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PREDICTION MODEL OF CORONARY HEART DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE: ROLE OF PLASMA FIBRINOGEN AS A NEW PROGNOSTIC VARIABLE

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A b s t r a c t: ***Background****:* The Framingham–Anderson (FA) risk equation can predict coronary heart disease (CHD) risk in the general population. However, this formula's validity in predicting CHD risk in chronic kidney disease (CKD) patients is not extensively evaluated.

Methods*:* In a group of 96 patients with CKD stage 2 to 4, free of CHD at the time of the start of follow-up, and prospectively followed for 4 to 12 years (7.4 ± 2.2 years, mean ± SD), we calculated the FA index.

Results*:* During the follow-up period, twenty-one patients experienced fatal and non-fatal myocardial infarction (CHD_{obs}+), and 75 remain free of CHD (CHD_{obs}–). The median FA index was 7.1% for CHD_{obs}– patients and 10.3% for CHD_{obs}+ patients. The specificity of the model was acceptable (89%), but the sensitivity was low (24%). Sensitivity analysis by adding fibrinogen led to an improvement in the CHD risk index and the sensitivity of the model (48%) as well. However, despite the addition of fibrinogen to the FA risk factors, full CHD risk in CKD patients remains underestimated.

Conclusions*:* Our results show that the FA index is a weak predictor of CHD in CKD stage 2 to 4 patients, and emphasized the role of inflammation in predicting the CHD risk.

Key words: Chronic kidney disease, Renal Failure, Prediction model, Coronary artery disease, fibrinogen, inflammation.

Introduction

Coronary heart disease (CHD) is an important cause of morbidity and mortality in chronic kidney disease (CKD) [1, 3]. Predicting CHD is of primary importance for its prevention and treatment. Traditional risk factors, recognized as contributing to CHD in the general population, are present in patients with CRF [4]. In an effort to quantify CHD risk based on traditional risk factors alone, Sarnak *et al.* applied the Framingham risk equation to 1795 patients with CRF enrolled in the baseline period of Modification of Diet in Renal Disease study, and found that predicted CHD risk is similar to the risk in the general population [4]. In another study, the projected 5-year cardiovascular disease risk based on the Framingham risk equation among end-stage renal disease (CKD stage 5) patients older than 40 years without previous CVD was higher in CHOICE study participants (13%) than in the NHANES III participants (6%) [5]. However, neither of these studies was able to assess the validity of the Framingham–Anderson risk equation in predicting CHD risk in CKD patients relative to their cross-sectional nature.

In our nephrology division, we prospectively determined clinical and laboratory parameters relevant to atherogenesis in a cohort of patients with CKD stage 2 to 4, and evaluated the incidence and risk factors of cardiovascular events over a 10-year period [1]. In the present paper we extend this follow-up period to December 31, 1999. Data from our study provide an opportunity to prospectively examine the validity of the Framingham risk equation in predicting CHD risk in CKD patients.

Patients and methods

Patients

Between January 1985 and December 1997, 147 patients (99 male, 48 female, all Caucasian) with progressive CKD, defined by a creatinine clearance (Ccr) of 20–70 ml/min, were referred and regularly followed in our nephrology division. Recruitment started as of January 1, 1985 and terminated as of April 30, 1994. The date of the last follow-up was December 31, 1999. Patient follow-up has been performed at our division from baseline Ccr either until the start of hemodialysis (HD), or until the end of the follow-up period. Nine out of the 147 patients were on lipid-lowering therapy and were excluded. Thus, 138 patients were included in the current evaluation. Of these, 96 patients were free of cardiovascular events at the time of the start of follow-up, had a follow-up time of between 4–12 years, and therefore fulfilled the requirements of the Framingham–Anderson index [6]. All patients were ambulatory and managed as outpatients. Informed consent to participate in this study of the risk factors of atherosclerosis was collected. The outcome measure was the occurrence of a myocardial infarction with or without revascularisation, For the 96 patients included, the covariables required for the calculation of the Anderson's index were collected, including age and gender, systolic blood pressure, tobacco consumption, diabetes, total and HDL cholesterol. Left ventricular hypertrophy (LVH) by electrocardiogram (EKG) criteria were not recorded at baseline, and therefore were not included in the initial calculation of the Framingham–Anderson' index. We also evaluate serum fibrinogen levels and estimated creatinine clearance for each subject by using the Gault and Cockroft formula. The patients' clinical characteristics at inclusion are presented in Table 1. Eighty-six percent of patients were under antihypertensive therapies, and twenty-four percent were under angiotensin converting enzyme (ACE) inhibitors. The mean duration of follow-up was 7.4 ± 2.2 years. During the follow-up period, twenty-one patients experienced fatal or non-fatal myocardial infarction.

Table 1 – Табела 1

Patients' characteristics at inclusion
Карактеристики на пациентите при вклучување во студијата

A: Patients' clinical and laboratory data characteristics at inclusion
A: Клинички и лабораториски податоци за пациентите при вклучување во студијата

	N	*Gender men %*	*Age (years)*	*Syst BP (mmHg)*	*total Chol (mM)*	*HDL Chol (mM)*	*smokers %*	*BMI (kg/m²)*	*Fib (g/l)*	*Creat clear (ml/mn)*
CDH_{obs-}	75	61	64.5	150	6.21	1.38	44.0	24.5	4.65	39.5
CDH_{obs+}	21	81	68.1	156	6.24	1.23	52.4	25.3	5.67	37.3
All	96	66	65.3	151	6.22	1.35	45.8	24.7	4.88	39.0

N: number of patients, BMI: body mass index, total Chol: total serum cholesterol, HDL Chol: High density lipoprotein serum cholesterol, Fib: serum fibrinogen; Creat clear: creatinine clearance. For the numeric variable the results are expressed as mean.

B: Patients' CKD etiology at inclusion
B. Основно бубрежно заболување кај пациентите со ХБС при вклучување во студијата

	N	*Diagnosis (%)*				
		CGN	NAS	CIN	PKD	other
CHD_{obs}-	75	16	29	39	15	1
CHD_{obs}+	21	10	43	29	14	5
All	96	15	32	37	15	2

CGN: Chronic Glomerulonephritis; NAS: Nephroangiosclerosis; CIN: Chronic interstitial nephritis; PKD: Polycystic Kidney Disease; other including diabetes.

Methods

In this cohort of CKD patients, the probability of presenting CHD was calculated for each patient according to his (her) own follow-up duration. The patients who suffered from fatal or non-fatal myocardial infarction were classified as CHD_{obs}+ group, and those without CHD during the study period were classified as CHD_{obs}– group. A box plot was used to show the probabilities of MI for each group. Because of the concern that LVH prevalence is higher in CKD than in the general population, we performed a sensitivity analysis assuming that the prevalence of LVH on EKG was 20%. This percentage corresponds to the average prevalence of LVH on EKG observed in dialysis patients [5, 7], which is probably higher than those observed in CKD stage 2–4, but probably lower than the prevalence rates of LVH by echocardiogram in these patients [3]. Simulations based upon a 20% prevalence of LVH were performed using n 10 000 iterations.

The threshold retained for the patient categorization into the "high risk group" was 0.20. These patients were allocated to the CHD_{And}+, or otherwise they were allocated to the CHD_{And}–group. Considering CHD_{obs}– and CHD_{obs}+ groups, sensitivity, specificity and % correctly classified cases were calculated for CHD_{And}. We also looked for the link between complementary covariables, not specified in Framingham–Anderson's model, and the outcome using a Weibull model. This accelerated failure time model is closest to the Anderson model. This model was also used to identify "high risk" patients according to the definition given above. The hypothesis of proportional-hazards was tested using the Cox.zph procedure of the « R » software [8]. Survival plots were drawn according to the limit-product method. Type one error was set to 0.05. Analyses were performed using the « R » software [9].

Results

The probabilities obtained with Framingham–Anderson's formula on our sample of CKD patients appear in Figure 1. In our sample, Framingham–Anderson's model gave very low probabilities of occurrence of the outcome; lower than 0.307, even for the 21 patients CHD_{obs}+ (16 CHD_{And}– and 5 CHD_{And}+). The distributions of the 2 groups of patients were very close. Framingham – Anderson's formula thus appeared to be poorly informative in this sample. The difference between the two medians was 3.2%, 7.1% for the CHD_{obs}– group and 10.3% for the CHD_{obs}+, respectively (Figure 1). Three out of 4 patients were correctly classified and the specificity was 89%. However, the sensitivity was low, namely 24%: In our sample, Framingham–Anderson's model did not appear to efficiently detect «high risk» patients. Sensitivity analysis, assuming that LVH on EKG was present in 20% of patients, led to improve sensitivity (31%), but it nevertheless remained low.

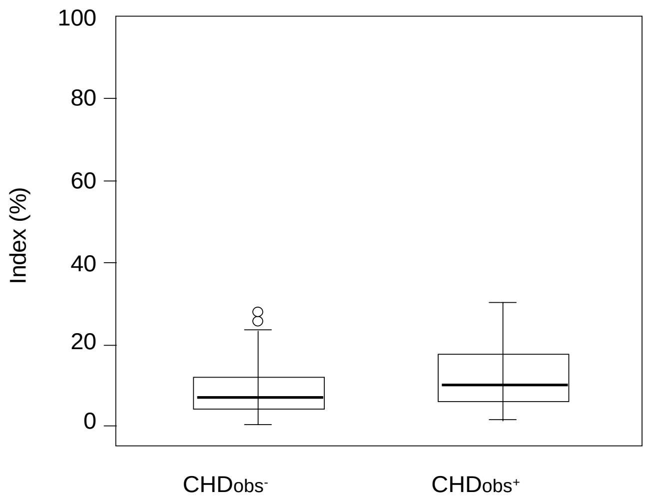

Figure 1 – *Distribution of probabilities according to Framingham–Anderson's formula for patients who suffered (CHD_{obs}+) and not (CHD_{obs}–) from fatal and non-fatal myocardial infarction during the follow-up*

Слика 1 – *Дистрибуција на веројатности во склад со формулата на Фрамингам и Андерсон за пациенти кои имале (КАБ$_{обс}$+)*

или останале без (КАБ$_{обс}$–), за развој на фатален или не-фатален миокарден нфаркт во тек на следењето

In order to improve the model's sensitivity, we evaluated two other variables (i.e. fibrinogen and creatinine clearance). Using a univariate Weibull model, a strong association was demonstrated between plasma fibrinogen and the CHD outcome variable ($p = 6.10^{-6}$). The hypothesis of proportional-hazards was not rejected ($p = 0.34$). Product limit curves are shown in Figure 2 for the group of patients who presented with plasma fibrinogen at a level higher or lower than 4.5 (median value, g/l). On the other hand, we found no relationship between the creatinine clearance and the CHD outcome ($p = 0.057$).

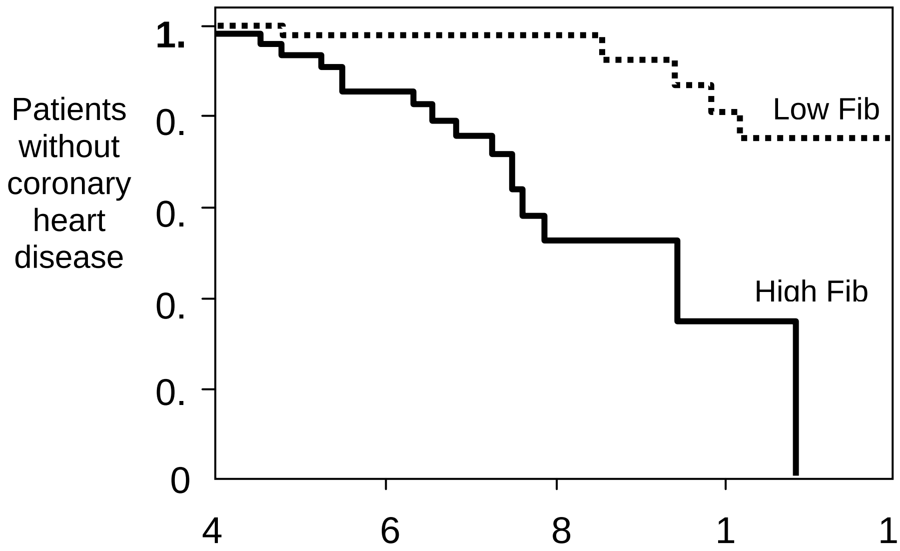

Figure 2 – *Plots of Kaplan-Meier product-limit estimates of non-occurrence of fatal and non-fatal myocardial infarction in patients with plasma fibrinogen (Fib) at a level higher (High) or lower (Low) than 4.5 g/l (median value)*

Слика 2 – *Плотирање на продукт-лимит вредностите според Каплан-Маер за неслучување на фатален или не-фатален миокарден инфаркт кај пациенти со плазма фибриноген (Фиб) на вредности повисоки (В) или пониски (Н) од 4.5 г/л (средишна вредност)*

A multivariate Weibull model was thereafter adjusted to explore whether fibrinogen produced additional prognostic information for high risk patients. The multivariate model included the 6 variables included in the Framingham–Anderson model (age gender, systolic blood pressure, total serum cholesterol to HDL cholesterol ratio, diabetes, smoking status), associated with two additional variables, plasma fibrinogen and creatinine clearance. Proportional-hazards hypothesis was not rejected (p = 0.41). Table 2 summarizes the results. The only significant covariable was plasma fibrinogen [p = 10^{-3}]. Given a lack of scope, (limited number of patients and of events), our model did not detect the 6 covariables of Framingham–Anderson's model nor the creatinine clearance as predictive factors for CHD.

Table 2 – Табела 2

Weibull Model including the covariates of the Framingham–Anderson's model and 2 additional variables: plasma fibrinogen and creatinine clearance

Модел на Веибул кој ги вклучува варијаблите на моделот на Фрамингам и Андерсон и две дополнителни варијабли: плазма фибриноген и креатинин клиренс

Covariable	*p*
Total serum cholesterol/HDL	0.61
Age	0.49
Systolic blood pressure	0.15
Smoker	0.41
Gender	0.28
Plasma fibrinogen	0.001
Creatinine clearance	0.12

Given the model's coefficients, we calculated the theoretical probabilities of CHD occurrence. Table 3 gives the distributions of probabilities according to the CHD_{obs} category. The difference of the median values for the CHD_{obs}– (7%) and CHD_{obs}+ (19.1%) groups was 12% (Figure 3). When considering CHD_{weib}+ and CHD_{weib}– patients according to the threshold of 0.20 for the definition of high risk patients, 73% of the patients were appropriately classified according to the CHD_{obs} categories (Table 3). Sensitivity was 48% and specificity 80%.

Table 3 – Табела 3

High risk patients according to the Weibull (weib) model by Coronary heart disease (CHD) categories.

Пациентите со висок ризик според моделот на Веибул поделени према катерогиријата на коронарна артериска болест (КАБ)

	CHD_{weib}–	**CHD_{weib}+**

CHD_{obs}–	60	15
CHD_{obs}+	11	10

Figure 3 – *Distributions of probability for CHD_{obs}+ and CHD_{obs}– patients (see figure 1 for definition) selected by the Weibull model including the six Framingha–Anderson's covariables and 2 additional covariates: serum fibrinogen and creatinine clearance*

Слика 3 – *Дистрибуција на веројатности за $\text{КАБ}_{\text{обс}}$+ и $\text{КАБ}_{\text{обс}}$– пациентите (види фигура 1 за дефиниција) селектирани според моделот на Веибул кој ги вклучува шесте коваријабли на Фрамингам и Андерсон и дополнителните варијабли: серум фибриноген и креатинин клиренс*

Given that our model was run on our sample, we explored whether this favored its predictive performances compared to the Framingham–Anderson model. We therefore adjusted a Weibull model excluding fibrinogen and creatinine clearance. The predicted probabilities appear in figure 4. The medians were 9.5% for the CHD_{obs}– group and 12.3% for CHD_{obs}+, respectively, attesting to the absence of improvement of the predictions in this instance. This result confirms that the predictive ability of our model was mainly due to the presence of the fibrinogen rather than to over fitting.

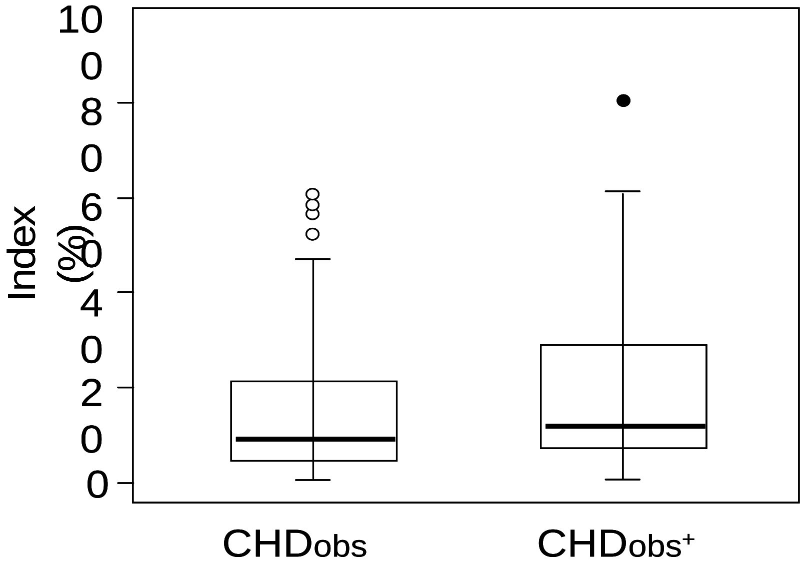

Figure 4 – *Distributions of probability for CHD_{obs}+ and CHD_{obs}– patients (see figure 1 for definition) selected by the Weibull model including the six Framingham–Anderson's covariates*

Слика 4 – Дистрибуција на веројатности за $КАБ_{обс}$+ и $КАБ_{обс}$– пациентите (види фигура 1 за дефиниција) селектирани според моделот на Веибул кој ги вклучува шесте коваријабли на Фрамингам и Андерсон

Discussion

Our findings show that the Framingham–Anderson index is a weak predictor of CHD in CKD stage 2 to 4 patients and that the CHD prediction could be improved by adding fibrinogen to a predictive model. To the best of our knowledge, the present study is the first long-term prospective study, which examines the validity of the Framingham–Anderson risk equation in predicting CHD risk in CKD stage 2 to 4 patients.

In the present prospective study, we are able to demonstrate that the Framingham–Anderson index is a poor predictor of CHD risk in CKD stage 2 to 4 patients. Actually, the poor predictability of CHD by the Framingham–Anderson risk equation may be even worse in our patients, since Framingham–

Anderson's risk equation, adapted to the French male population by changing the intercept to estimate CHD risk, would lead to an even lower predictive performance [10]. Our data confirm and extend the results of previous cross-sectional and short longitudinal studies. They have suggested that Framingham–Anderson's risk equation was insufficient in capturing the extent of CHD risk in subjects with CKD, although they were not able to assess its poor ability in predicting CHD risk in these patients, given their limited time of follow-up [4, 5, 11]. One possible explanation could be due to the fact that the Framingham–Anderson risk equation has not been specifically designed for patients with CKD [6]. In diabetic patients, another high risk population, the Framingham–Anderson index has been shown to underestimate the prediction of CHD [12].

The fact that LVH by EKG criteria were not recorded at baseline, and therefore were not included in the initial calculation of Framingham–Anderson's index did not account for the poor predictability observed in the present study. The inclusion of LVH in the Framingham–Anderson index did not substantially improve the sensitivity of the model (24% vs 31%, before and after the inclusion of LVH as a covariate, respectively). The diagnosis of LVH by EKG criteria, however, may be challenging in CKD patients in whom the prevalence of LVH by echography criteria is estimated at 25 to 75 % according to the level of kidney function [3]. Framingham–Anderson's index, using LVH by echography criteria, is not available in the general population, and therefore cannot be used in CKD patients.

Chronic micro-inflammation is commonly observed in patients with CKD [13]. Inflammation markers, such as C-reactive protein (CRP) or Fibrinogen, powerfully predict overall and/or cardiovascular mortality in CKD patients [1, 4, 15]. In the present study, we confirm our previous observation in the same group of patients but with an extended follow-up, which showed that fibrinogen is a strong independent risk factor for CHD [1]. The addition of fibrinogen to Framingham–Anderson's risk factors improves the sensitivity and predictability of our model. Our data point out one possible explanation for the poor predictability of CHD in CKD patients by the Framingham–Anderson risk equation. Indeed, inflammation markers, that were not included in the initial Framingham–Anderson equation, might play a role in promoting CHD in CKD patients. It is interesting to note that high-sensitive CRP can also improve prognostic information on CHD risk at all levels of the Framingham–Anderson risk score in the general population, as recently demonstrated by Ridker *et al.* in a large cohort of healthy American women [16]. Unfortunately, CRP determinations are lacking in the present study, and so it is impossible to make a direct comparison with the previous data observed in the general population. We are also aware that fibrinogen may not be only a marker of inflammation, since it is involved in both inflammation and thrombosis, and that its measurement is poorly standardized [17]. Moreover, increased levels of fibrinogen in hemodialysis patients may result in a dual stimulation of inflammation and increased plasma volume [18]. On the other hand, its has been shown that fibrinogen is an independent predictor of fatal and non-fatal cardiovascular events in a model including traditional risk factors and CRP in CKD stage 5 patients [14]. Therefore, additional studies and particularly in an external cohort to the current data set are needed to determine the respective role of fibrinogen and CRP in the prognostic information on CHD risk in CKD patients, which is currently under investigation.

Reduced glomerular filtration rate (GFR) is associated with a number of uremic, toxin-related risk factors, and therefore may be useful for improving the predictability observed in the present study. Estimated creatinine clearance by using the Gault and Cockroft formula has been used in the present study to determine the GFR. Our model, however, did not detect creatinine clearance as a predictive factor for CHD. Levin *et al.* could not find an impact of creatinine clearance on cardiovascular prevalence or incidence independent of the Framingham–Anderson risk factors [2]. Moreover, the presence of reduced GFR is either not a risk, or at most a modest, independent risk factor for cardiovascular outcomes in a low-risk population without defined CKD [3]. On the other hand, in high risk-populations most, but not all, studies have suggested that decreased GFR is an independent risk factor for cardiovascular outcomes [3]. In a secondary analysis, Manjunath *et al.* have recently demonstrated that GFR estimated by equation derived from MDRD study is an independent risk factor for cardiovascular disease over 3 years, in the elderly [19]. Potential reasons for the lack of predictive value of creatinine clearance for CHD in the present study include a limited number of patients and events, and use of estimated creatinine clearance and not a true GFR measurement. However, it is of interest that fibrinogen, not creatinine clearance, was a marked predictor of CHD in this small cohort of CKD patients, underlying the key role of inflammation in these patients.

To evaluate the role of new covariates we used a Weibull model instead of the Framingham–Anderson model. The latter does not rely on the hypothesis of proportionality of hazards, however our model did and this hypothesis was tested. Moreover, since the Framingham–Anderson model is not available, and in view of the limited size of our cohort of patients, we estimated that there was a limited benefit in rewriting the Framingham–Anderson model. Despite the addition of inflammation markers to the Framingham–Anderson risk factors, we were unable to estimate the full CHD risk in CKD patients underlying the role of additional uremic toxin-related risk factors such as p-cresol or oxidative stress markers [20–22]. The results of the present study may have been hampered by several limitations related to small sample size (chance effects), and the fact that some of our variables such as systolic blood pressure and cholesterol may be confounded by treatment, or by disease. However, since it has been shown that the use of ACE inhibitors or Beta-blokers were associated with a reduction of the inflammatory response [23, 24], and since the majority of our patients were under antihypertensive therapies, the relationship between inflammation and CHD in the present study may be become even stronger. Moreover, less than ten percent of patients had total cholesterol levels <4.7 mM (<180 mg/dl), which excludes a possible confounding effect related to the presence of malnutrition status. Of note, patients who were under lipid-lowering therapy were also excluded. Finally, the limited size of the present study did not allow us to propose a new formula to improve the prediction of CHD risk in CKD patients.

In conclusion, our study demonstrated the limitations of the Framingham–Anderson model in predicting CHD in CKD stage 2 to 4 patients, and emphasized the role of inflammation in predicting the CHD risk. However, our data should considered as preliminary in view of several limitations discussed above, and adequate powered studies are necessary to test the hypothesis that inflammation markers in CKD patients outweigh traditional risk factors in the prediction of CHD, and before developing a new reliable model to estimate CHD risk index in CKD patients as well.

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Резиме

МОДЕЛ ЗА ПРЕДИКЦИЈА НА КОРОНАРНАТА АРТЕРИСКА БОЛЕСТ КАЈ ПАЦИЕНТИ СО ХРОНИЧНА БУБРЕЖНА СЛАБОСТ: УЛОГА НА ПЛАЗМА ФИБРИНОГЕНОТ КАКО НОВА ПРОГНОСТИЧКА ВАРИЈАБЛА

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Формулата на Фрамингам и Андерсон (ФА) може да го предвиди ризикот за коронарна артериска болест (КАБ) кај општата популација. Но, валидноста на оваа формула во предвидување на ризикот за КАБ кај пациентите со хронична бубрежна слабост (ХБС) не е соодветно проучена.

Ние го калкулиравме ФА индексот кај група од 96 пациенти со ХБС од 2 до 4 стадиум, без наод на КАБ на почетокот на следењето, кои беа проспективно следени во текот на 4–12 години (7.4 ± 2.2 години, средна вредност ± СД).

Во текот на следењето, 21 пациент имаше фатален или нефетален миокарден инфаркт (КАБ$_{обс}$+), а 75 останаа без КАБ (КАБ$_{обс}$–). Средишниот индекс на ФА беше 7.1% кај КАБ$_{обс}$+ пациенти и 10.3% кај КАБ$_{обс}$– пациенти. Моделот имаше прифатлива специфичност (89%), но сензитивноста беше ниска (24%). Анализата на сензитивноста со додавање на варијаблата фибриноген доведе до подобрување на индексот на ризик за КАБ, а исто така и на сензитивноста на моделот (48%). Но, и покрај додавањето на фибриногенот во ризик факторите од ФА, целосниот ризик за КАБ кај пациентите со ХБИ остана потценет.

Нашите резултати покажуваат дека ФА индексот е слаб показател за КАБ кај пациентите со ХБС стадиум 2 до 4 и ја потенцираат улогата на инфламацијата во предвидување на ризикот за КАБ.

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