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ORIGINAL ARTICLE

The usefulness of D-dimer in diagnosis and prediction of venous thromboembolism in patients with abdominal malignancy

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

The aim: of the study was to evaluate the usefulness of D-dimer evaluation in the diagnosis and prediction of venous thromboembolism (VTE) of lower extremities in patients operated on for abdominal tumors depending on the chosen cut-off point for this parameter.

Material and methods: We included 150 patients operated on for abdominal cancer in our department between October 2014 and June 2016. In these patients, concentration of D-dimer was determined, medical histories were taken, and physical examinations were performed. Ultrasound exams of the veins of the lower limbs were performed three times in every patient in order to confirm or exclude VTE.

Results: When a standard cut-off point (500 ng/ml) was used, in 46% of cancer patients D-dimer values were elevated despite the lack of VTE. We did not detect any influence of cancer stage on the value of D-dimer. However, if cut-off point was 1440 ng/ml, which has been suggested in the literature, only 14% of patients were false positive. When the upper cut-off value for D-dimer was raised, the effect of cancer stage on the value of this parameter could be seen.

Conclusion: The concentration of D-dimer is often elevated in patients with active cancer, but is not a sufficient criterion for diagnosis of VTE. The concentration of D-dimer before surgery does not determine the risk of postoperative thromboembolic complications. This is undoubtedly related to the widespread use of effective thromboprophylaxis. According to the literature, ultrasound is the optimum method for detection of VTE in surgically treated cancer patients. The effect of cancer stage on the value of D-dimer is revealed only when the cut-off point in this group is 1440 ng/ml, instead of 500 ng/ml which is used for the general population.

KEYWORDS: D-dimer, venous thromboembolic disease, cancer

INTRODUCTION

It is commonly accepted that D-dimer is the most useful laboratory parameter that aids in the diagnosis of venous thromboembolism (VTE). [1] When present in serum, D-dimer indicates simultaneous activation of coagulation and fibrinolysis pathways. Assays that determine the concentration of D-dimer in serum or whole blood have both high sensitivity and negative predictive value (ca. 100%), but their specificity is low. This means that such assays are very helpful in excluding VTE, i.e., when the results are negative. In contrast, high values of D-dimer are not sufficient for diagnosis of VTE due low specificity and positive predictive value. [2]

False positive results, i.e., elevated D-dimer values in patients without VTE, are often found in patients with cancer, infections, myocardial infraction, stable and unstable angina pectoris, thrombotic superficial phlebitis, rheumatoid arthritis, septicemia, pregnancy, after trauma or surgery, and in elderly patients. [3]

In this study, we included 150 patients treated surgically for active cancers of the gastrointestinal tract. For that reason, one should not suspect D-dimer to be helpful in diagnosing VTE in these patients. [4]

On the other hand, there are studies that suggest that D-dimer can be useful in predicting thromboembolic complications in cancer patients, with proposed cut-off values at the 75th percentile of the population of cancer patients (1.44 ug/ml).[5] D-dimer is viewed by some authors as a valuable parameter that helps predict thrombosis or its recurrence. [6]

We aimed to evaluate the usefulness of D-dimer in diagnosing venous thrombosis of the lower extremities in patients with cancers. Moreover, we assessed the role of D-dimer in predicting thromboembolic complications in the early postoperative period depending on the accepted D-dimer cutoffs.

MATERIALS AND METHODS

Patients

In this prospective study, we enrolled 150 patients who were operated on for active cancers of the digestive system in our department between October 2014 and June 2016. We included patients with primary cancers of the digestive tract – colon cancer, gastric cancer, pancreatic cancer, patients with tumors that infiltrated the gastrointestinal tract – primarily cancers of the genital system, and patients with local or reginal recurrence of these cancers.

The primary location of tumors is given in Tab. 1. In 150 patients, there were 152 cancers – 2 patients had 2 cancers. Patient TK was diagnosed with and operated on for gastric cancer and transverse colon cancer. Patient JK was admitted and operated on for sigmoid colon cancer, but during the hospital stay she was also diagnosed with breast cancer that was treated later.

Tumor stage is presented in Table 2.

The types of surgery performed are given in Table 3. Radical resection means removal (total or partial) of one organ with lym-

Tab. I. Primary locations of tumors

	COLON	RECTUM	STOMACH	PANCREAS	OVARY	SMALL INTESTINE	ANUS	GALLBLADDER	BREAST	IN TOTAL
Count	72	39	25	6	5	2	1	1	1	152
Percent	47,3%	25,7%	16,4%	3,9%	3,3%	1,3%	0,7%	0,7%	0,7%	100%

phadenectomy. Extended resection means radical excision (total or partial) of at least two organs with lymphadenectomy. Palliative/diagnostic procedure means surgery that did not involve radical resection.

METHODS

Before surgery, we determined D-dimer concentrations in all patients, carried out structured medical history regarding symptoms of VTE, and performed physical examination and complete Doppler ultrasound examinations of the lower extremities.

The advantage of ultrasonography over other imaging studies, such as phlebography, plethysmography, magnetic resonance angiography, and isotope phlebography) in detecting venous thrombosis in the lower extremities is documented in detail in the book "Thrombi and emboli" (ed. Prof. Łopaciuk)[3] , including its newer edition (ed. Prof. WIndyga).[13] In these books, the reader will find extensive information on the practical use of ultrasonography in contrast to the above-mentioned methods. Briefly, ultrasonography is noninvasive, short, cost-effective, easy, does not require contrast administration or full patient cooperation, and can be repeated. For these reasons, ultrasonography is optimal for patients after extensive surgery due to cancer.

Ultrasound examinations of the venous system comprise the following 4 elements:

- morphological assessment of the venous wall and lumen (normal contents of veins are anechoic, whereas thrombi appear hypoechoic or hyperechoic, depending on disease duration)
- compression test (normal veins collapse fully on compression, which is not observed in veins affected by thrombi).
- blood flow on color Doppler (normal veins completely fill with color, and thrombi cause color voids; there is no color filling in the case of total occlusion of the studied vein).
- analysis of flow spectrum on pulse-wave (PW) Doppler

It has been shown that the compression test is the most sensitive of the above-mentioned elements. [7] The sensitivity in symptomatic proximal thrombosis is 96% [8], and in asymptomatic thrombosis ranges between 76% [8] and 89% [9] (screening studies).

Sensitivity of ultrasonography in detecting VTE distally to the popliteal vein, i.e., in the calf, is lower – 30%-50%. [11-12]

Medical history, physical examination, and ultrasonography data were acquired twice more:

- on the 6-10th postoperative day (usually on discharge)
- in the 4-6th week after surgery (after completion of extended thromboprophylaxis, which in line with the current recommendations was used in all patients). [12]

Tab. II. Tumor stage

	I°	II°	III°	IV°	IN TOTAL
Patient number	3	57	56	34	150
Patient percent	2%	38%	37,33%	22,67%	100%

Tab. III. Types of procedures performed

	RADICAL RESECTION	EXTENDED RESECTION	PALLIATIVE/DIAGNOSTIC PROCEDURE	IN TOTAL
Number of procedures	114	19	17	150
Percentage of procedures	76%	12,7%	11,3%	100%

RESULTS

Laboratory results (D-Dimer) are given in two versions (Tab. 4 and 5), according to cancer stage. In Table 4, the accepted cutoff for D-Dimer was 500 ng/ml, which is a commonly acceptance norm. In Table 5, the accepted cutoff for D-Dimer was 1440 ng/ml, as suggested by Ay et al.[5]

We did not find any symptoms of venous thromboembolism in any of the 150 patients in medical history, physical examination, and ultrasonography before surgery, on discharge, and after completion of extended thromboprophylaxis.

One patient died before the third examination. In that patient, there were no signs of thromboembolic complications on autopsy.

DISCUSSION

Cancer patients have an increased risk of thromboembolic complications. Based on the available literature [14], the likelihood of venous thrombosis in patients with cancer is 4%-20%. It is even greater on post-mortem examinations and approaches 50%. [15-17] D-Dimer is the most commonly used laboratory parameter for diagnosing venous thrombosis. [1,6] However, D-Dimer results can be false positive in a large proportion of patients with cancer. [2,3]

In this study, we compared the concentration of D-Dimer with other signs of venous thromboembolism from medical history, physical examination, and Doppler ultrasonography. Based on numerous reports, Doppler ultrasonography is the most helpful imaging technique that can be used for detecting thrombosis. [3]

Despite a large variability of D-Dimer concentration, including elevated concentrations, before surgery, we did not detect venous thromboembolism in any of the operated patients on the basis of medical history, physical examination, or Doppler ultrasonography.

Moreover, regardless of the preoperative D-Dimer concentration, none of the patients developed thromboembolic complications in the early postoperative period. This is undoubtedly due to the use of extended thromboprophylaxis, which is not discussed herein.

Tab. IV. D-dimer concentration according to cancer stage (cutoff of 500 ng/ml)

D-DIMER	I° 3 PATIENTS	II° 57 PATIENTS	III° 56 PATIENTS	IV° 34 PATIENTS	IN TOTAL 150 PATIENTS
Below 500 ng/ml – patient number	2	34	27	18	81
Below 500 ng/ml – percentage of patients	66,66%	59,65%	48,21%	52,94%	54%
Above 500 ng/ml – patient number	1	23	29	16	69
Above 500 ng/ml – percentage of patients	33,33%	40,35%	51,79%	47,06%	46%
Total patient number	3	57	56	34	150
Total percentage of patients	100%	100%	100%	100%	100%

Tab. V. Wartości D-dimeru a zaawansowanie nowotworu (wartość odcięcia: 1440 ng/ml)

D-DIMER	I° 3 PATIENTS	II° 57 PATIENTS	III° 56 PATIENTS	IV° 34 PATIENTS	IN TOTAL 150 PATIENTS
Below 1440 ng/ml – patient number	3	51	48	27	129
Below 1440 ng/ml – percentage of patients	100%	89,5%	85,7%	79,4%	86%
Above 1440 ng/ml – patient number	0	6	8	7	21
Above 1440 ng/ml – percentage of patients	0%	10,5%	14,3%	20,6%	14%
Total – patient number	3	57	56	34	150
Total – percentage of patients	100%	100%	100%	100%	100%

In 54% patients (81/150), the concentration of D-Dimer before surgery was normal, i.e., within the range used for the general population. That was observed in 66.66% of patients with stage I cancers (2/3), 59.65% of patients with stage II cancers (34/57), 48.21% of patients with stage III cancer (27/56), and 52.94% of patients with stage IV cancer (18/34).

If the commonly cutoff value is accepted (500 ng/ml), as much as 46% of patients (59/150) will have an elevated D-Dimer concentration in spite of not having VTE. That was seen in 33.33% of patients with stage I cancers (1/3), 40.35% of patients with stage II cancers (23/57) , 51.79% of patients with stage III cancers (29/56), and 47.06% of patients with stage IV cancers (16/34).

With this cutoff value, there are no visible effects of cancer of D-Dimer concentration, i.e., there are no differences in the frequency of abnormal D-Dimer concentration (above 500 ng/ml) between patients with different stages of the disease.

However, when the cutoff for D-dimer is accepted at 1440 ng/ml (Ay i wsp.[5]), the proportion of patients with elevated D-Dimer concentration will be only 14%. Specifically, it will be 0% in patients with stage I cancers (0/3), 10.5% in patients with stage II cancers (6/57), 14.3% in patients with stage III cancers (8/56), and 20.6% in patients with stage IV cancers (7/34).

Based on this cutoff value, there are differences in the frequency of elevated D-Dimer concertation (above 1440/ ng/ml) between patients with different stages of the disease, with patients in more advanced stages of cancers having a higher risk of elevated D-Dimer concentrations.

In conclusion, it seems justified to use the serum D-Dimer cutoff value of 1440 ng/ml in diagnosing venous thromboembolism in patients with cancer rather than the value used in the general population, i.e., 500 ng/ml.

CONCLUSIONS

D-Dimer concentration is often elevated in patients with active cancer and therefore is should not be used as an isolated marker for diagnosis VTE in these patients.

Preoperative D-Dimer concentration does not predict the risk postoperative thromboembolic complications. This is undoubtedly due the use of efficacious thromboprophylaxis.

Based on the available literature, Doppler ultrasonography is the optimal and most practical method for diagnosing VTE in patients treated surgically for active cancer.

The influence of cancer on the concentration of D-Dimer can be seen only when the cutoff value of 1440 ng/ml is accepted, in contrast to the value of 500 ng/ml that is used for the general population.

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