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Evaluation of venous thromboembolism prophylaxis in cancer patients: a retrospective study

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ABSTRACT

This study aims to evaluate the prophylaxis of venous thromboembolism (VTE) in cancer patients. This retrospective study included 100 adult patients of different ages and genders who applied to the University Hospital between January and November 2021, who were diagnosed with cancer, admitted to the intensive care unit (ICU), and received chemotherapy. The patients were evaluated by clinical pharmacists during their ICU hospital stay in accordance with recommendations from the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the International Society for Thrombosis and Homeostasis Recommendations. Anticoagulant prophylaxis was indicated in all of our patients (100 patients) admitted to the ICU, and 38 (38%) of our patients received anticoagulant prophylaxis during their hospital stay.

Enoxaparin sodium was the preferred anticoagulant drug for 38 patients. During outpatient cancer treatment of patients, 27 of our 100 patients had a Khorana risk score greater than 2 and these patients were recommended to receive prophylactic anticoagulant therapy during outpatient treatment.

Results of this study showed that, oncology team members should be educated about factors that significantly increase VTE risk, and there is an urgent need to improve VTE awareness and practice of thromboprophylaxis in clinical practice.

Keywords: Venous thromboembolism, cancer, thromboprophylaxis, anticoagulants

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INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is a disease associated with high morbidity and mortality in cancer patients. It occurs in about 10% of cancer patients and is the second leading cause of death after cancer [1]. The risk of developing VTE, recurrent VTE and bleeding complications during VTE treatment is 4 to 7 times higher in cancer patients than in people without cancer, depending on age and gender [2].

Multiple mechanisms are believed to underlie the pathogenesis of the hypercoagulable state. The etiology is diverse and attributable to patient, cancer, and therapeutic factors. Cancer cells can directly or indirectly activate the coagulation pathway [3]. The direct mechanism involves the appearance of procoagulant factors such as tissue factor. Indirect mechanisms include the production of cytokines such as Interloukine-2 (IL2), Tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) that activate monocytes, platelets, and endothelial cells that induce expression of the procoagulant phenotype. In addition, cancer cells have surface adhesion molecules that can bind to monocytes, platelets, and endothelial cells that activate and stimulate fibrin production [4].

Cancer treatments such as conventional chemotherapy, hormone treatments, and biologics can increase the risk of VTE by up to 15% per year, depending on the type and combination of drugs chosen or the addition of radiation therapy to the treatment. Chemotherapy can contribute to the development of VTE by causing acute or delayed damage to the vessel walls. In addition, certain predisposing factors such as hospitalization, systemic inflammatory state, and tumor compression stasis may increase prothrombotic risk. Furthermore, the significant improvement in cancer patient survival in recent years prolongs the time that cancer patients may be exposed to VTE [4,2].

Adequate knowledge of VTE risk assessment and VTE sensitization in cancer patients is essential. Cancer patients should be assessed for VTE risk using an approved risk assessment tool, particularly at the start of systemic cancer treatment, during hospitalization and periodically thereafter [5].

National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and International Society for Thrombosis and Homeostasis guidelines for cancer-associated VTE in hospitalized cancer patients with underlying medical conditions and/or restricted mobility in the absence of other contraindications recommend thromboprophylaxis. Careful selection of treatment modalities with optimal efficacy in terms of safety is crucial to achieve the best outcomes [3,6,7].

The 2021 update made significant changes to the NCCN guidelines by adding detailed information on prophylactic dosing of anticoagulants based on inpatient/outpatient status for surgical and cancer patients. Dose adjustments for conditions such as obesity, renal failure and thrombocytopenia are the main changes to consider [3].

Although thromboprophylaxis is effective in reducing VTE risk, current guidelines do not advocate its routine use in cancer outpatients, possibly due to the large number of patients requiring treatment, the risk of bleeding, and the difficulty of daily administration of low molecular weight heparin (LMWH) by injection [8].

Risk stratification tools guide the selection of cancer patients at high risk of VTE. An ideal tool should help identify negligible and very high-risk patients in need of intervention. It should also ensure that patients who could benefit most from VTE prophylaxis are identified [9]. To date, only the Khorana score has been successfully used in prospective randomized trials on thromboprophylaxis for risk assessment. The Khorana score is the most well-known risk stratification tool that has been included in the latest updated ASCO and NCCN guidelines for assessing VTE risk in community cancer patients. Five clinical and biological parameters are evaluated prior to chemotherapy [10,11]. According to the updated 2019 ASCO guideline, patients with a low VTE risk are those with a Khorana score less than 2 who do not require routine VTE prophylaxis. Patients at intermediate or high risk of VTE are those with a Khorana score of 2 or greater and VTE prophylaxis for up to 6 months or longer should be considered. In the previous version of the Khorana score, VTE prophylaxis was recommended for patients with a score of 3 or higher [6].

The 2021 NCCN guideline recommends additional dose adjustments for outpatients. Prophylactic anticoagulant therapy should be excluded in cancer patients with platelet counts below 50,000/μl, and a reduced dose of enoxaparin can be used in patients with platelet counts between 50,000 and 75,000/μl^3. Although the relationship between cancer and VTE is well established, it is interesting to note that patient and physician knowledge of VTE risk is extremely low[3]. This study reports the status of prophylaxis demand and adherence to guidelines in cancer patients with VTE prophylaxis at ICU admission. The aim is to assess the status of the considered deficiency by assessing the VTE risk during the outpatient treatment period.

METHODOLOGY

Our group of patients undergoing chemotherapy was admitted to the ICU for various diseases; consists of patients for whom VTE prophylaxis is indicated by National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and International Society for Thrombosis and Homeostasis guidelines.

This study included 100 adult patients of different age groups and genders who have applied for admission to the University Hospital with ethical approval of the Hospital Ethics Committee (İstanbul Medipol University Non-Interventional Clinical Studies, E-10840098 -772.02-4020, 08/ 24/2021) who had cancer between January 2021 and November 2021, were admitted to the intensive care unit and received chemotherapy. As the study was retrospective no informed consent was obtained.

Hospital data collection parameters were patient data, medical history (especially VTE history and type of cancer), laboratory values (serum creatinine to calculate Khorana score [*The Khorana score is a guideline-recommended point-based risk score used to estimate the risk of incident VTE in ambulatory cancer patients*], platelet count, hemoglobin and white blood cell count before chemotherapy), body mass index, glomerular filtration rate (GFR) value, medical history, metastatic status, surgical planning status, anticoagulant used in VTE prophylactic treatment, and dose and duration of administration. Among these data, our primary priority is to understand and evaluate the efficacy of anticoagulant use in the prophylactic treatment of VTA, and only the results of the statistical evaluation of this are highlighted here.

Patients in the study were evaluated by clinical pharmacists for VTE prophylaxis during their hospitalization in the ICU according to National Comprehensive Cancer Network, American Society of Clinical Oncology and International Society of Clinical Oncology recommendations and homeostasis (Table 1 and Table 2) [3,4].

Table 1. VTE prophylaxis options for hospitalized medical oncology patients[3]

Agent	Standart dosing[a,b]	Renal dose	Obesity dosing (BMI ≥40 kg/m^2)[c]
Dalteparin	5,000 units SC daily	Avoid if CrCl<30 mL/min	Consider 7,500 units SC daily or 5,000 units SC every 12 hours or 40-75 units/kg SC daily
Enoxaparin	40 mg SC daily	Recommended 30 mg SC daily if CrCl<30 mL/min	Consider 40 mg SC every 12 hours or 0.5 mg/kg SC daily
Fondaparinux	2.5 mg SC daily Avoid in patient weighing<50 kg	Caution if CrCl 30-49 mL/min Avoid if CrCl<30 mL/min	Consider 5 mg SC daily
Unfractionated Heparin (UFH)	5,000 units SC every 8-12 hours	Same as standard dose	Consider 7,500 units SC every 8 hours

CrCl: Estimated creatinine clearance
SC: Subcutaneous
BMI: Body mass index

[a]Recommendation derived from patients hospitalized with medical illness (Hospitalized>6 days, immobile/bed rest >3 days, age≥ 40 years, plus additional risk factors for VTE)

[b]Thromboprophylaxis for duration of hospital stay or 6-14 days or until patient is fully ambulatory

[c]Limited data available to support recommendations. Recommended doses are derived from non-oncology populations[3].

Table 2. Treatment of established VTE[4]

Agent		Dosing
Initial	UFH	80 U/kg IV bolus, then 18 U/kg/h IV and adjust dose based on aPTT[k]
	Dalteparin[j,l,m]	100 U/kg every 12 hours 200 U/kg once daily
	Enoxaparin[j,l,m,n]	1 mg/kg every 12 hours 1,5 mg/kg once daily
	Tinzaparin[j,l,m,o]	175 U/kg once daily
	Fondaparinux[j,l,p]	< 50 kg: 5.0 mg once daily 50-100 kg: 7.5 mg once dailiy >100 kg: 10 mg once daily
	Rivaroxaban	15 mg orally every 12 hours for 21 days
Long Term[p,q,r]	Dalteparin[l,m,s]	200 U/kg once daily for 1 month, then 150 U/kg once daily
	Enoxaparin[l,m,n]	1.5 mg/kg once daily 1 mg/kg every 12 hours
	Tinzaparin[m,o]	175 U/kg once daily
	Warfarin	Adjust dose to maintain INR 2-3
	Rivaroxaban[m,t]	15 mg orally every 12 hours for 21 days, followed by 20 mg once daily there after (both doses with food)
	Edoxaban[m,t]	Needs at least 5 days of parenteral anticoagulation prior to its started, then switch to 60 mg orally once daily or 30 mg orally daily in those weighing≤ 60 kg, who have creatinine clearance between 30 and 50 mL/min, or who need concomitant use of a P-glycoprotein inhibitor

aPTT: Activated partial thromboplastin time
INR: International normalized ratio
IV: Intravenous
UFH: Unfractionated heparin
VTE: Venous thromboembolism

[j]Parenteral anticoagulants should overlap with warfarin for 5-7 days minimum and should be continued until the INR is in the therapeutic range for 2 consecutive days.

[k]UFH infusion rate should be adjusted to maintain the aPTT within the therapeutic range in accordance with local protocols to correspond with a heparin level of 0.3-0.7 U/mL using a chromogenic antifactor Xa assay.

[l]Dependent on significant renal clearance, avoid in patient with creatinine clearance≤ 30 mL/ minor adjust dose based on antifactor Xa levels.

[m]Optimal dose unclear in patient> 120 kg

[n]Twice-daily dosing may be more efficacious than once-daily dosing for enoxaparin based on post hoc. data.

[o]This medicine is not available in the United States.

[p]Fondaparinux had a higher rate of recurrent thrombosis and no difference in hemorrhage compared with enoxaparin in patients with cancer in a post hoc. Subgroup analysis. It is not

a standard option but may be used for long term anticoagulation if standard LMWH or direct oral anticoagulants (DOACs) are not a feasible option for the patient. Dosing for long term treatment with fondaparinux is the same as for initial treatment.

[q]Total duration of therapy depends on clinical circumstances.

[r]Apixaban and dabigatran do not have fully published results from cancer-specific clinical trials. Prospective randomized trial data in patients with cancer with active diseases of cancer therapy are needed prior to their use. Therefore, they are currently not recommended for routine use in patients with cancer with active diseases.

[s]This is the only LMWH with US food and Drug Administration approval for extended therapy to prevent recurrent thrombosis in patients with cancer.

[t]Edoxaban has the highest level of evidence for patients with cancer among all the DOACs, followed by rivaroxaban. Limited data from, small, unpublished patient series suggest that the effectiveness of DOACs in patient with a weight> 120 kg might be reasonable based on anti-Xa levels. The data are very limited, however, and LMWH is still likely to be preferred in this setting. Please refer to the package inserts for detailed information regarding potential dosing adjustment needs, especially as regards renal impairment, liver failure, weight extremes, or drug-drug interaction [4].

During outpatient cancer treatment, a VTE risk assessment was performed at least one month prior to ICU admission, taking into account the Khorana score and National Comprehensive Cancer Network recommendations for further dose adjustments prior to receiving systemic chemotherapy (Table 3 and Table 4) [3].

Table 3. Dosing regimens for prophylaxis VTE in cancer outpatients[b3]

Agent	Dosing
Dalteparin[d,g]	5,000 U once daily
Enoxaparin[d,g]	40 mg once daily
Fondaparinux[d,h]	2.5 mg once daily
Apixaban[d]	2.5 mg orally twice daily
Rivaroxaban[d]	10 mg orally once daily

[b]Duration for medical patients is for the length of hospital stay or until fully ambulatory. For surgical patients, prophylaxis should be continued for at least 7-10 days. Extended prophylaxis for up to 4 weeks should be considered for high-risk patient. Duration for outpatient prophylaxis is somewhat uncertain, as most studies did not assess beyond 6 months. [d]This drug is not approved by the US Food and Drug Administration for this indication.[g] Higher prophylactic doses were used for patients with pancreatic cancer: dalteparin 200 IU/kg once daily for 4 weeks followed by a step down to 150 IU/kg for a further 8 weeks in FRAGEM andenoxaparin 1 mg/kg once daily in CONCO-OO4.[h] Fondaparinux has not been studied in outpatient prophylaxis setting. It should only be considered if the patient has contraindications for other LMWH and DOAC use is considered an inferior option[3].

Table 4. Other dose modifications for ambulatory patients with cancer[3]

Prophylactic anticoagulation therapy should be ruled out in medical oncology patients whose platelet count is less than 50,000/ml
A reduced dose of enoxaparin can be used in patients with platelet count between 50,000 and 75,000/ml

Our study includes the assessment of cancer patients in relation to renal impairment and obesity doses for thromboprophylactic treatment, updated in the 2021 NCCN guidelines [3]. This study may be one of a leading study in the literature as it was conducted during the ICU hospitalization and the risk of VTE during the period when they received outpatient treatment, taking into account the Khorana score and other dose modification updates according to the 2021 NCCN guideline.

Descriptive statistics were analyzed using SPSS Statistics software (version 21.0.). Results are presented as arithmetic means ± standard errors of means where required. The study population was considered as a group and no subgroup analysis was performed.

RESULTS AND DISCUSSION

Inpatients

Of our 100 patients, 50 (50%) were male and 50 (50%) were female. The mean age of our patients was calculated as 59.44 years. All of our patients received chemotherapy. 26% of our patients had lung cancer, 18% had breast cancer, 13% had bladder cancer; 9% had colon cancer, 9% had gynecologic cancer, 5% had pancreatic cancer, 2% had brain cancer, 1% had kidney cancer, 1% had bladder cancer, and 16% had other cancers. In addition, 11 (%11) of our patients had a history of VTE. Anticoagulant prophylaxis was indicated in all of our patients admitted to the ICU and 38 (38%) of our patients received anticoagulant prophylaxis during their hospitalization. All 38 patients preferred enoxaparin sodium as the anticoagulant drug. In 62 patients (62%) no anticoagulant prophylaxis was administered, although it was indicated [3].

The enoxaparin dose had to be increased in 5 of 38 patients due to a history of VTE and the dose had to be reduced in 1 patient due to renal dysfunction. None of our patients required an obesity test. No bleeding, bruising or side effects associated with the administration of antithrombotic prophylaxis have been reported.

All of our patients who received coagulation prophylaxis received prophylactic

treatment during their stay in the intensive care unit. The mean number of days on anticoagulant prophylaxis was 22.55 (minimum: 1 day; maximum: 48 days).

Outpatients

During outpatient cancer treatment, 27 of our 100 patients had a Khorana score greater than 2, and it is recommended that these patients receive prophylactic anticoagulant therapy during outpatient treatment. Prophylactic treatment with anticoagulants according to the Khorana scale was recommended for 2 of the patients; It was also suggested to exclude prophylactic anticoagulant therapy according to the other dose adjustment recommendations in the NCCN 2021 guidelines [3].

In a study with 199 patients (75 men [37.7%] and 124 women [62.3%]), the medical records of the patients with an average age of 50.6 years were reviewed[12]. In another study conducted with 100 inpatients with cancer, 48 (48%) of the patients were women and 52 (52%) were men, with a mean age of 59 years[11].On the other hand, 50% of the patients included in our study were women and 50% men, with a mean age of 59.44 years.

In a study of 100 inpatients with cancer, the majority of patients (n=34, 34%) had gastrointestinal cancers (8 gastric, 8 pancreatic, 8 colon, 4 hepatocellular, 4 esophageal, and 2 cholangiocellular) and Lung tumors diagnosed in 17 (17%) cancer patients. Eleven of the patients (11%) had a history of VTE [11].

In our study, 26% of our patients had lung cancer, 18% breast cancer, 13% bladder cancer; 9% had colon cancer, 9% had gynecologic cancer, 5% had pancreatic cancer, 2% had brain cancer, 1% had kidney cancer, 1% had bladder cancer, and 16% had other cancers. In addition, 11 of our patients had a history of VTE. The two studies are similar in that the most common types of cancer detected are lung cancer and cancer of the gastrointestinal tract.

The results of the DissolVE 2 study, conducted in China, which enrolled 1,535 cancer patients and aimed to assess the VTE risk profile and VTE prophylaxis in inpatient cancer patients, are as follows: 666 patients (93.9%) with high VTE risk had no VTE received VTE prophylaxis and only 11 (1.6%) patients received adequate VTE prophylaxis. The results reflect the poor management of VTE risk in hospitalized cancer patients in China [13]. In a retrospective study conducted at a university hospital in Lebanon, a 2-month retrospective review of hospitalized cancer patients for deep vein thrombosis (DVT) prophylaxis was performed and found that 21 (221%) of 95 patients with indications for DVT prophylaxis received DVT prophylaxis, while only 47.6% of patients receiving anticoagulant therapy received prophylaxis with the right drug and dose. The

results suggest that there is a need to improve awareness and practice of VTE prophylaxis [14].

The findings of our study show that 38 (38%) of 100 patients received anticoagulant prophylaxis and appropriate thromboprophylaxis was applied to 32 of these patients (84.21%). Although it was indicated in 62 patients, no anticoagulant treatment was administered (%62).

An international survey study shows that physicians do not carry out prophylactic treatment in about 30% of hospitalized cancer patients for whom VTE prophylaxis is indicated because of the perceived high risk of bleeding [15]. In another study of 100 inpatient cancer patients, 36 (36%) of the patients did not receive any anticoagulant therapy during the hospital stay [11]. Our study showed more negative results regarding VTE prophylaxis than these two studies, in which 62% of the patients for whom VTE prophylaxis was indicated did not use anticoagulant prophylaxis.

Recent meta-analyses have confirmed previous findings that LMWHs are more effective than vitamin K recurrence in cancer antagonists in reducing VTE patients [6]. In a study of 199 patients, only 2 patients received unfractionated heparin prophylaxis and the remaining 197 patients preferred enoxaparin as thromboprophylaxis. In 3 patients (6.4%) an insufficient dose of the drug was administered. No dose adjustment was made in 2 patients due to renal failure, although it was necessary. In addition, no dose adjustment was made in 1 obese patient. The mean duration of thromboprophylactic treatment was calculated to be 4.1 days (minimum: 1 day; maximum: 36 days). No bleeding, bruising, or serious side effects associated with heparin or enoxaparin administration have been reported. In the study, which included 100 inpatient cancer patients, enoxaparin (96.9%) and apixaban (3%) were the preferred treatment options during hospitalization [12].

In a study from Lebanon, enoxaparin was the most commonly prescribed anticoagulant at 76.2%[14]. In the study, which included 100 cancer inpatients, enoxaparin (96.9%) and apixaban (3%) were the preferred treatment options during the hospital stay. The length of hospital stay was determined to be between 10 and 11 days (minimum: 2 days; maximum: 70 days) [11].

According to the data obtained in our study, enoxaparin sodium was the preferred anticoagulant in the 38 patients receiving prophylactic anticoagulant treatment, consistent with the preferred anticoagulant option in other studies. As a practical clinical decision by the physicians, 5 patients had their enoxaparin dose increased due to a history of VTE, and 1 patient had their dose reduced

due to renal dysfunction. There were no obese patients in our study group and for this reason there was no need for dose adjustment for obese patients according to the guideline[3]. In addition, no bleeding, hematoma or serious adverse events related to the use of thromboprophylaxis were not report. The hospital stay of our patients was calculated to be 22.55 (minimum: 1 day; maximum: 48 days) days.

A single-center retrospective cohort study of patients with pancreatic and gastric cancer aimed to examine the prescription rates of prophylactic anticoagulants in patients at high risk of VTE using the Khorana risk score. Of 437 patients, 181 (41%) had a Khorana score greater than 3 and none had an alternative. No anticoagulant has been used prophylactically without an indication for treatment [3]. In another study that assessed VTE risk in 200 cancer outpatients using the Khorana risk score, 11 (5.5%) patients were at high risk and 117 (58.5%) had an intermediate risk. The consultant was informed of the patient's risk scores; however, anticoagulant therapy was not started because the doctors decided to mobilize the patients[11].In our study, 27 (27%) of 100 patients had a Khorana score greater than 2 (high risk) during their outpatient cancer treatment. It is recommended that these patients receive prophylactic anticoagulant therapy during outpatient treatment. In 2 of 27 patients recommended to receive prophylactic anticoagulation therapy according to Khorana risk score, however, prophylactic anticoagulation was not recommended according to the 2021 NCCN guidelines [3]. Based on a comprehensive literature review, our study is one of the leading to evaluate VTE prophylaxis in cancer patients in the light of recent guideline updates. Although the association between cancer and VTE is well characterized, the awareness of both patients and clinicians about the risk of VTE remains low. Members of the oncology team should be educated about factors that significantly increase the risk of VTE, especially major surgery, hospitalization, and systemic antineoplastic therapy. VTE awareness and prophylaxis in clinical practice urgently need to be improved.

Consistent with the obtain findings of the previous studies, consensus guideline by clinical pharmacists could significantly improve the implementation of appropriate VTE prophylaxis, reduce the development of VTE and have a positive impact on the safety of patients.

The weakness of our study is that it was conducted retrospectively. There is a need for larger studies aiming to improve VTE prophylaxis practices, to identify deficiencies and problems in practice, and to evaluate the effectiveness of therapeutic interventions to address them.

STATEMENT OF ETHICS

We confirm that we have read and understood the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

Idea/Concept: Neda Taner, Betül Şirin, Design: Neda Taner, Betül Şirin, Data Collection/Processing: Neda Taner, Analysis/Interpretation: Neda Taner, Betül Şirin, Literature Review: Betül Şirin, Drafting/Writing: Neda Taner, Betül Şirin, Critical Review: Neda Taner, Betül Şirin

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REFERENCES

1. Kabashneh S, Alkassis S, Shanah L, Alkofahi AA. Venous Thromboembolism in Patients with Brain Cancer: Focus on Prophylaxis and Management. Cureus. 2020; 12(6). https://doi.org/10.7759/cureus.877

2. Becattini C, Verso M, Muňoz A, Agnelli G. Updated meta-analysis on prevention of venous thromboembolism in ambulatory cancer patients. Haematologica. 2020; 105(3): 838-848. https://doi.org/10.3324%2Fhaematol.2019.221424

3. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Elshoury A, Fanikos J, et al. Cancer-Associated Venous Thromboembolic Disease, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19(10): 1181-1201. https://doi.org/10.6004/jnccn.2021.0047

4. Labianca A, Bosetti T, Indini A, Negrini G, Labianca RF. Risk predictionand new prophylaxis strategies for thromboembolism in cancer. Cancers. 2020; 12(8): 2070. doi: 10.3390/cancers12082070

5. Kahale LA, Hakoum MB, Tsolakian IG, Alturki F, Matar CF, Terrenato I, et al. Anticoagulation for the long-termtreatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev. 2018; 6(6): CD006650. doi: 10.1002/14651858.CD006650.pub5

6. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2020; 38(5): 496-520. doi: 10.1200/JCO.19.01461.

7. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2019; 20(10): e566-e581. doi: 10.1016/S1470-2045(19)30336-5.

8. Mulder FI, Candeloro M, Kamphuisen PW, Nisio MD, Bossuyt PM, Guman N, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica. 2019; 104(6): 1277-1287. doi: 10.3324/haematol.2018.209114

9. Moik F, Ay C, Pabinger I. Risk prediction for cancer-associated thrombosis in ambulatory patients with cancer: past, present and future. Thromb Res. 2020; 191: S3-S11. https://doi.org/10.1016/S0049-3848(20)30389-3

10. Lyman GH, Bohlke K, Khorana AA, Kuderer NM., Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update 2014. J Clin Oncol. 2015; 33(6): 654-656. doi: 10.1200/JCO.2014.59.7351

11. Kandemir EA, Bayraktar-Ekincioglu A, Kilickap S. Assessment of adherence to cancer-associated venous thromboembolism guideline and pharmacist's impact on anticoagulant therapy. Support Care Cancer. 2021; 29(3): 1699-1709. doi: https://doi.org/10.1007/s00520-020-05669-6

12. Mohammadi M, Ebrahimpour S, Jahangard-Rafsanjani Z. Evaluation of venous thromboembolic event prophylaxis in hospitalized cancer patients: a single-centered retrospective study. J Res Pharm Pract. 2019; 8(1): 25-28. doi: 10.4103/jrpp.JRPP_18_28

13. Xu RH, Shi YK, Gao Y, Li WM, Qin XY, Qu JM, et al. Venous thromboembolism risk and prophylaxis status of cancer inpatient. Chin J Oncol. 2021; 43(10): 1100-1104. doi: 10.3760/cma.j.cn112152-20210607-00437

14. Awar Z, Sheikh-Taha M. Use of deep vein thrombosis prophylaxis in hospitalized cancer pa-

tients. Blood Coagul Fibrinolysis. 2009; 20(7): 571-574. doi: 10.1097/MBC.0b013e32832fa7df

15. Verso M, Dinisio M. Management of venous thromboembolism in cancer patients: Considerations about the clinical practice guideline update of the American society of clinical oncology. Eur J Intern Med. 2020; 71: 4-7. doi: https://doi.org/10.1016/j.ejim.2019.10.033