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CLINICAL STUDY

Markers of activation of coagulation in cancer patients

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ABSTRACT
BACKGROUND: Prothrombotic tendency is characteristic of tumors. The aim of the study is to investigate the changes in the laboratory parameters for coagulation and fibrinolysis, namely in fibrinogen, thrombin-antithrombin complex (TAT), tissue factor (TF), prothrombin fragment (F1+2), antithrombin III (AT III), D-dimer and screening coagulation tests in cancer patients before initiation of chemotherapy.
MATERIALS AND METHODS: Levels of F1+2, fibrinogen, TAT, AT III, TF, D-dimer, PT, aPTT and TT were measured baseline in 80 patients with breast and lung cancer before systemic treatment. The same parameters were investigated in 65 healthy volunteers. TF, TAT, F1+2 were measured by ELISA; AT III, D-dimer, fibrinogen and screening coagulation tests were measured by automated coagulation system Sysmex CS 2000i.
RESULTS: Levels of F1+2, fibrinogen, TAT, TF, and D-dimer in cancer patients were significantly higher than those in the control group, while the levels of ATIII activity were significantly lower ($p < 0.001$). The highest area under the ROC curve was for D-dimer, which made it a good marker for the risk of thrombosis.
CONCLUSION: Higher levels of TF, TAT, F1+2, fibrinogen and D-dimer and lower activity of AT III in cancer patients support our hypothesis of an association between malignant disease and coagulation disorders. Cancer patients are at an increased risk of thrombosis wherefore antithrombotic prophylaxis may be considered *(Tab. 6, Fig. 2, Ref. 34)*. Text in PDF *www.elis.sk*
KEY WORDS: coagulation, fibrinolysis, cancer.

Introduction

One of common complications in patients with malignant pathology is thrombosis. The link between malignancies and thrombosis was first presented and described in the medical literature by the famous French physician Armand Trousseau, whose observations were published by the New Syndenham Society in 1865 (1). Abnormalities in coagulation are found in up to 50 % of all patients with malignancies and up to 90 % of those with metastases, with thrombosis being the second most common cause of death in these patients (2).

The pathogenetic mechanisms of thrombogenesis in these patients are complex and involve many interrelated processes between the tumor and host´s physiological response to the tumor itself. Changes in laboratory parameters that indicate activation of coagulation and fibrinolysis in cancer patients are a result of tumor growth, neoangiogenesis and impaired organ function. This applies mainly to the procoagulant properties of tumor cells, endothelial and inflammatory cells. In addition, there are abnormalities in the body's normal defense mechanisms, particularly in vascular endothelial dysfunction, decreased circulating inhibitors and cell-related anticoagulants, and fibrinolytic activators. On the other hand, the use of chemotherapeutic agents can also lead to clotting disorders (3, 4). The hemostasis system is an anatomically and functionally integral part of the vascular system. Thus, coagulopathy and angiogenesis in fact contribute to thrombotic events and complications in the presence of cancer. Blood fluidity is maintained by the dynamic balance between the coagulation and fibrinolysis systems. In the latter, under the action of plasmin, cross-linked fibrin is degraded and fibrin degradation products (FDPs) are obtained, part of which is a D-dimer. The measurement of D-dimer plasma concentration of is one of the earliest tests to prove fibrin formation in the body. *In vivo*, fibrinolysis starts at the same time as fibrin formation. Elevated D-dimer concentrations are an indicator of thrombosis or risk of thrombosis. Prothrombin fragment 1 + 2 and thrombin-antithrombin complex are markers of coagulation activation. They are produced by the generation of thrombin. F 1 + 2 is released from prothrombin upon its conversion to thrombin

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by the prothrombinase complex, which includes factors Xa and Va, calcium ions, and a negatively charged phospholipid surface. Thrombin is very rapidly inhibited by binding covalently to AT III and forming thrombin-antithrombin complexes (TAT).

Increased levels of F 1 + 2 are due to increased conversion of prothrombin to thrombin with subsequent formation of TAT complexes which reflect the activation of the coagulation system. The determination of plasma levels of TAT is informative for intravascular thrombin formation and is a good marker in the diagnosis of thrombotic events.

Activation of coagulation and fibrinolysis processes in tumor tissue also contributes to tumor growth, angiogenesis and metastasis. Data from different studies show that plasma concentration of coagulation activation markers are associated with stage, prognosis and survival in patients with cancer of the lung, prostate, pancreas, mammary gland and stomach (5–7).

The aim of the study is to investigate the changes in the laboratory parameters for coagulation and fibrinolysis, namely in fibrinogen, thrombin-antithrombin complex (TAT), tissue factor (TF), prothrombin fragment (F1+2), antithrombin III (AT III), D-dimer and screening coagulation tests in breast and lung cancer patients.

Materials and methods

Eighty patients with confirmed malignant tumors from the department of Medical Oncology, University Hospital "Sveti Georgi" in Plovdiv, Bulgaria were included in the study. They were divided into 2 patient groups, namely breast cancer (n = 38) and lung cancer (n = 42) groups. We studied a control group of 65 clinically healthy volunteers comprised of 30 women and 35 men. The study was approved by Ethics Committee of Medical University in Plovdiv. The clinical laboratory tests were performed at the department of Clinical Laboratory of the University Hospital "Sveti Georgi" in Plovdiv. The inclusion criteria were used for selection of the target patient groups were as follows: age ≥ 18 years; disease stage, histology type, newly diagnosed, patients on chemotherapy. Patients were not on treatment with vitamin K antagonists, new oral direct anticoagulants, low-molecular-weight heparins (LMWH) or unfractionated heparin (UFH) in the last three months. Written informed consent was obtained from all participants enrolled in the study. The socio-demographic and health data of each of the participants in the study are included in an individual patient record.

Biological material

Closed venous blood collection systems were used as follows: for complete blood count (CBC) – Monovette Sarstedt EDTA, 2.7 ml; Monovette Sarstedt Serum, 2.6 ml was used for clinical chemical analyses and tumor markers. Also, Monovette Sarstedt 3.8 % Sodium Citrate, 2.9 ml (in concentration 9:1 blood to sodium citrate as an anticoagulant) was used for screening coagulation tests and markers for coagulation and fibrinolysis.

Platelet-poor plasma is used for screening coagulation tests and markers of activation of coagulation. It is obtained by centrifugation of the blood with sodium citrate at 3,000 – 3,500 U/min and 2,000 x g for 10–15 minutes. Aliquots were frozen and stored at –80 °C for serial measurement for TF, TAT, F1+2.

Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, AT III, D-dimer, complete blood count, tumor markers and clinical-chemical parameters were immediately analyzed. CBC was measured on ADVIA 2120i hematology analyzer (Siemens Diagnostica), routine clinical-chemical parameters on AU 480 Beckman Coulter, and tumor markers on Architect i2000SR Immunology Analyzer (Abbott Diagnostics).

PT, aPTT, TT, fibrinogen, AT III and D-dimer were measured on an automated coagulation analyzer Sysmex SC 2000i, Japan (Siemens Diagnostica). Fibrinogen was measured by von Clauss chronometric method; quantitative assessment of the functional activity of AT III was performed by chromogenic substrate method; determination of D-dimer plasma concentration was carried out by automated, immunoturbidimetric method.

Plasma concentration of prothrombin fragment 1 + 2 (F 1 + 2) was determined by enzyme-linked immunosorbent assay (Cloud-Clone Corp., USA). The analytical characteristics of the assay, i.e.,intra-assay imprecision and inter-assay imprecision are CV < 10 % and CV < 12 %, respectively. Plasma TAT concentrations

Tab. 1. Markers of coagulation and fibrinolysis in breast cancer patients and controls.

Parameter	Group	n	Mean	Standard deviation	Median	25th percentile	75th percentile	p
D-dimer mg/l	breast cancer	38	1.13	0.91	0.87*	0.54	1.34	<0.001
	controls	30	0.35	0.14	0.33*	0.23	0.42	
TAT ng/ml	breast cancer	38	10.03	4.87	8.52*	6.28	12.64	<0.001
	controls	30	5.43	2.23	4.77*	3.81	6.74	
F 1+2 ng/ml	breast cancer	38	19.70	8.27	21.10*	11.73	25.93	<0.001
	controls	30	9.97	4.94	10.60	5.33	12.45	
fibrinogen g/l	breast cancer	38	3.61	1.09	3.23*	2.85	4.37	=0.003
	controls	30	2.97	0.57	2.88	2.60	3.23	
AT III %	breast cancer	38	87.30	8.21	87.40	81.80	93.73	=0.001
	controls	30	93.65	6.93	93.85	89.00	98.53	
TF pg/ml	breast cancer	38	196.17	92.08	198.15	112.15	263.68	<0.001
	controls	30	138.81	54.41	140.45	101.25	169.28	

* Variable is not with normal distribution

Tab. 2. Screening coagulation tests in breast cancer patients and controls.

Parameter	Group	n	Mean	Standard deviation	p
PT sec	controls	30	11.42	0.49	=0.036
	breast cancer	38	11.09	0.74	
PT INR	controls	30	1.01	0.05	=0.034
	breast cancer	38	0.98	0.07	
PT%	controls	30	87.98	9.64	=0.017
	breast cancer	38	95.14	13.44	
aPTT	controls	30	27.81	2.55	<0.001
	breast cancer	38	24.34	1.63	
TT	controls	30	16.85	0.65	=0.143
	breast cancer	38	16.58	0.81	

were determined by classical sandwich enzyme-linked immunosorbent assay (AssayMax, USA) according to the manufacturer's instructions. Characteristics of analytical reliability of ELISA for TAT, i.e., intra-assay imprecision and inter-assay imprecision are CV < 4.8 %, and CV < 10 %, respectively. Plasma tissue factor concentration was determined by ELISA (Abcam, UK) according to the instructions of manufacturer. Analytical reliability reflected as intra-assay imprecision and inter-assay imprecision are CV < 4.0 % and CV < 10 %, respectively.

Statistical analyses

IBM SPSS Statistics v. 26 statistical package was used for statistical analyses. Shapiro-Wilk test was used for assessing the distribution of variables. Differences between the groups were investigated by independent t-test for variables with normal distribution and Mann-Whitney U test for data with nonnormal distribution. The relationship between the parameters was assessed by Spearman's correlation coefficient analysis. The difference is statistically significant at P<0.05. Receiver-operating characteristic (ROC) analysis was used for assessing specificity and sensitivity of the parameters.

Results

Thirty-eight women with breast cancer and 42 men with lung cancer were included in the study. Sixty-five clinically healthy volunteers (30 women and 35 men) were used as a control group.

Mean age of the women with breast cancer was 56.47 ± 9.64 years, and that of the control group of 30 women was 59.20 ± 11.74 years.

The distribution of cancer stages I, II, III and IV in patients with breast cancer was 39.5 % (n = 15), 21.1 % (n = 8), 26.3 % (n = 10), and 13.2 % (n = 5), respectively.

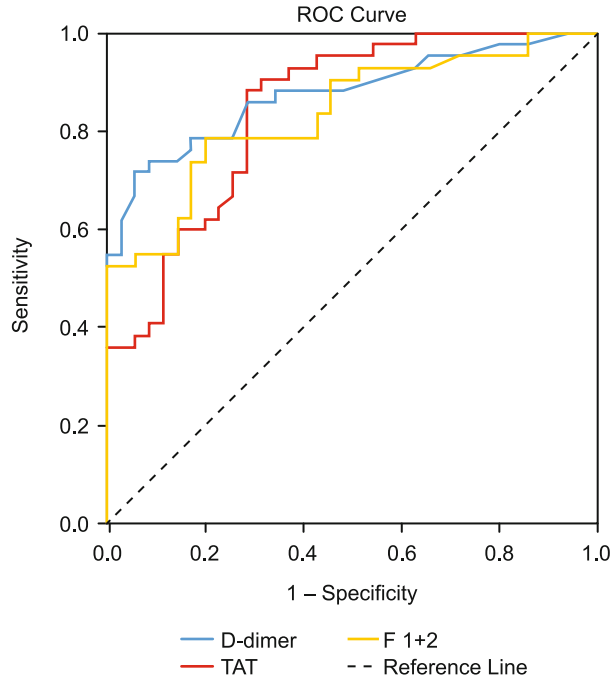

Fig.1. ROC curves of D-dimer, TAT and F1+2 in breast cancer patients.

We found that plasma concentrations of D-dimer, TAT, and F1+2 were significantly higher in breast cancer patients than in the control group (p < 0.001). TF and fibrinogen levels were also significantly higher in cancer patients than in the control group (p < 0.001 and p = 0.003, respectively), while the activity of AT III was significantly lower (p = 0.001) (Tab. 1). The comparative analysis of screening coagulation tests between breast cancer patients and controls showed significantly shortened aPTT and PT (sec), increase in PT% and decrease in INR values. No statistically significant difference in thrombin time (sec) was found between patients and controls. The values of the three parameters remained in the reference range in both groups (Tab. 2). The sensitivity and specificity of the markers for activation of coagulation were assessed using ROC analysis. The highest area under curve was for D-dimer which was an indication of a good marker for distinguishing patients at increased risk of thrombotic complications (Fig. 1, Tab. 3).

In breast cancer patients, there was a significant, positive correlation between TAT and D-dimer (r = 0.811; p < 0.001) and between F1 + 2 and D-dimer (r = 0.825; p < 0.001). A significant, but negative correlation is observed between D-dimer and AT III (r = –0.658; p < 0.001), TAT and AT III (r = –0.651; p < 0.001), F1 + 2 and AT III (r = –0.600; p < 0.001).

Tab. 3. Accuracy indices of D-dimer, TAT and F1+2 in breast cancer patients.

Parameter	AUC	95% CI		Cut-off value	Sensitivity %	Specificity %	Youden index
D-dimer	0.872	0.789	0.956	0.49 mg/l	78.9	86.7	0.656
TAT	0.821	0.723	0.920	6.10 ng/ml	81.6	70.0	0.516
F1+2	0.823	0.727	0.919	13.75 ng/ml	63.2	90.0	0.532

Tab. 4. Markers of coagulation and fibrinolysis in lung cancer patients and controls.

Parameters	Group	n	Mean	Standard deviation	Median	25 percentile	75 percentile	p
D-dimer mg/l	lung cancer	42	1.67	1.60	1.08*	0.56	2.41	<0.001
	controls	35	0.38	0.17	0.33*	0.23	0.48	
TAT ng/ml	lung cancer	42	11.35	5.60	9.42*	6.89	16.55	<0.001
	controls	35	5.56	2.96	4.90*	3.70	7.72	
F 1+2 ng/ml	lung cancer	42	21.49	9.57	22.90	14.35	28.83	<0.001
	controls	35	10.10	5.33	9.80	5.40	13.30	
fibrinogen g/l	lung cancer	42	4.30	1.39	4.26*	2.90	5.31	=0.003
	controls	35	3.08	0.56	2.90	2.80	3.45	
AT III %	lung cancer	42	82.69	9.02	83.70*	74.88	91.20	p<0.001
	controls	35	91.68	6.85	93.00	85.80	96.90	
TF pg/ml	lung cancer	42	210.35	92.26	202.3	122.93	290.58	<0.001
	controls	35	142.3	53.96	138.80*	105.60	153.60	

* Variable with non-normal distribution

Tab. 5. Screening coagulation tests in lung cancer patients and controls.

Parameter	Group	n	Mean	Standard deviation	p
PT %	controls	35	89.79	12.36	=0.026
	lung cancer	42	96.37	12.86	
PT s	controls	35	11.34	0.65	=0.027
	lung cancer	42	11.01	0.63	
PT INR	controls	35	1.00	0.06	=0.035
	lung cancer	42	0.97	0.06	
aPTT	controls	35	26.84	2.01	<0.001
	lung cancer	42	24.05	2.03	
TT	controls	35	16.67	0.80	=0.069
	lung cancer	42	17.05	0.97	

The second patient group included 42 men with lung cancer with mean age of 59.69 ± 8.42 years. The control group of 35 healthy men was with mean age of 58.14 ± 9.99 years. The distribution of stages I, II, III and IV of lung cancer in patients with lung cancer was 14.2 % (n = 6), 23.8 % (n= 10), 31.0 % (n = 13), and 31.0 % (n = 13).

In our study, plasma concentrations of D-dimer, TAT, F1+2, TF and fibrinogen were significantly higher in lung cancer patients than in the control group, while the activity of AT III was significantly lower (Tab. 4). These results are similar to those in breast cancer patients.

The comparative analysis of screening coagulation tests between lung cancer patients and controls revealed significantly shortened aPTT and PT (sec), increase in PT% and decrease in INR values. No statistically significant difference in thrombin time (sec) was found between patients and controls. The values of the three parameters remain in the reference range in both groups (Tab. 5). Cut-off values, sensitivity and specificity of D-dimer, TAT and F1+2 were assessed using ROC analysis. The area under curve again was the highest for D-dimer (Fig. 2, Tab. 6).

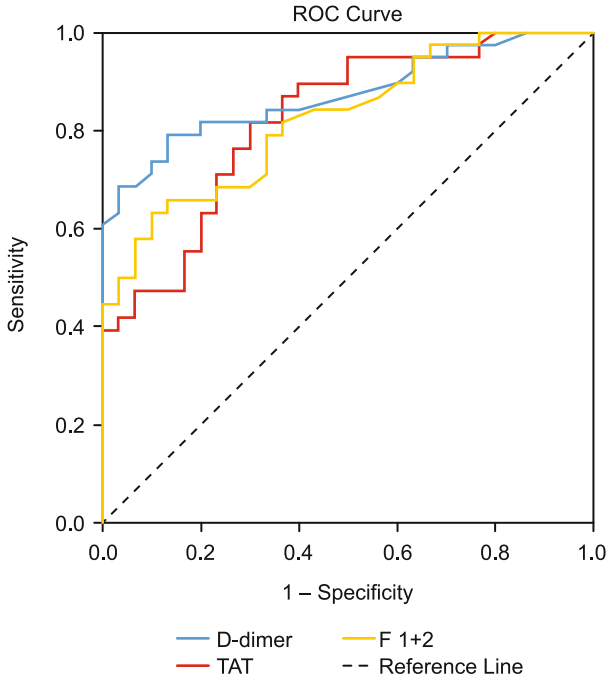

Fig. 2. ROC curves of D-dimer, TAT and F1+2 in lung cancer patients.

Correlation between markers of activation of coagulation were tested in lung cancer patients. A significantly positive correlation was found between F1+2 and TAT ($r = 0.635$; $p < 0.001$), D-dimer and TAT ($r = 0.626$; $p < 0.001$), D-dimer and F1+2 ($r = 0.793$; $p < 0.001$). Significant, but negative correlation is observed between

Tab. 6. Accuracy indices of D-dimer, TAT and F1+2 in lung cancer patients.

Parameter	AUC	95% CI		Cut-off value	Sensitivity %	Specificity %	Youden index
D-dimer	0.874	0.796	0.953	0.68 mg/l	71.4	94.3	0.657
TAT	0.843	0.756	0.930	5.7 ng/ml	88.1	71.4	0.595
F1+2	0.836	0.748	0.924	14.85 ng/ml	73.8	82.9	0.567

D-dimer and AT III ($r = –0.610$; $p < 0.001$) and F1+2 and AT III ($r = –0.562$; $p < 0.001$).

Discussion

In patients with malignancies, changes in hemostasis parameters are often observed, and tumor pathology is one of the most common causes of venous thromboembolism. In our study, we focused on changes in coagulation and fibrinolysis system in patients with lung and breast cancer. D-dimer, fibrinogen, F 1 + 2, TAT, AT III and screening coagulation tests were studied in patient groups and in healthy controls.

We found significantly higher levels of TF in patients with breast and lung cancer compared to the control groups, which is comparable to data from other authors (8, 9) Since there is an association between TF, the major initiator of the external pathway of blood clotting activation and angiogenesis, which plays a major role in tumor pathology, our results support their hypothesis of an association between carcinogenesis and coagulation disorders. There is a correlation of TF with the degree of microvascular density and increased plasma levels of VEGF in various tumors, which confirms the role of TF in the process of angiogenesis (10–12). A number of studies have found that tissue overexpression of TF correlates with the presence of metastases, invasive potential and aggressive tumor course (13–15). Significantly higher TF levels were found in patients with stage IV lymphoma, but without statistical significance depending on the histological type (16).

Elevated D-dimer is an indicator of fibrin formation and accumulation, making it a good marker of risk of thrombosis (thrombophlebitis, pulmonary thromboembolism). In patients with malignancies, the tumor tissue is covered with a fibrin network, which is a source of FDP, in particular D-dimer. As compared to the control groups, the significantly higher levels of D-dimer found in our patient groups coincided with the results published in other studies (17, 18).

Although our study did not show a statistically significant difference in D-dimer levels between two patient groups, it was observed that in patients with lung cancer they were higher compared to those in patients with breast cancer. This may be associated with increased coagulation activity in carcinoma, especially when it is at a more advanced stage and/or poorly differentiated histological type. A number of authors have reported an association between plasma D-dimer levels, stage, and prognosis in patients with malignant disease (19–21).

Pathologically increased thrombin formation and fibrin accumulation, which is characteristic of patients with malignancies, leads to increased formation of F1 + 2 and TAT. In our study, we found statistically significantly higher levels of F1 + 2 and TAT in patients as compared to healthy controls. TAT levels have been observed to be higher in patients with metastases. This is not necessarily due only to the greater tumor mass, leading to more pronounced changes in the markers of coagulation activation. Another possible cause is the fact that thrombin, which is formed mainly in the tumor tissue, "leaks" into the circulation when the tumor spreads. Our results are similar to data published in other studies (22–24).

Patients with malignancies may have a decreased production of coagulation inhibitors and/or increased consumption. AT III regulates procoagulant activity and is an important natural thrombin inhibitor. It inactivates thrombin by an irreversible reaction leading to the formation of thrombin-antithrombin complexes. Our data indicate that the activity of AT III is significantly lower in patient groups as compared to healthy controls. This can be explained by pathologically increased thrombin formation in patients with tumor pathology and its increased consumption for the formation of TAT complexes. Although there are some studies that do not find a statistically significant difference between patients and the control group (28), other authors demonstrate results that are in line with those achieved in our study (25–27),

In patients with breast and lung cancer we found statistically significantly higher fibrinogen levels than in healthy controls. In addition to coagulation factors, fibrinogen is an acute-phase protein that helps platelets attach to tumor cells, which leads to increased thrombin production. All these changes lead to hypercoagulability in patients with tumor pathology. The results in our study are similar to data published by other authors (29–31).

When comparing the coagulation and fibrinolysis parameters between the two patient groups, the only statistically significant difference was in the plasma fibrinogen levels. The mean fibrinogen level in the lung cancer patients was 4.30 ± 1.39 g/l which was significantly higher ($p = 0.039$) than that in patients with breast cancer (3.61 ± 1.09 g/ l). Although no statistically significant difference was found in other markers for activation of coagulation and fibrinolysis, higher levels of TF, D-dimer, F 1 + 2, TAT in patients with lung cancer could be explained by the advanced stage of the disease in these patients.

The comparative analysis of screening hemostasis tests between patients and controls revealed significantly shortened aPTT and PT (sec), increase in PT% and lower INR values in the two patient groups. No statistically significant difference in thrombin time (sec) was found between patients and controls. The parameters remain in the reference range for both groups. Data in the literature on routine coagulation tests in patients with tumors are controversial. Mi et al reported shortened PT and aPTT in patients with breast cancer as compared to controls (32). Di Micco et al also found shortened PT and aPTT in patients with breast and stomach cancer as compared to controls, but without a statistically significant difference between them (28). Prolonged PT and aPTT have also been reported in patients with tumors (33). Conventional hemostasis tests do not have the specificity and sensitivity to assess the thrombotic risk in this group of patients.

Elevated plasma levels of D-dimer, F1 + 2, TAT, fibrinogen and TF are associated with a decrease in the activity of AT, which shows the consumption of this natural inhibitor of coagulation. A significantly positive correlation between D-dimer and F1 + 2 ($r = 0.65$, $p < 0.001$), D-dimer and TAT ($r = 0.71$, $p < 0.001$), TAT and F1 + 2 ($r = 0.76$, $p < 0.001$) was demonstrated by other authors in patients with suspected venous thromboembolism (34). The Vienna

CATS study found a positive correlation between D-dimer and F1 + 2 ($r = 0.5$; $p < 0.001$) (6).

Conclusion

Our study presents results of the analysis of the changes in clinical laboratory parameters for coagulation and fibrinolysis, namely in fibrinogen, thrombin-antithrombin complex (TAT), tissue factor (TF), prothrombin fragment (F1+2), antithrombin III (AT III), D-dimer and screening coagulation tests in cancer patients before initiation of chemotherapy. It could be assumed that in newly diagnosed patients with tumor diseases, the prothrombotic state is characteristic. It is due to specific procoagulant activity of tumor cells, changes in the systems of coagulation and fibrinolysis, and interaction of hemostasis factors with the components of the inflammatory response. Subclinical abnormalities in coagulation status are common in patients with malignancies. In our opinion, it is important to study specific hemostasis markers such as D-dimer, TAT, F1 + 2, which are indicative of increased thrombin accumulation. This would be helpful in determining the risk of thrombotic complications and individualizing anticoagulant therapy in these patients.

Learning points

- Cancer patients are at an increased risk of thrombosis and antithrombotic prophylaxis may be considered.
- Screening coagulation tests are not sufficiently informative of the changes in hemostatic system
- The area under curve was the highest for D-dimer which made it a good marker for distinguishing patients at increased risk of thrombotic complications.

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