

PROGNOSTIC IMPORTANCE OF HAEMOSTATIC PARAMETERS IN POLYARTERIAL DISEASE

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Abstract: The goal of our study was to evaluate the value of fibrinogen, D-dimers and antithrombin III plasma levels in prognosticating mortality in patients suffering from both peripheral arterial disease (PAD) and coronary artery disease (CAD).

Patients and methods: 90 patients with coexistent PAD and CAD were enrolled in a 36 months study, and evaluated for the following parameters: age, sex, current smoking, ankle-brachial index, claudicating distance, ejection fraction, triglycerides, cholesterol, LDL, fibrinogen, D-Dimers, antithrombin III, creatinine, glycaemia, histories of myocardial infarction, stroke, diabetes and previous revascularization, as well as a number of other concurrent diseases.

We developed a linear regression model for identification of variables, associated with cardiovascular events, and a multivariate regression model to define the predictors of mortality.

Results: We registered 126 cardiovascular events during three years' follow-up. The number of cardiovascular events correlated with fibrinogen ($r = 0.59$, $p = 0.01$) and with D-dimers ($r = 0.48$, $p = 0.01$).

A mortality of 8.89% was found for the period of three years in patients with coexistent PAD and CAD. The variables independently associated with mortality found by multivariate analysis were fibrinogen ($r = 0.21$, $p = 0.02$, score = 2.78), DD ($r = 0.94$, $p = 0.01$, score = 17.24) and ankle-brachial index ($r = 0.40$, $p = 0.03$, score = 4.84).

Conclusions: The reported data demonstrated fibrinogen and D-dimers as independent predictors of mortality in patients with polyarterial disease.

Key words: polyarterial disease, peripheral arterial disease, coronary artery disease, prognosis, fibrinogen, D-dimers.

Introduction

Patients with polyarterial disease: peripheral (PAD) and coronary artery disease (CAD) have a high rate of mortality, reported as 20% to 30% over 10 years, which is twice to three times more than in the common populations [1,2].

The mortality in these patients is due to cardiovascular events: 35–60% of all deaths are from coronary artery disease, 7–17% from cerebrovascular disease, and 8% from aortic dissection [3, 4, 5].

Derangements in haemostatic parameters are risk factors for the development of PAD and CAD. Haemostatic dysbalances have their origin in life habit (smoking), are associated with some diseases (diabetes), or are otherwise identified as congenital coagulopathies [1, 6].

Elevated fibrinogen and D-dimers plasma levels, also a reduction of antithrombin III level were detected in patients with peripheral and with coronary artery disease.

Fibrinogen has atherogenic vascular effects noted by fibrin endothelial deposition and altered endothelial permeability by fibrin peptides [7]. The plasma level of fibrinogen correlates with a subclinical form of cardiovascular disease and its evolution to a clinical form. The Cardiovascular Health Study, APSIS, ECAT, Speedwell study and Northwick Park Heart Study have identified fibrinogen as a prognostic factor of CAD (4.8–18).

The values of D-Dimers as fibrin degradation products are associated with the extent of atherosclerosis and future cardiovascular events in patients with CAB [19–26].

Antithrombin III has been presented as a prognostic marker for coronary patients [12,24].

Their role in the prognostication of peripheral arterial disease is still under debate.

The goal of our study is to define the role of fibrinogen, D-dimers and antithrombin III in prognosticating the mortality of patients suffering from both peripheral and coronary artery disease.

Patients and methods

From March 1st 2000 to 2003, 90 patients with coexistent PAD and CAD were enrolled in a prospective observational study. PAD was defined with value of ankle-brachial index < 0.9. CAD was defined as previous myocardial infarction or myocardial revascularization, or clinical symptoms confirmed with coronary angiography.

The examination methods used in the study were: anamnesis and history of disease, continuous Doppler sonography, peripheral and coronary angiography, and echocardiography for ejection fraction. Basic biochemical and haematological analyses were done. Plasma levels of fibrinogen were analysed with a modified Claus method.

D-dimers were turbidimetrically determined, antithrombin III was chromogenically analysed. We used Dade-Behring reagents for these methods.

All the patients were followed up for three years for future cardiovascular events and deaths. We used SPSS 8.0 for Windows package for statistical analysis.

Spearman's coefficient was used to find the relation between the estimated parameters.

A linear regression model was built for identification of variables associated with cardiovascular events, and a multivariate regression model to define the predictors of mortality.

Results

The mean age of sample was 62.3 ± 6.9 years. 73% of the population were men. The basic characteristics of the defined population are presented in Table 1.

Table 1 – Табела 1

Basic characteristics of patients
Основни карактеристики на пациенти

men	73.3 % (66)
histories of:	
myocardial infarction	54.4 % (49)
stroke	7.7 % (7)
previous revascularization	21.1 % (19)

arterial hypertension	61.1 % (55)
diabetes mellitus	55.5 % (50)
current smoking	60 % (54/90)
comorbity	1.9 + 0.8
EF (%)	49.86 ± 10.55
NYHA III/IV % (pts)	27.8 (25)
Systolic blood pressure(mmHg)	157.5 ± 18.3
Ankle-brachial index	0.58 ± 0.23
Glycaemia(mmol/L)	6.72 ± 2.03
Urea	8.12 ± 4.82
Creatinine	87.52 ± 41.21
Na	139.52 ± 4.51
K	4.74 ± 0.52
Tryglicerids	2.07 ± 0.96
Cholesterol.	5.64 ± 1.21
HDL	1.19 ± 0.85
LDL	3.52 ± 1.29
Fibrinogen (g/L)	4.29 ± 1.22
antithrombin III	0.197 ± 0.061
D-dimers (µg/ml)	1101.24 ± 1730.37

The data show the elevation of values of fibrinogen plasma level $4.29 \text{ g/L} \pm 1.22$ (normal value 2–4 g/L), and D-dimers $1101.24 \text{ µg/ml} \pm 1730.37$ in the study group at study startpoint (normal value 0–350 µg/ml). Mean AT III was $0.19 \text{ g/L} \pm 0.06$ (normal value 0.17–0.3 g/L).

There is a strong correlation with values of fibrinogen and the presence of diabetes mellitus ($r = 0.40$), but a poor correlation with smoking ($r = 0.05$), dislipidemia ($r = 0.17$), arterial hypertension ($r = 0.16$) and age ($r = 0.19$). A correlation between D-dimers and DM was found ($r = 0.53$). Significant correlation coefficients between D-dimers and smoking, age, dislipidemia and arterial hypertension were not found.

During three years of follow-up 126 events were registered. The most frequent events were: acute myocardial infarction, heart failure and peripheral thrombembolism.

The linear regression model reported correlations between cumulative incidences of cardiovascular events for three years and values of: fibrinogen (with $r = 0.59$, $p = 0.01$) and D-Dimers ($r = 0.48$, $p = 0.01$) (Figs. 1, 2). Clearly, a significant relation between antithrombin III and events was not found ($r = 0.13$, $p = 0.01$).

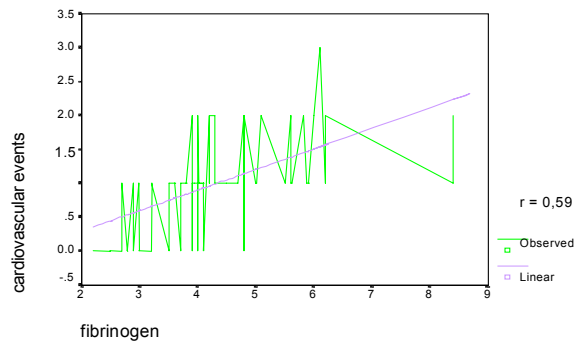


Figure 1 – Relation between cumulative rate of events and plasma fibrinogen level

Слика 1 – Сооднос помеѓу кумулативната стапка на збиднувањата и нивојто на фибриноген во плазма

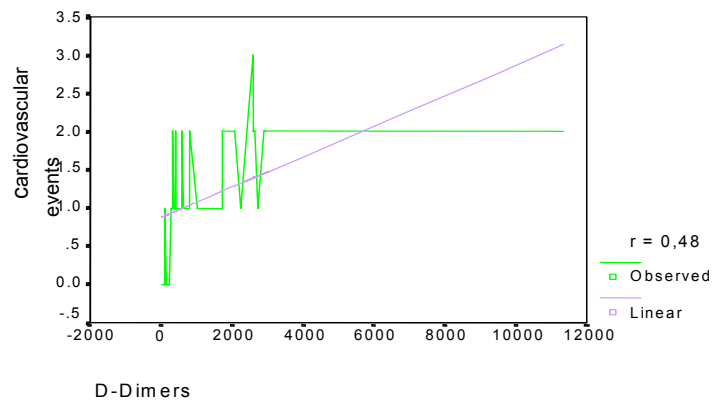


Figure 2 – Relation between cumulative rate of events and D-dimers

Слика 2 – Сооднос помеѓу кумулативната стапка на збиднувања и Д-димерите

Univariate analysis defined the risk of elevated values of fibrinogen and D-Dimers for the onset of cardiovascular events with Hazard ratio 1.07 for fibrinogen and 2.55 for D-dimers.

These results identified fibrinogen and D-Dimers as factors for the prognosis of coexistent peripheral and coronary artery disease.

The data obtained present three years' mortality 8.89%, or 2.96% as a one-year rate, respectively.

Only fibrinogen, D-dimers and ankle-brachial index were identified as predictors of mortality of patients with coexistent PAD and CAB, presented by multivariate analysis (Table 2).

Table 2 – Табела 2

Prognostic value of variables (Cox regression analysis)

Прогностичка вредносћ на варијаблности

(Коксова регресиона анализа)

Variables	OR	df	p	R
Categorical variables				
male	1,5062	1	0,2197	0,0000
smoking	3,0187	1	0,0823	0,2424
diabetes	0,1409	1	0,5002	0,0000
myocardial infarction	0,1049	1	0,7460	0,0000
stroke	0,1769	1	0,6741	0,0000
previous revascularization	0,4423	1	0,5060	0,0000
Continuous variables				
age	1.4923	1	0,2219	0,4050
ankle-brachial index	4,8433	1	0,0278	0,0000
ejection fraction	1,2100	1	0,2713	0,0000
systolic blood pressure	0,4600	1	0,4976	0,0000
glycemia	0,2274	1	0,6334	0,0000
Fibrinogen	2,7771	1	0,0500	0,2117
D-Dimers	17,2445	1	0,0100	0,9377
tryglicerids	0,0692	1	0,7925	0,0000
cholesterol	0,0533	1	0,8174	0,0000
LDL	0,2524	1	0,6154	0,0000
Comorbidity	0,0423	1	0,8370	0,0000

Residual Chi Square = 32.37 with 18 df p (Sig) = 0.199

The prognostic importance of fibrinogen and D-Dimers was evaluated by a Kaplan-Meier curve of mortality with $p = 0.05$, log. likelihood 41.32. Patients stratified for elevated plasma level of $F > 4.5$ g/L and $DD > 300$ μ g/ml, have a higher mortality than the other patients (Figure 3).

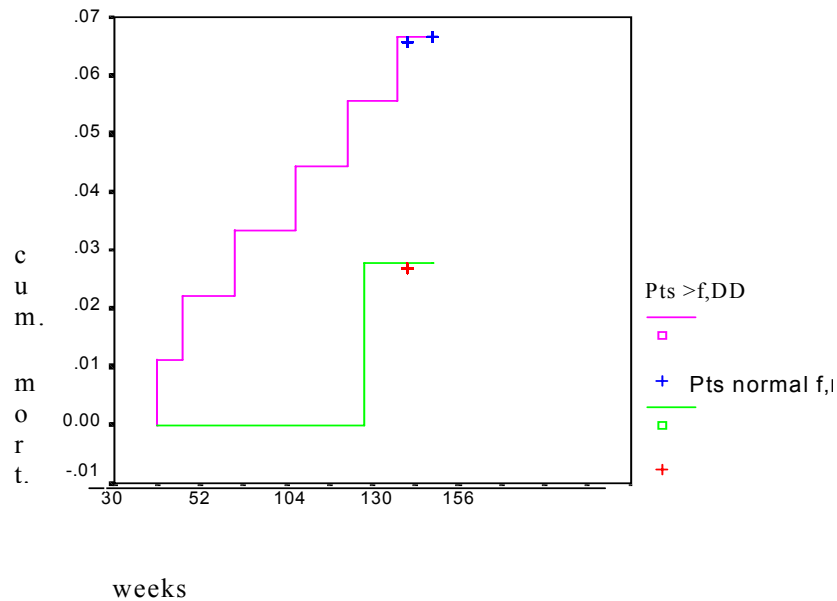


Figure 3 – Cumulative rate of mortality of patients with PAD and CAD stratified with elevated plasma level of fibrinogen and D-dimers

Слика 3 – Кумулативна стапка на морталитетот на пациентите со ПАБ и КАБ, стратифицирани за покачени вредности на фибриноген и Д-димери

Discussion

The results of the study show an overall three-years mortality of 8.89%.

Our results are comparable with studies on patients with PAD, and on patients with CAD and low ABI: Criqui's study (3.4% for one year) and BARI (2.1%) (Table 3) (7.29).

All reported deaths were due to cardiovascular events.

The most frequent fatal event was myocardial infarction. Our results are identical with studies by Smith and Leng, reporting myocardial infarction as the most frequent event [27].

Our study's multivariate analysis found fibrinogen, D-dimers and ankle-brachial index as predictors of mortality of patients with polyarterial disease.

Table 3 –Табела 3

*Mortality in patients with peripheral arterial disease**Морталитетот на пациентите со периферна артериска болест*

<i>Studies</i>	<i>ts.</i>	<i>mortality (a year rate %)</i>
Jelnes1986	57	2,2
Criqui 1992	65	3,3
CASS 1995	834	2,8
BARI 1999	9	2,1
Our study 2002	0	2,9

The ankle-brachial index is a predictor of mortality with a score of 4.84 ($r = 0.40$, $p = 0.03$). ABI is a predictor of mortality in patients with PAD with a relative overall risk of mortality of 1.8 (Trans-Atlantic Consensus of PAD), or for cardiovascular mortality with a relative risk of 2.2 (Cardiovascular Health study, Lang) [4, 27, 30]. A possible mechanism could be based on that ABI defined extent of atherosclerosis. Polyarterial involvement is also in relation to a higher rate of future events.

The Northwick, Speadwell, APSIS and ADEP studies and the investigation of Wilhelmesen, Stone identified hyperfibrinogenemia as a risk factor for coronary and peripheral arterial disease (11–16). Only the ADEP group found fibrinogen as a predictor of events and Banerjee as predictor of mortality [31, 32]. Our study reports fibrinogen as a predictor of mortality in patients with PAD with of score 2.78 ($r = 0.21$, $p = 0.05$).

A strong predictor of mortality of patients with PAD and CAD are D-dimers (score = 17.24, $r = 0.94$, $p = 0.01$). This finding supports the thesis of the association of intravascular fibrin with atherothrombosis. [36]

The concept that activated thrombogenesis dictates the clinical outcome of patients with vascular disease in peripheral and coronary territories is strongly supported by these results. Thus, the detection of haemostatic parameters: fibrinogen and D-dimers seems to be very useful. Future studies on the prognostic importance of other haemostatic parameters are necessary.

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Резиме

ПРОГНОСТИЧКО ЗНАЧЕЊЕ НА ХЕМОСТАТСКИТЕ ПАРАМЕТРИ КАЈ ПОЛИАРТЕРИСКАТА БОЛЕСТ

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Цел на студијата: Процена на влијанието на фибриногенот, Д-димерите и антиромбинот III врз стапката на морталитет кај пациентите со

полиартериска болест: периферна артериска болест (ПАБ) и коронарна артериска болест (КАБ).

Пациенти и методи: 90 пациенти беа вклучени во оваа 36 месечна студија:

Со цел да се испита влијанието на возраста, полот, пушењето, глужно-надлакотниот индекс (АБИ), клаудикационата дистанца (КД), ежекционата фракција, триглицеридите, холестеролот, ЛДЛ, хемостатските параметри: фибриноген, Д-димери (ДД), антитромбин III, креатининот, гликемијата, историјата на миокардниот инфаркт, мозочен удар, дијабет, претходна реваскуларизација, како и бројот на придружните заболувања. Користен беше линеарниот регресионен модел за одредување на факторите поврзани со кардиоваскуларните збиднувања и мултиваријантен регресионен модел за дефинирање на предикторите на mortalитетот.

Резултати: За период од три годни беа регистрирани 126 кардиоваскуларни збиднувања. Бројот на збиднувањата корелираше со вредностите на фибриногенот ($r = 0.59$, $p = 0.01$), и ДД ($r = 0.48$, $p = 0.01$).

Беше пронајден mortalитет од 8,89% за период од три години кај пациентите со коегзистирачка ПАБ и КАБ. Фактори независно поврзани со mortalитет, врз основа на мултиваријантната анализа се фибриногенот (score 2.78, $r = 0.21$, $p = 0.05$), Д-димерите (score 17.24, $r = 0.94$, $p = 0.01$) и АБИ (score 4.84, $r = 0.40$, $p = 0.03$).

Заклучок: Резултатите од оваа студија ги препознаваат фибриногенот и Д-димерите за предиктори на mortalитет на полиартериската болест.

Клучни зборови: полиартериска болест, периферна артериска болест, коронарна артериска болест, прогноза, фибриноген, Д-димери.