0.017, OR=4.32; 95% CI: 1.3–14.35). Furthermore, patients with recurrent hospitalizations (p=0.024, OR=1.49; 95% CI: 1.05–2.11) and higher fibrinogen levels (p=0.028, OR=1; 95% CI: 1–1.006) were under an increased risk of thrombosis.

CONCLUSION: Venous thrombosis is frequently seen in hospitalized patients with hematologic malignancies. A universally accepted risk scoring system is required for detection of patients, under a high risk for thrombosis.

Keywords: Acute leukemia; lymphoma; multiple myeloma; thrombophlebitis; venous thrombosis.

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Venous and arterial thrombosis are important causes of morbidity and mortality for cancer patients. The incidence of venous thromboembolism (VTE) in hematologic malignancy is comparable to that in solid tumors [1–3]. A recent study has demonstrated that the overall incidence of VTE was 5.3% among hospitalized patients with hematologic malignancies [4]. Duration of hospitalization increases the risk of thrombosis and anticoagulant thromboprophylaxis is routinely used in patients with solid tumors. However, in patients with hematologic malignancies, risk of hemorrhage is significantly more prevalent and severe thrombocytopenia restricts

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the use of thromboprophylaxis. Khorana et al. [5] have identified the clinical risk factors and laboratory characteristics, correlated with an increase in the risk of VTE among cancer patients. They have described 5 parameters: the site of cancer, platelet count of ≥350,000/μL, hemoglobin count of <10 g/dL and/or use of erythropoiesis-stimulating agents, leukocyte count of >11,000/μL and body mass index of ≥35 kg/m^2 [5]. In order to predict VTE risk in lymphoma patients, the ThroLy score has recently been developed [6]. ThroLy score includes 7 parameters, namely, prior history of VTE, acute myocardial infarction (AMI) or cerebrovascular event, reduced mobility (ECOG 2–4), body mass index (BMI) of >30 kg/m^2, extranodal location, mediastinal involvement, neutrophil count of <1×10^9/L and hemoglobin count of <10g/dL. However, each of these scoring systems has limited clinical utility in a heterogenous group of patients with hematologic malignancies, including acute leukemias, myeloma, lymphomas, and myeloproliferative neoplasms.

Determination of risk factors for venous thrombosis is important in planning thromboprophylaxis. Recently, a Spanish research group released a consensus report on the prevention of venous thrombosis in hematologic malignancies in inpatient as well as outpatient settings [7].

By combining clinical and laboratory characteristics with physical examination findings, the objectives of this study were to investigate the incidence and risk factors for venous thrombosis in hospitalized patients with hematologic malignancies and to assess whether thromboprophylaxis reduced the risk of thrombosis in this group of patients.

MATERIALS AND METHODS

The study was conducted at Pamukkale University Department of Hematology, a tertiary care center for adult patients with hematologic diseases. We designed an observational prospective cohort study to investigate the incidence of and risk factors for thrombosis in hospitalized adult patients with hematologic malignancies between October 2020 and October 2021, starting from their hospitalization until discharge. Patients, who were 18 years old or older, had a hematologic malignancy and had been hospitalized for 48 hours or longer, were included in the study. Patients, who had benign hematologic diseases or were receiving anticoagulant therapy for any reason (any thrombosis event or cardiovascular disease) or did not give informed consent, were excluded from the study. Diagnoses of diseases were made using international diagnostic criteria for respective disease. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) were categorized as acute leukemias and Hodgkin lymphoma (HL) and non-Hodgkin lymphomas were categorized as lymphomas. Patients with multiple myeloma (MM) and myeloproliferative neoplasm (MPN) were also included in the study.

Highlight key points

- Rate of deep vein thrombosis in hospitalized patients with hematologic malignancy is 7.5% in our study.
- Recurrent hospitalization, higher fibrinogen levels and having more than three predefined risk factors for venous thrombosis increase the risk of thrombosis.
- Defining patients, who need prophylaxis for venous thrombosis, is important for patients with hematologic malignancy.

Detailed physical examinations were performed on the patients. In line with patients' histories and daily physical examinations, certain predefined risk factors for thrombosis were recorded [8–11]. These risk factors for venous thrombosis were:

1. Body mass index (BMI) ≥30,
2. Immobility,
3. Presence of central venous catheter,
4. History of smoking,
5. Lower extremity edema,
6. Varicose veins,
7. Compressing lymphadenopathy or mass,
8. Relapsed disease,
9. Presence of comorbidity,
10. Presence of multiple comorbidities,
11. Development of tumor lysis,
12. Catheter infection,
13. Nosocomial infection,
14. History of thrombosis,
15. Familial history of thrombosis.

A sum of risk factors was calculated for each patient. Routine blood tests, consisting of complete blood count, coagulation assays and biochemical tests, were performed on the first day of hospitalization. Anticoagulation prophylaxis was given to patients who had more than one risk factor for thrombosis, with the exception of those, who had a risk of hemorrhage (thrombocytopenia <30.000/mcL, patients, requiring invasive procedures) and had active bleeding.

During inpatient follow-up, development of any infections and catheter-related infections were recorded. The patients were carefully monitored for the development of thrombosis; diameter differences between the extremities, swelling or erythema in the extremities, tenderness or pain at the catheter site, abdominal pain or new onset ascites, shortness of breath or tachypnea and erythema or pain around the peripheral catheter, were checked and physical examinations were performed daily. On detection of signs for thrombosis, further evaluation was conducted with Doppler ultrasonography, angiography or venography for confirmation.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Pamukkale University (date: 10.11.2020, number: 21) and written informed consents were obtained from each patient.

Statistical Considerations

All statistical analyses were performed using SPSS 25.0 [IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)] software. Continuous variables were defined as mean±standard deviation and median (IQR: 25th and 75th percentiles). Shapiro-Wilk test was used for determination of normal distribution. Mann-Whitney U test was used for comparison of two independent groups. Differences between categorical variables were evaluated using chi-square test and Fisher exact test. Logistic regression analysis was used for determination of the risk factors for development of thrombosis. ROC analysis was used to investigate the cut-off point for the total risk factor values. Statistical significance was determined as $p \leq 0.05$.

RESULTS

Characteristics of Patients

There were a total of 410 hospitalizations between October 2020 and October 2021 and 163 patients were evaluated. Among these, 62 patients had been diagnosed with non-malignant hematologic disease, 7 patients were receiving anticoagulant treatment. Therefore, remaining 94 patients were enrolled for the study. Table 1 shows the characteristics and laboratory value of the patients. Median age of the patients was 67 (20–90) years and median duration of hospital stay was 13 days (2–114). There were 30 (31.9%) patients with acute leukemias (26 AML and 4 ALL), 35 (37.2%) patients with lymphomas, 20 (21.3%) patients with multiple myeloma and 9 (9.6%) patients with chronic myeloproliferative neoplasms. Also 43.6% of all patients had relapsed disease and 56.4% of patients were newly diagnosed.

Thrombosis Events

Eighteen (19.1%) thrombosis events were detected during hospitalization period, consisting of superficial vein thrombosis of upper extremities (thrombophlebitis) in 61.1% (n=11) of these cases, lower extremity deep vein thrombosis in 16.7% (n=3), pulmonary embolism in 11.1% (n=2), catheter thrombosis in one patient (5.6%) and deep vein thrombosis of the upper extremity in one (5.6%) patient. Median time to thrombosis was 10.5 days (2–32) and 38.8% of the thrombosis events occurred in the first 7 days of hospitalization.

When the thrombosis incidence rates were examined by each disease category; it was seen that there were seven thrombosis events (23%) in acute leukemia patients, consisting of five cases of superficial vein thrombophlebitis of the upper extremities and two cases of deep vein thrombosis of the lower extremities. There were eight thrombosis events (one DVT, one upper extremity DVT, one PE and five thrombophlebitis cases) in lymphoma patients and three thrombosis events (one thrombophlebitis, one PE, one catheter thrombosis case) in multiple myeloma patients (Table 2). No significant difference was found between disease groups in terms of development of thrombosis.

Table 3 shows a comparison of two groups (with venous thrombosis vs. without venous thrombosis). Patients, who developed thrombosis, had significantly longer hospital stays (21 vs. 11.5 days, p=0.023) and a higher number of hospitalizations (1 vs. 3, p=0.015) compared to those, who did not develop thrombosis. Also, most of the patients, who developed thrombosis, had more than three thrombosis risk factors (77.78% vs. 44.74%, p=0.012).

Anticoagulation prophylaxis was given to 47.9% of patients (n=45), who had a lower risk of hemorrhage and more than one risk factor for thrombosis. Anticoagulation prophylaxis had been given to nine (50%) cases with thrombosis and 40 (52.63%) cases without thrombosis (p=0.841), and it was not associated with a significantly decreased risk of thrombosis (OR=1.111, 95% CI: 0.398–3.105).

Table 1. Patient characteristics and laboratory values

	n	%	Mean±SD	Med (Min–Max)
Gender				
Male	54	57.4		
Female	40	42.6		
Age (years)			63.61±14.11	67 (20–90)
BMI (kg/m²)				
<30	70	74.5		
>30	24	25.5		
Family history				
No	89	94.7		
Yes	5	5.3		
History of smoking				
No	59	62.8		
Yes	35	37.2		
Comorbidities				
No	24	25.5		
Yes	70	74.5		
Multiple comorbidities				
No	59	62.8		
Yes	35	37.2		
Infection				
No	38	40.4		
Yes	56	59.6		
Platelet count /mcL			161501.06±177209.36	126500 (6000–1468000)
WBC count/mcl			22983.1012±63817.71256	5805 (4.48–493470)
Hb level (g/dl)			9.554±2.3804	9.15 (3–15.6)
CRP (mg/L)			52.9±62.89	28.39 (0.09–302)
D-dimer (ng/ml)			1207.36±2819.63	427.5 (50–19185)
Fibrinogen (mg/dl)			395.33±183.6	355 (96–902)
Prophylactic anticoagulation				
No	49	52.1		
Yes	45	47.9		
Diagnosis				
Acute leukemia	30	31.9		
MM	20	21.3		
Lymphoma	35	37.2		
Myeloproliferative neoplasm	9	9.6		
Duration of hospitalization			18.9±19.12	13 (2–114)
Relapsed disease				
No	53	56.4		
Yes	41	43.6		
Compressing LAP/mass				
No	74	78.7		
Yes	20	21.3		

Table 1 (cont). Patient characteristics and laboratory values

	n	%	Mean±SD	Med (Min–Max)
Central vein catheter				
No	64	68.1		
Yes	30	31.9		
Lower extremity edema				
No	68	72.3		
Yes	26	27.7		
Immobility				
No	58	61.7		
Yes	36	38.3		
Thrombosis history				
No	87	92.6		
Yes	7	7.4		
Thrombosis risk score			3.96±2.2	4 (0–9)
Thrombosis event				
No	76	80.9		
Yes	18	19.1		
Thrombosis type				
Superficial veins	11	61.1		
Lower extremity DVT	3	16.7		
Pulmonary embolism	2	11.1		
Catheter thrombosis	1	5.6		
Upper extremity DVT	1	5.6		

SD: Standard deviation; BMI: Body mass index; CRP: C-reactive protein; Hb: Hemoglobin; DVT: Deep vein thrombosis; LAP: Lymphadenopathy; MM: Multiple myeloma; WBC: White blood cell.

Relationship Between Risk Factors and Thrombosis Development

According to logistic regression analysis, it was seen that age, gender, body mass index, disease type, disease status and duration of hospitalization did not have a statistically significant effect on the development of thrombosis (Table 4).

It was determined that increased number of hospitalizations (p=0.024, OR=1.49; 95% CI: 1.05–2.11) and higher fibrinogen levels on the first day of hospitalization (p=0.028, OR=1; 95% CI: 1–1.006) were associated with statistically significantly increased risk of thrombosis.

Furthermore, we investigated whether the sum of the thrombosis risk factors (as defined in the method section) had any effects on thrombosis risk and therefore, a cut-off value was obtained by performing ROC analysis. The area under the curve (AUC), obtained from total risk score, was found as 0.633. From this analysis, the cut-off point was found as "3.5" (sensitivity: 77.8%, specificity: 55.3%). As a result of the logistic regression model performed on the basis of this cut-off point, it was observed that having more than three risk factors has a statistically significant increase (4.3-fold) in the risk of development of thrombosis compared to having less than three risk factors (p=0.017, OR=4.32; 95% CI: 1.3–14.35). D-dimer levels, neutrophil/lymphocyte ratio, thrombocyte and leucocyte numbers on the first day of hospitalization did not have a statistically significant effect on the development of thrombosis (Table 4).

Immobility was thought to be associated with increased risk of thrombosis, yet this association was not found to be statistically significant (p=0.63, OR=0.767, 95% CI: 0.26–2.263).

DISCUSSION

In this prospective cohort study, we evaluated the incidence of venous thrombosis and risk factors for the same

TABLE 2. Thrombosis rates by disease type

	Acute leukemia n=30		Multiple myeloma n=20		Lymphoma n=35		MPN n=9		Total n=94	
	n	%	n	%	n	%	n	%	n	%
Diagnosis										
Superficial vein thrombosis	5	16.7	1	5	5	14.3	0	0	11	11.7
Lower extremity DVT	2	6.7	0	0	1	2.9	0	0	3	3.2
Pulmonary embolism	0	0	1	5	1	2.9	0	0	2	2.1
Catheter thrombosis	0	0	1	5	0	0	0	0	1	1.1
Upper extremity DVT	0	0	0	0	1	2.9	0	0	1	1.1
Total	7	23.4	3	15	8	23	0	18	19.1	

DVT: Deep vein thrombosis; MPN: Myeloproliferative neoplasm.

among hospitalized patients with hematologic malignancies. Venous thrombosis developed in 19.1% of the patients and 61.1% of these cases consisted of superficial vein thrombophlebitis (SVT) of the upper extremity due to intervention for vascular access. After exclusion of superficial vein thrombophlebitis, incidence of venous thrombosis (DVT and pulmonary embolism) was found as 7.5%. The incidence of VTE was similar to other studies [12–14]. According to a study, conducted in the United States, VTE has been observed in 5.3% of hospitalized patients with hematologic malignancies [4]. In another trial, investigating thromboembolism in hospitalized neutropenic cancer patients, VTE was reported in 5.4% of patients [13].

Mechanism of cancer-associated thrombosis consists of three components of Virchow triad: Invasion of vascular structure by tumor cells, inflammation induced by cytokines and endothelial damage, caused by widespread use of central venous catheters. Immobility and compression of vasculature by tumor mass, cause venous stasis. Tumor cells release extracellular vesicles, which contain procoagulant molecules, such as tissue factor and phospholipids, thereby causing hypercoagulable state [15, 16].

A recent trial, conducted in Denmark, has shown that the risk of venous thromboembolism in hematologic malignancies was higher than expected, especially in multiple myeloma (HR: 20.3) and non-Hodgkin's lymphoma (HR: 20.1), compared to normal population [17]. Nevertheless, results of this study have also shown that VTE risk was 4.5-fold higher for AML and 7.42-fold higher for ALL, compared to normal population. Incidence rate of VTE was 12.4% for AML and 11.24% for ALL [18]. We evaluated AML and ALL patients in the same category as acute leukemias and incidence rate of VTE in this population was 6.7% for VTE and 16.7% for superficial vein thrombosis.

Patients with MM have an increased risk for VTE due to the disease biology and treatment-related factors [19]. A large retrospective study, conducted in the United States, has demonstrated an almost nine-fold (8.7-fold) increase in the risk of VTE in patients with myeloma and the risk was highest during the first year of diagnosis [20]. Bakalov et al. [4] have reported that the mean rate of VTE was 3.4% in 615 hospitalized myeloma patients and an increased rate of 4.4% has been reported in patients treated with chemotherapy. In our study, thrombosis incidence in patients with myeloma was very high (VTE was 20%, superficial vein thrombosis was 5%), yet this could be due to the small number of patients and inclusion of only hospitalized patients, most of whom were newly diagnosed or relapsed multiple myeloma patients.

In lymphoma patients, thrombosis risk varies depending on subtype and the incidence is highest during the first two to three cycles of the treatment and declines over time [21]. The results of the prospective cohort study on Asian population have shown that 1-year incidence of VTE in patients with lymphoma was 7.6% [8]. Similarly, VTE rates in our lymphoma cohort were 8.7% and superficial vein thrombosis was detected in 14.3% of patients with lymphoma.

Table 3. Comparison of important clinical and laboratory findings between two groups

	Venous thrombosis		
	No (n=76)	Yes (n=18)	p
Age; Med (IQR)	68 (56–74)	66.5 (57.25–69.75)	0.554 (z=-0.592)
Age; n (%); ≥65	44 (57.9)	10 (55.6)	0.857 (cs=0.033)
Duration of hospitalization (days)	11.5 (6–21)	21 (13.75–31.25)	**0.023* (z=-2.276)**
Number of thrombosis risk factor	3 (2–5.75)	5 (3.75–6)	0.076 (z=-1.773)
Number of hospitalizations	1 (1–2.75)	3 (1–4)	**0.015*** (z=-2.438)
Laboratory value at the first day of hospitalization			
Hb level (g/dl); Median (IQR)	9.1 (7.93–11)	9.55 (7.95–11.25)	0.665 (z=-0.433)
WBC count/mcL; Median (IQR)	5805 (2780–10255)	5485 (1370–9937.5)	0.513 (z=-0.653)
Platelet count /mcL; Median (IQR)	122500 (38250–226750)	163000 (46750–274000)	0.232 (z=-1.196)
LDH level U/L: Median (IQR)	261 (213–429.25)	236.5 (186.5–395.25)	0.465 (z=-0.73)
CRP mg/L; Median (IQR)	20.63 (3.65–71.9)	48.86 (6.67–122.62)	0.161 (z=-1.403)
D-dimer mcg/L; Median (IQR)	405.5 (234.2–848.75)	477.5 (249.75–1157.5)	0.683 (z=-0.408)
Fibrinogen mg/dl; Median (IQR)	340 (263.25–484.5)	436 (329.5–674.25)	0.05 (z=-1.941)
BMI; n (%); ≥30	18 (23.7)	6 (33.3)	0.386 (cs=0.713)
Relapsed disease; n (%); yes	35 (46.1)	6 (33.3)	0.328 (cs=0.957)
Immobility; n (%); yes	30 (39.47)	6 (33.33)	0.630 (cs=0.232)
Central venous catheter; n (%); yes	23 (30,3)	7 (38,9)	0.480 (cs=0.498)
Varicose veins; n (%); yes	12 (15.8)	2 (11.1)	1.00 (cs=0.251)
Lower extremity edema; n (%); yes	19 (25)	7 (38.9)	0.252 (cs=1.403)
Compressing LAP or mass; n (%); yes	15 (19.7)	5 (27.8)	0.524 (cs=0.562)
Tumor lysis; n (%); yes	9 (11.8)	5 (27.8)	0.34 (cs=2.916)
History of thrombosis; n (%); yes	4 (5.3)	3 (16.7)	0.126 (cs=2.746)
Familial history of thrombosis; n (%); yes	4 (5.3)	1 (5.6)	1.00 (cs=0.002)
Smoking history; n (%); yes	29 (38.16)	6 (33.33)	0.703 (cs=0.145)
Comorbidity; n (%); yes	54 (71.05)	16 (88.89)	0.144 φ
Multiple comorbidities; n (%); yes	27 (35.53)	8 (44.44)	0.482 (cs=0.495)
Infection; n (%); yes	43 (56.58)	13 (72.22)	0.224 (cs=1.479)
Catheter infection; n (%); yes	6 (7.89)	3 (16.67)	0.366 φ
Prophylactic anticoagulation; n (%); no	40 (52.63)	9 (50)	0.841 (cs=0.04)
Number of thrombosis risk factor; n (%); >3	34 (44.74)	14 (77.78)	**0.012*** (cs=6.358)

*P<0.05: Statistically significant; IQR: (25^{th}–75^{th} percentiles); z: Mann-Whitney U test; cs: Chi- Square test; φ: Fisher exact test; Hb: Hemoglobin; WBC: White blood cell; CRP: C-reactive protein; LDH: Lactate dehydrogenase; BMI: Body mass index; LAP: Lymphadenopathy.

Hospitalization of patients with hematologic malignancies harbors additional risk for thrombosis. The most widely used risk scoring system for cancer patients is Khorana risk score (KRS), which consists of leukocyte count, thrombocyte count, hemoglobin level or ESA, BMI and site of cancer [5]. However, KRS is insufficient for predicting risk of thrombosis in patients with acute leukemias and myeloma [22, 23]. In a study on patients with Non-Hodgkin Lymphoma, conducted with a large cohort, prediction of thrombosis using Khorana score was found to be successful [24]. However, another trial has shown that KRS did not adequately predict VTE in patients with lymphoid malignancies [25]. In our study, patients, who developed thrombosis, had longer hospital stays (p=0.023) and a higher number of hospitalizations (p=0.015). We also investigated the possible predefined risk factors for venous thromboembolism and found that most of patients who developed thrombosis had more

Table 4. Calculated odds ratio of potential risk factors for thrombosis

	Wald	p	OR	95% CI for OR	
				Lower	Upper
Gender (female vs. male)	1.927	0.165	0.451	0.146	1.389
Age	0.008	0.927	0.998	0.963	1.035
Age ≥65 vs. <65	0.033	0.857	0.909	0.323	2.56
BMI ≥30 vs. <30	0.705	0.401	1.611	0.529	4.906
Duration of hospitalization (days, median)	0.817	0.366	1.011	0.987	1.036
Number of hospitalizations	5.105	**0.024***	1.493	1.055	2.114
Tumor lysis vs. none	2.746	0.097	2.863	0.825	9.936
Compressing mass vs. none	0.556	0.456	1.564	0.483	5.07
Central venous catheter vs. none	0.495	0.482	1.466	0.505	4.26
Lower extremity edema vs. none	1.376	0.241	1.909	0.648	5.625
Paraplegia paraphasia vs. none	0.025	0.873	0.835	0.092	7.624
Immobility vs. none	0.231	0.63	0.767	0.26	2.263
Thrombosis history vs. none	2.471	0.116	3.6	0.729	17.777
Varicose veins vs none	0.249	0.618	0.667	0.135	3.282
Family history vs. none	0.002	0.96	1.059	0.111	10.088
History of smoking vs. none	0.145	0.704	0.81	0.274	2.395
Any comorbidity vs. none	1.709	0.191	0.349	0.072	1.691
Multiple comorbidities vs. none	0.492	0.483	1.452	0.512	4.114
Infection vs. none	1.444	0.229	1.995	0.647	6.157
Catheter infection v. none	1.236	0.266	2.333	0.524	10.394
Prophylactic anticoagulation vs. none	0.04	0.841	1.111	0.398	3.105
Hb (g/dl, mean)	0.072	0.789	1.030	0.830	1.277
WBC (count, mean)	1.088	0.297	1	1	1
Platelet (count, mean)	0.199	0.655	1	1	1
LDH (U/L, mean)	0.336	0.562	0.999	0.997	1.002
CRP (mg/L, mean)	2.216	0.137	1.006	0.998	1.013
D-dimer (ng/ml, mean)	0.042	0.838	1	1	1
Fibrinogen (mg/dl, mean)	4.834	**0.028***	1.003	1	1.006
Number of risk factors for thrombosis ≤3 vs >3	5.721	**0.017***	4.324	1.303	14.35

*P<0.05 statistically significant; OR: Odds ratio; CI: Confidence interval; Binary Logistic Regression Analysis; LDH: Lactate dehydrogenase; BMI: Body mass index; CRP: C-reactive protein; WBC: White blood cell; Hb: Hemoglobin.

than three thrombosis risk factors (p=0.012) and having more than three risk factors increased the risk of thrombosis (OR: 4.32). Furthermore, higher fibrinogen levels (OR: 1) and increased number of hospitalizations (OR: 1.49) increased the VTE risk in our study group.

Central venous catheters (CVC) have been identified as an important risk factor for VTE in cancer patients [26]. Among our heterogeneous patient group, analysis with logistic regression showed that presence of CVC did not significantly increase the risk of venous thrombosis. Ku et al. [27] have reported that the presence of CVC was strongly associated with VTE in patients with acute leukemias. Also, Vu et al. [28] have determined that the overall prevalence of VTE was 10.7% in patients with acute leukemia (17.7% for ALL and 8.6% for AML) and CVC-related VTE constituted more than 50% of all VTE events in patients with AML and ALL. However, in our study, only one patient, who had been diagnosed with MM and was on a hemodialysis program, developed CVC-related VTE. The striking point in our study was the observation

of a high incidence of superficial vein thrombophlebitis especially in patients with acute leukemia at a rate of 16.7%. The reason was the material of the intravenous cannulae and these were replaced after observation of the increased incidence of superficial vein thrombosis. In addition, since it is difficult to place the CVC in acute leukemia patients with thrombocytopenia due to high risk of hemorrhage, peripheral intravenous cannulae were widely used in the initial weeks of treatment.

Thromboprophylaxis for high-risk patients with cancer reduces the risk of VTE [5, 29, 30]. American Society of Hematology recommends thromboprophylaxis using low molecular weight heparin (LMWH) for hospitalized patients with cancer only during hospitalization period and only for ambulatory cancer patients, who are at a higher risk for VTE [31]. Yet, prophylaxis for venous thrombosis remains a challenging issue in cases of hematologic malignancies, due to the risk of hemorrhage. Although we used thromboprophylaxis in patients with low risk of hemorrhage and more than one risk factor for VTE, rate of venous thrombosis in patients who received prophylaxis in our study, was not different from patients, who did not receive medical thromboprophylaxis.

The most important feature of our study is its prospective design. However, our cohort was very heterogenous and consisted of a small number of patients. Therefore, the results of this study cannot be generalized to the entire population. Another limitation of our study is the follow-up period. This period is too short and restricted to the hospitalization period only. It must be considered that the risk of thrombosis persists after discharge. When designing the study, we did not plan to investigate the risk and incidence of hemorrhage in patients, who were given thromboprophylaxis and therefore, lack of data related to hemorrhage was also considered as an important limitation.

Conclusion

According to the results of this prospective study, we found that rate of superficial vein thrombosis was 11.7% and rate of deep vein thrombosis was 7.5% in hospitalized patients with hematologic malignancies. Higher fibrinogen levels, recurrent hospitalization and having more than three risk factors for thrombosis, were associated with increased risk of thrombosis. There is a need for national-level studies with larger patient populations to identify risk factors associated with thrombosis and to establish appropriate prophylaxis strategies.

Ethics Committee Approval: The Pamukkale University Non-interventional Clinical Research Ethics Committee granted approval for this study (date: 10.11.2020, number: 21).

Authorship Contributions: Concept – NAA, OE, CK, HS, AHH, NG; Design – NAA, OE, CK, HS, AHH, NG; Supervision – NAA, OE, CK, HS, AHH, NG; Fundings – NAA, OE; Materials – NAA, OE, NG, CK; Data collection and/or processing – NAA, OE, CK, NG, AHH; Analysis and/or interpretation – NAA, OE, NG, HS; Literature review – NAA, NG, OE, HS, CK, AHH; Writing – NAA; Critical review – NAA, OE, CK, HS, AHH, NG.

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