



# Elevated plasma D-dimer as a predictor of postoperative complications after radical cystectomy

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**rezime** Detailed preoperative evaluation is essential in prevention of perioperative complications. As thorough anamnesis, physical examination and standard laboratory investigation do not contribute much in prediction of perioperative complications and outcome, and detection of tumor markers is also insufficient in means of prognosis, some molecular marker have emerged lately as prognostic markers in surgery. Recent data on pathophysiological processes stress response, derangements of hemostasis, in sepsis or in thromboembolism as well as in malignancy, indicate that presence or elevation of some molecular markers of fibrinolysis can indicate possibility of perioperative complications and even predict outcome. As it is evident that neoplastic cells enhance thrombin and other procoagulant production, detection of degree of activation of coagulation and fibrinolysis can contribute in prediction of treatment outcome in patients with bladder carcinoma scheduled for radical surgical procedures.

Key words: D-dimer, radical cystectomy, postoperative complications

## BACKGROUND

The role of D-dimer, the final product and only specific marker of fibrinolysis is thoroughly evaluated in studies of thromboembolism, but still investigated in studies of progression of systemic inflammatory response and multiple organ dysfunction in critically ill and in determination of progression of carcinoma. Endothelial dysfunction in thrombosis, inflammation and in malignancy has the same pathophysiological origin: thrombin generation induction by tissue factor, dysfunction of coagulation and derangement of fibrinolysis.

In malignancy interaction of inflammation and coagulation results in systemic inflammatory response syndrome that leads to microvascular thrombosis and modulation of inflammation itself. Intravascular deposition of fibrine

and microaggregation of thrombocytes, neutrophil and red blood cells can lead to tissue ischemia and multiple organ failure<sup>1,2</sup>.

In malignancy and in radical surgery with significant tissue destruction and derangement of circulation, direct activation of coagulation occurs with interaction of endothelial microparticles and proinflammatory cytokines from malignantly altered tissues<sup>3,4</sup>. Subclinical activation of coagulation in malignancy is proven through direct procoagulant activity of malignant cells, through direct cellular interaction and through cytokine production<sup>5</sup>. Cellular interaction and mediator action on endothelium modulates vascular tone, platelet adhesion, inflammation, fibrinolysis and vascular growth<sup>6</sup>.

All mentioned give reason for recent studies that track progression of malignancy through evaluation of coagulation markers, and they indicate that degree of coagulation activation can give insight in advance of malignancy, poor prognosis and short survival of surgical patients<sup>7,8,9,10</sup>.

In patients with urologic malignancy data indicate elevation of markers of fibrinolysis (fibrinogen, F1+2, D-dimer) in prostate cancer patients and in patients<sup>11</sup> that underwent radical cystectomy with elevation of values of urokinase-type plasminogen activator (u-PA) with degree of lymphovascular invasion, tumor progression and survival<sup>12,13</sup>.

In search for more accurate tumor markers, particularly of bladder cancer, more detailed investigation of preoperative procoagulant and thrombophilic activity could help prediction of surgical outcome and choice of treatment options.

In the present study we examined association of preoperative plasma D-dimer level with tumor stage in patients who underwent radical cystectomy with urine derivation. We also examined prognostic significance of plasma D-dimer levels for occurrence of postoperative complications and perioperative survival.

**MATERIALS AND METHODS**

The conducted prospective randomised investigation of preoperative plasma D-dimer values in patients with bladder carcinoma who underwent radical cystectomy in six months period at the Urologic Clinic of Institute of Urology and Nephrology, Clinical Center of Serbia. Of 54 bladder cancer patients 28 were excluded for following reasons: other surgery one month prior to radical cystectomy, presence of significant preoperative uroinfection, previous chemotherapy and deep vein thrombosis. Preoperative plasma D-dimer level was measured, and postoperatively patients were monitored for postoperative complications (infection, sepsis, venous thromboembolism and cardiologic events). Preoperative plasma D-dimer values in bladder carcinoma patients were compared with values in 20 patients with benign noninfective bladder disorders, such as stress incontinence prior to surgical treatment.

In order to measure plasma D-dimer level blood was obtained from cubital vein 24-72 hours prior to surgery. Levels of D-dimer were measured by quantitative latex turbidimetric method on Behring Coagulation Timer. Because of sensitivity of assay all values below 50 µg/l were set to equal 50 µg/l, cut-off value was set at 195 µg/l, while values over 500 µg/l were considered as significantly elevated. Data were statistically analysed in SPSS ver.12 package, and values of  $p < 0,05$  were considered statistically significant.

**RESULTS**

Study group comprised 26 patients who underwent radical cystectomy with urinary diversion. There were 23 men and 3 woman. The mean age was 65,7, range 38-76 years. Average value of plasma D-dimer was  $258,85 \pm 136,89$  µg/l, compared to 20 patients without bladder carcinoma in whom average plasma D-dimer was  $155,14 \pm 47,207$  µg/l ( $p,05$ ). Approximately one third (34,6%) of bladder cancer patient had normal values of plasma D-dimer (• µg/l), while 65,4% of them had elevated values of plasma D-dimer preoperatively ( $331,35 \pm 109,54$  µg/l), range 201-567 µg/l. (Figure 1.)

There was no statistically significant difference in plasma D-dimer level in grade 2 (15,4 %) and 3 (84,6 %) bladder cancer patients,  $206$  µg/l and  $268,5$  µg/l. In spite small number of patients for definitive conclusions, 50% of grade 3 bladder carcinoma patients had elevated preoperative plasma D-dimer value over 200 µg/l.

Postoperatively 12 patients (46,2%) had documented infection, 75% of them had elevated plasma D-dimer above cut-off value. Eight of them had signs of sepsis, and all patients who developed septic syndrome had preoperative plasma D-dimer value above normal range, average  $298,6$  µg/l. Postoperative cardiovascular disorders with suspected thrombotic event occurred in 3 patients, only one of them had elevated preoperative plasma D-dimer at  $519$  µg/l. There were two lethal outcomes, one due to massive pulmonary embolism (normal preoperative

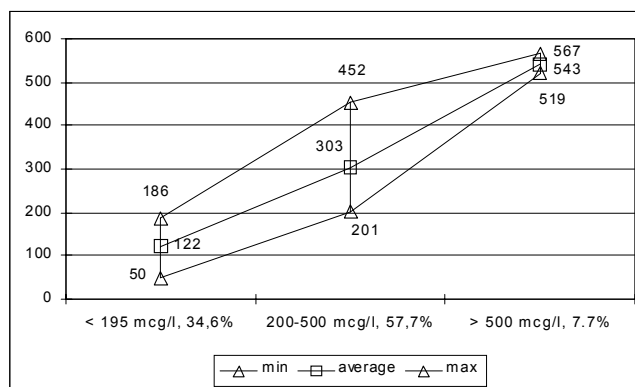


FIGURE 1  
VALUES OF PREOPERATIVE PLAZMA D-DIMER IN BLADDER CANCER PATIENTS

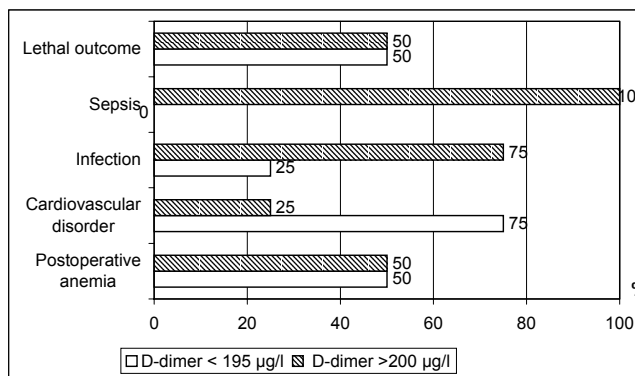


FIGURE 2  
DISTRIBUTION OF NORMAL AND ELEVATED PREOPERATIVE PLAZMA D-DIMER IN POSTOPERATIVE COMPLICATIONS AFTER RADICAL CYSTECTOMY (NUMBER OF PATIENTS IN PERCENTAGE).

plasma D-dimer) and one in sepsis with multiple organ failure ( preoperative plasma D-dimer  $418$  g/l). (Table 1.)

It was significant that majority of patients who has documented infection and septic syndrome had preoperatively elevated plasma D-dimer levels. (Figure 2,3.) Both patients with preoperative plasma D-dimer over 500 g/l developed serious infection, one died in septic syndrome.

**DISCUSSION**

Although small number of subjects did not provide statistical confirmation, data in this study indicate that majority of bladder cancer patients have increased plasma D-dimer preoperatively (65,4%), and as patients in any state of health that could contribute to the activation of coagulation and fibrinolysis were excluded from the study, it seems that reason for elevated specific fibrinolytic marker is malignancy. Plasma D-dimer is reported in other cancer patients as well, in patients with prostate cancer, colorectal cancer<sup>9</sup>, lung cancer, cervical cancer of uterus, ovarian malignancies, and in breast cancer. Increased concentration of coagulation activation markers in bladder carci-

TABLE 1  
POSTOPERATIVE COMPLICATIONS AND  
PREOPERATIVE PLASMA D-DIMER VALUE IN  
BLADDER CANCER PATIENTS

	No of pts = 26	average D-dimer ug/l
Postoperative anemia	15,4% (4)	261
Cardiovascular disorder	11.5%(3)	227
Infection	46.2% (12)	295
Sepsis	30.7% (8)	298,6
Lethal outcome	7.7% (2)	271,5

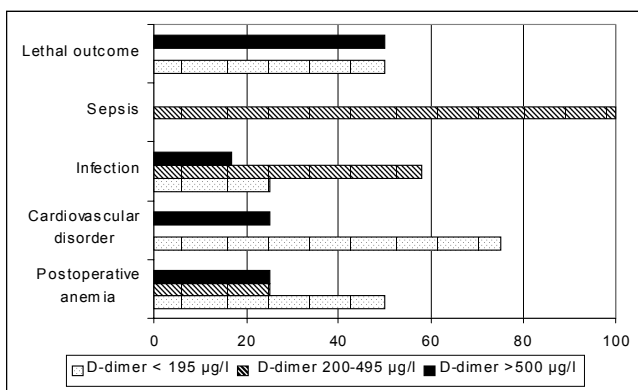


FIGURE 3.  
DISTRIBUTION OF PREOPERATIVE PLASMA D-DIMER IN THREE RANGES IN POSTOPERATIVE COMPLICATIONS AFTER RADICAL CYSTECTOMY (NUMBER OF PATIENTS IN PERCENTAGE).

noma patients is connected with poor outcome of surgical treatment according to data published recently'.

Postoperatively 12 patients had documented infection, 75% of them with elevated preoperative plasma D-dimer above cut-off value. Eight of them had signs of sepsis, and all patients who developed septic syndrome had preoperative plasma D-dimer value above normal range, average 298,6 g/l. Untill recently data concerning urologic malignancies considered correlation of elevated plasma D-dimer in light of coagulation disorders and haemorrhagic complications, and this correlation has not been proved. But data indicate correlation of enhanced fibrinolysis as marker of severity of inflammatory response, with postoperative outcome in surgery. Average preoperative plasma D-dimer in this study was 296µg/l in patients who developed postoperative complications, as in patients without complications plasma D-dimer was 206,4 µg/l (p).

Postoperative cardiovascular disorders with suspected thrombotic event occurred in 3 patients, only one of them had elevated preoperative plasma D-dimer at 519µg/l. There were two lethal outcomes, one due to massive pul-

monary embolism ( normal preoperative plasma D-dimer) and one in sepsis with multiple organ failure ( preoperative plasma D-dimer 418µg/l).

As small number of subjects reflects statistically insignificant correlation of preoperative elevation of plasma D-dimer and postoperative complications in bladder cancer patients, data should be considered preliminary. However, preoperative determination of coagulation activation in patients scheduled for radical cystectomy raise important issues. Radical cystectomy as treatment option for advanced bladder carcinoma still carries certain burden of postoperatively complicated course, and any improvement in decision making, with better insight in prognosis, can contribute in better quality of life and survival of these patients.

### CONCLUSION

If measurement of plasma D-dimer would be included in the routine preoperative laboratory examination of patients with bladder cancer, it could provide supplementary information on tumor stage and prognosis. Although the number of patients in this study is not large enough to establish the usefulness of the measurement of preoperative plasma D-dimer levels, it appears that further prospective studies with a larger number of subjects would be worthwhile.

The issues that could contribute in prediction of treatment outcomes are determination of correlation of preoperatively activated coagulation and fibrinolysis and survival of patients undergoing radical surgery. Even more interesting would be determination of discriminative values of coagulation activation markers in means of confirmation of defensive systemic inflammatory response, and early detection of postoperative complications.

### SUMMARY

#### POVIŠENE VREDNOSTI PLAZMA D-DIMERA U PROCENI NASTANKA POSTOPERATIVNIH KOMPLIKACIJA POSLE RADIKALNE CISTETOMIJE

U cilju prevencije nastanka komplikacija hirurškog lečenja pažljivo preoperativno sagledavanje stanja zdravlja pacijenta se nameće kao osnovni korak. Medjutim, detaljna anamneza, standardni preoperativni fizikalni pregled i rutinski laboratorijski testovi ne pružaju nam mogućnost tačnog preoperativnog predviđanja nastanka komplikacija ili dužine preživljavanja. Preoperativno određivanje tumorskih markera karcinoma mokraćne bešike samo donekle odražava uznapredovalost bolesti. Nova saznanja o patofiziološkim procesima u odgovoru organizma na stres, poremećajima hemostaze, sepsi, tromboembolizmu i malignitetu, ukazuju na značaj pojedinih markera koji bi mogli svojim prisustvom ili povećanim koncentracijama u preoperativnom periodu tačnije da ukažu na moguće pravce postoperativnog toka, dužinu preživljavanja i pomognu u složenoj proceni boljitka od izabranog načina lečenja. Kako je odavno poznato da neoplastične ćelije pospešuju stvaranje trombina i proizvode razne prokoagulate, detekcija stepena aktivacije koagu-

lacionog i fibrinolitičkog sistema može u mnogome doprineti u sagledavanju uznapredovalosti karcinomske bolesti i predviđanju mogućih komplikacija i ishoda radikalnog hirurškog lečenja.

Ključne reči: D-dimer, radikalna cistektomija, postoperativne komplikacije

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