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Prospects for the application of mathematical modeling in clinical medicine

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Aims

The aims of the study are to follow the correlation of CAD development with various clinical and laboratory parameters and risk factors in a cohort of patients with multiple medical conditions and evaluate the effect of various parameters in the development of the disease using a new mathematical model approach.

Materials and methods

This study covers a limited patient cohort (n = 12) formed according to the rules of a local register. We have applied the methods of probabilistic mathematical modeling of cardiovascular disease with the formation of an aggregated matrix. Matrix fields were presented the instrumental methods of diagnosis and clinical and biochemical blood tests of patients.

Results

When using various methods of mathematical and statistical analysis (including cluster and factor analysis), created has been a graphic model of interaction of clinical, biochemical and instrumental parameters with the development of CAD. The mathematical and statistical completeness of the description of the patient's condition by the parameters of pathology on the basis of the measure of reliability of the completeness of the description was R=0,98-1,0, the coefficient of determination was equal to R2=92,0-98,0%. The main clinical and laboratory parameters that affect the progression of the disease, as well as the main triggers for the initiation of the process have been identified in the application of this method.

Conclusions

The results of the study, obtained by applying a new mathematical analysis of the data, confirmed the theory of atherosclerosis. Total cholesterol and LDL cholesterol were the main factors in the formation of CAD in this model. Blood pressure, GGT and triglycerides become essential trigger-factors in the development of disease. The presence of atherosclerotic plaque in the carotid artery appeared as the marker of the disease. This method requires further study, creating models of other pathological conditions, and interactions of the essential trigger-factors should be investigated.

Keywords

CAD, Risk factors, Mathematical modeling, Triggers, Interaction graph, Aggregated matrix

Imprint

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Introduction

Cardiovascular diseases (CVD) are the main cause of death and disability of the population, and therefore society suffers large human and financial losses [1]. How to minimize costs while maintaining maximum diagnostic accuracy and thereby optimize treatment costs? Numerous studies in the field of preventive cardiology, focused on the analysis of risk factors for cardiovascular diseases, and an attempt to answer these questions have been carried out over the past decades [2-5], many investigations are still ongoing and new ones are being planned. Despite the fact that some years ago the international medical society celebrated the 100th anniversary of the publication of the first studies of the outstanding Russian scientist N.N. Anichkov on the pathogenesis of atherosclerosis and its infiltrative theory [6-7], the search for new risk factors for cardiovascular diseases is still an urgent task in preventive cardiology [8].

At the same time, it is worth noting that in medical studies, as a rule, limited data are analyzed and we do not take into account the influence of other conditions and diseases that the patient has. For example, in the prediction of cardiovascular diseases, we estimate known indicators and risk factors for cardiovascular diseases and as a rule do not take into account other biochemical markers that are not related to the development of CVD, clinical conditions and other factors.

This "linear" approach leads to certain limitations in knowledge and understanding of which factors in a particular patient ultimately lead to the development of the disease and its complications. Our work in this direction was devoted to the complex analysis of the causes of development of disease and the joint influence of various factors on it. This publication reflects the cardiological part of this study, namely the analysis of the factors that influenced the formation of coronary artery disease (CAD) in this category of patients.

Aims & Objectives

Our aims and objectives are to follow the correlation of CAD development with various clinical and laboratory parameters and risk factors in a cohort of patients with multiple medical conditions and evaluate the effect of various parameters in the development of the disease using a new mathematical model approach.

Materials and methods

The study was retrospective. A survey of patients being treated and evaluated by the Department of Cardiology and Internal Diseases of the United Hospital with outpatient department has been completed in the period from January to December 2012, when the patients were subsequently selected and included in the present study, based on the rules of the local register [9].

Our applicable exclusion criteria were as follows:

1. Persons under the age of 18 years.
2. Female representatives.
3. Lack of information to meet the inclusion criteria.

Our applicable inclusion criteria were as follows:

1. An examination for the detection of cardiovascular diseases and cancer during the hospitalization period.
2. The surveys for verification of diagnosis of CAD (as confirmed by medical records). Verified methods of the existing recommendations [10] were considered as follows: treadmill exercise stress test, multislice computed tomography with intravenous contrast and evaluation of coronary artery calcium score (MSCT CA) and / or coronary angiography (CAG).
3. Surveys for verification of the diagnosis of prostate adenoma (as confirmed by medical records). Verified methods of the existing recommendations [11] were as follows: examination by an urologist, a blood test for PSA and TRUS, and conducting a puncture prostate biopsy, when indicated, followed by histological examination of biopsy for final diagnosis verification.

As a result, 12 patients were included in the study. In accordance with the task, only cardiac pathology in these patients and the contribution of different characteristics in its development has been studied in the first part of the study. These co-morbidities, including urological, are deliberately ignored herein, since an analysis of cancer pathology is the second part of our study.

Comprehensive survey data of 12 patients were selected for the implementation of a new analytical approach in the medical research on the following parameters:

1. Gender, 2 Blood pressure, 3. Heart rate, 4. Hemoglobin, 5. Erythrocytes, 6. Leucocytes, 7. ESR, 8. Glucose, 9. Total cholesterol, 10. HDL, 11. LDL, 12. Triglycerides, 13. Uric acid, 14. Urea, 15. Creatinine, 16. Potassium, 17. Sodium, 18. Calcium, 19. AST, 20. ALT 21. HbAlc, 22. Creatine phosphokinase (CPK), 23. Amylase, 24. GGT, 25. Alkaline phosphatase, 26. CRP, 27. Bilirubin, 28. Fibrinogen, 29. Maximal aggregation of platelets (according to aggregatogram with ADP), 30. Disaggregation of platelets (according to aggregatogram with ADP), 31. ECG (Presence/absence of typical changes), 32. Holter-ECG monitoring (Presence/absence of pathological changes), 33. Treadmill test (negative/positive stress test), 34. Thickness of carotid artery intima, 35. Present of atherosclerotic plaque (AP) in the region of bifurcation of the left common carotid artery (CCA), 36. Present of atherosclerotic plaque (AP) in the region of bifurcation of the right CCA, 36. Atherosclerotic changes in coronary artery (CA) according to MSCT CA with intravenous contrast > 50%, 38. Atherosclerotic changes in CA according to MSCT CA with intravenous contrast < 50%, 39. Atherosclerotic changes in CA according to coronarography > 50%, 40. Atherosclerotic changes in CA according to coronarography < 50%, 41. Multiple lesions of CA according to coronarography.

Our research method can be structured as follows:

1. During stage one the most important was a qualified selection of a set of biochemical parameters and instrumental examination results for each patient. All parameters were grouped based on reference values (N – norm, BN - below norm, AN – above norm; parameters that did not require interpretation as reference values were groups as NN – not norm) or according to the category feature of its presence (yes/no).
2. During stage two a specific possibility of the presence of each parameter was determined using mathematic procedures [12, 13] for each patient individually.

Table 1. Factor loadings according to the study parameters in 12 patients

	Factor 1			Factor 2			Factor 3			Factor 4			Factor 5			Factor 6		
	(+1,0) – (+0,72)			(+0,71) – (+0,4)			(+0,39) – (0,0)			(-0,01) – (-0,39)			(-0,40) – (-0,71)			(-0,72) – (-1,0)		
	N	AN	BN	N	AN	BN	N	AN	BN	N	AN	BN	N	AN	BN	N	AN	BN
1								+										
2							+											
3																		
4									+								+	
5								+				+		+			+	
6								+		+								+
7							+		+	+								
8					+			+				+		+				
9								+	+	+								
10				+													+	
11								+		+								+
12							+				+	+						
13								+		+								+
14								+	+	+								
15								+	+	+								
16							+		+		+							
17								+		+		+						
18									+	+								+
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29								+	+	+								
30	+							+				+			+			
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32								+	+	+								
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35					+				+				+					
36					+							+	+					
37								+	+	+								
38					+											+		
39								+	+	+								
40								+	+							+		
41					+				+				+					

Note: levels of parameters of factor scales are dispersed in six intervals:
1) (+1.0) – (0.72) in this interval the average value of factor scales is 74.0% - this is qualified as a strong correlation with a plus. 2) (+0.71) – (-0.40) – average value of factor scales is +31.0%. This value is qualified as a reflection of reciprocal action of average strength parameters. 3) (+0.39) – (+ 0.01) – average value of factor scales is +4.0%. This is deemed as noticeable, but has a week effect with a plus sign 4) (-0.01) – (0.39) this is a noticeable value, and has a weak effect with a negative sign in context at minus 4.0%. 5) (-40.0) – (-0.71) this value is qualified as a fact of significant reciprocal action of moderate strength, average value is negative 31.0%. 6) (-0.72) – (-1.0) is qualified as a strong negative factor minus 74.0%.

Abbreviations "N" is norm; "AN" – above norm; "BN" – below norm

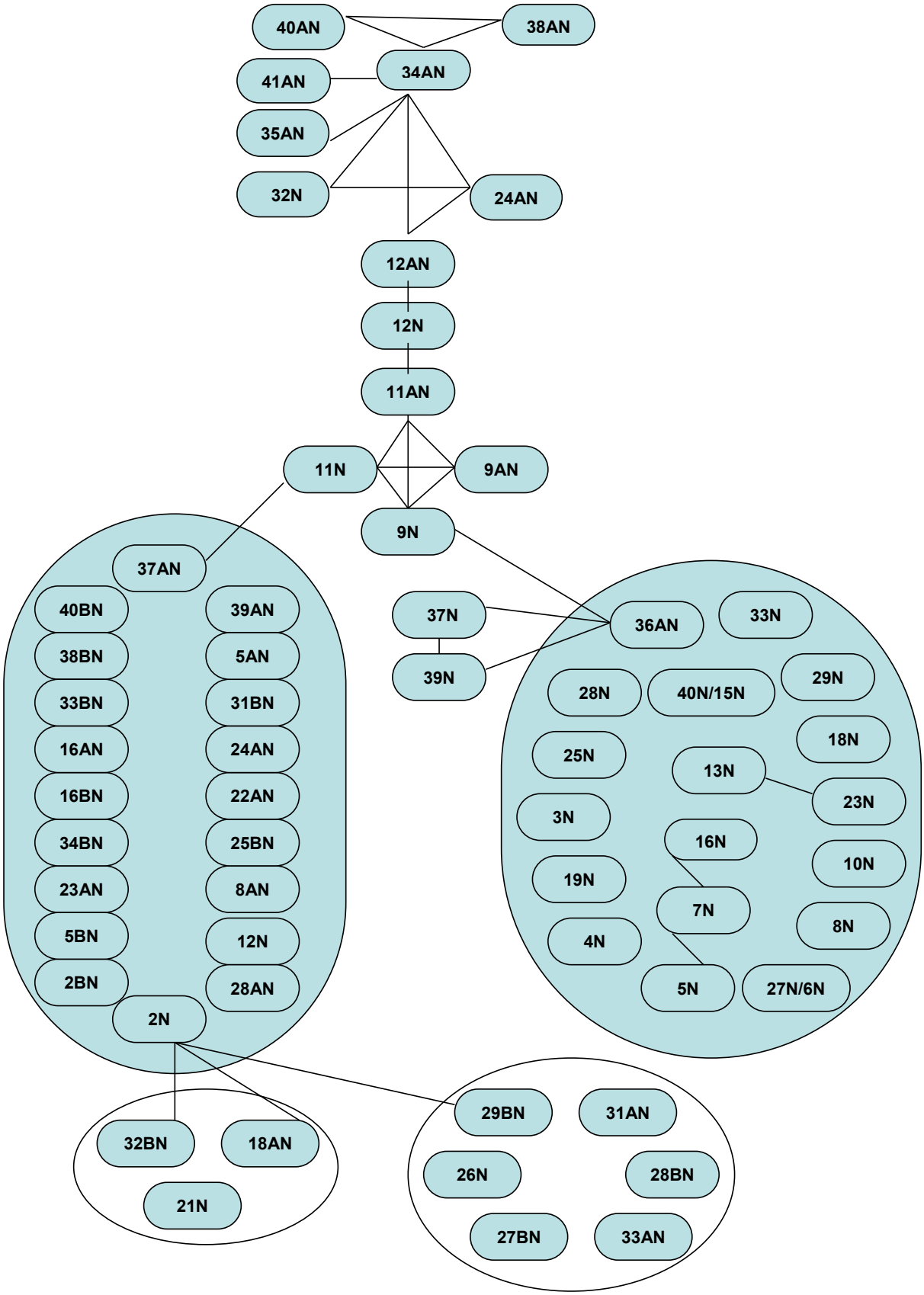

Figure 1. Graph of correlations of clinical, biochemistry and instrumental parameters

3. During stage three the use of factor analysis [14, 15] allowed determination of the effect of each parameter in each specific patient and obtained information was systematized for the whole study cohort. The results of the analysis of the study group in 41 parameters presented in Table 1. The parameters of the factor analysis grouped in it – the numerical values for the factor load calculated on the basis of an aggregated matrix for 12 patients. CAD was diagnosed in eight of all 12 patients on the basis of clinical and instrumental methods of examination.

Our task was to identify the parameters with significant effect on CAD development and a correlation between them in this cohort of patients by means of the probability mathematical model approach. At the same time, amongst the subgroup of patients without CAD diagnosis based on standard examination method, it was required to determine the combination of parameters responsible for such condition of the patients.

When analyzing data in Table No.1, it is noticeable that 2/3 of parameter values are centered in the field for factors 3 and 4, which have a significant effect on a formation of a cardiac pathological condition in this cohort of patients. Thus from the total of 41 parameters, only 7 parameters form the combination of parameters, which have been found correlated and primarily responsible for the development of CAD for the population of 12 patients: 9 (cholesterol), 14 (urea), 15 (creatinine), 20 (ALT), 25 (alkaline phosphatase), 27 (bilirubin), 29 (maximal platelet aggregation), 32 (Presence of changes during Holter monitoring ECG), 37 (MSCT CA – stenosis >50.0%), 39 (Coronarography – stenosis >50.%).

4. During stage four, the graph of correlation of parameters characterizing presence of cardiological pathological condition (i.e. development of CAD) was created according to the results of cluster analysis (see Fig No.1), based on the measurements of Euclid distances between the values of parameters [16].

An important task of the study in this case was the establishment of correlations between analyzed clinical and instrumental parameters and blood biochemistry tests. Since it was possible to propose that the presence of these systemic correlations itself characterizes the process of development of CAD.

Results

Creation of graph of correlations of clinical, biochemical and instrumental parameters revealed four correlated macrostructures (see Fig No.1).

Parameter No.34 (intima-media AN) located in the center of the first macrostructure, has demonstrated more correlations with other, primarily instrumental parameters.

The previous macrostructure through correlations with No.24 (GGT - N), No.12 (triglycerides - AN) and No.12 (triglycerides - N) is connected with the second macrostructure, which consists of four parameters: No.11 (LDL - AN), No.9 (cholesterol - AN), No.11 (LDL - N), No.9 (cholesterol - N). The second macrostructure is connected with the third one.

22 parameters in the third macrostructure are interlined, of which 9 have above norm (AN) value. Two of them are instrumental and reflect cardiological status of the patient (CAD presence). These parameters are No.37 and No.39, and they are above norm (MSCT CA >50%, and CAG >50%).

In other words the correlated parameters of the third macrostructure reflect CAD in patients. The correlated parameters of this structure reveal the condition of CAD in the shape of internal structure of correlation of instrumental, clinical and biochemical blood parameters. Seven of these correlated parameters are blood laboratory values above norm (AN): No.5 (erythrocytes - AN), No.24 (GGT - AN), No.22 (CPK - AN), No.8 (Glucose - AN), No.28 (Fibrinogen - AN), No.23 (Amylase - AN), No.16 (Potassium - AN).

Also, 11 other parameters included in the third macrostructure below norm (BN), norm (N) and not norm (NN) are of significance. 7 of them are clinical and instrumental parameters: No.34 (intima-media - BN), No.2 (BP - BN), No.2 (BP - N), No.31 (ECG - NN), No.33 (treadmill test - NN), No.38 (MSCT CA <50%), No.40 (CAG <50%). The other 4 correlated parameters are laboratory parameters: No.5 (erythrocytes - BN), No.25 (alkaline phosphatase - BN), No.12 (triglycerides - N), No.16 (potassium - BN).

The fourth macrostructure, also correlated, like the third, with the second macrostructure (which as a whole could be characterized as "cholesterol nucleus"), consists of 21 correlated parameters. However, only three of them: No.36 (AP in the area of bifurcation of the right CCA – stenosis – AN), No.33 (treadmill test – N), No.40 (CAG <50%) were instrumental.

Parameter No.36 has the maximal amount of correlations. The rest parameters of clinical and biochemical blood tests are normal: No.29 (maximal aggregation - N), No.18 (calcium - N), No.15 (creatinine - N), No.23 (amylase - N), No.22 (CPK - N), No.13

(uric acid - N), No.10 (HDL - N), No.8 (glucose - N), No.16 (potassium - N), No.7 (ESR – N), No.6 (leucocytes - N), No.5 (erythrocytes - N), No.27 (bilirubin - N), No.4 (hemoglobin - N), No.19 (AST - N), No.3 (HR – N), No.25 (alkaline phosphatase - N), No.28 (fibrinogen - N).

Discussion

In this study by using the mathematical model approach we have confirmed N.N. Anichkov`s atherosclerosis theory [17]. Formation of CAD has a complex nature and is developed in the "force" field of heterogenic "cholesterol" nucleus. Based on the graph of correlations one can differentiate the presence of absence of CAD on this model. The third and fourth macrostructure of multiple correlations of instrumental, clinical and biochemical blood parameters reflect various clinical conditions (the presence or absence of CAD, respectively) and have a common "cholesterol" nucleus of correlations (the second macrostructure). One of the trigger elements for the transition from the nucleus to third or fourth structures is its heterogenicity, i.e. the condition of norm or above norm for parameters No.9 and No.11 (cholesterol and LDL).

It is noticed that one third of parameters in the third and fourth macrostructures (with CAD and without CAD) are the same. This can be explained by the fact that the fourth macrostructure characterizes a borderline condition, where all patients are not yet in a state of "disease". At the same time in the third macrostructure there are factors which allow the process of development (formation) of CAD to be realized. Apart from standard lipid factors, other correlated with the disease parameters were as follows: No.14 (urea), No.15 (creatinine), No.20 (ALT), No.25 (alkaline phosphatase), No.27 (bilirubin), No.29 (maximal platelet aggregation), as well as No.5 (erythrocytes - AN), No.24 (GGT - AN), No.22 (CPK - AN), No.8 (Glucose - AN), No.28 (Fibrinogen - AN), No.23 (Amylase - AN), No.16 (Potassium - AN). These parameters were heterogenic and were outside of the limits of reference values and reflected changes of the other organs and systems, primarily in kidneys, liver and hemostasis.

But in order to initiate the process of the disease development, additional triggers must interfere (which until a certain time do not have its catalytic effect). Such triggers in our analysis were: BP, GGT and triglycerides.

The step for transition from the fourth to the third macrostructures upon combination of all of the parameters above is parameter No.36 (the presence of atherosclerotic plaque (AP) in CCA).

As a conclusion it should be noticed that the results presented in this article confirm the possibility of conduction medical scientific studies on small samples of patients. When using the described approach, we have realized a new method of preparation of databases and methods of their analysis (large samplings are not required as against the standard medical data research procedures).

Apart from that, our diagnostic method allows creation of numeric description, up to each individual patient, as a certain set. Evidence-based medicine in measurement suggested by the authors can gain the status of personified targeted diagnostics. Because evidence-based medicine is founded on analyzing large samples through a statistical computational culture using averaged parameters, it provides general knowledge. But at the same time, it explains the loss of a certain part of this knowledge due to the fact that, as a rule, parameters deviating from the mean (dispersion) are not studied with this approach.

Current publication is a result of scientific study presented as Patent for Scientific Invention No.2632509 "Method of diagnostics of non-infectious diseases based on the statistical methods of data processing" (Registration Number No. 2015125360 (OGRN [Primary State Registration Number] VOIS code ST-3.RU).

Conclusions

The results of the study, obtained by applying a new mathematical analysis of the data, confirmed the theory of atherosclerosis. Total cholesterol and LDL cholesterol were the main factors in the formation of CAD in this model. Blood pressure, GGT and triglycerides became essential trigger-factors in the development of disease. The presence of atherosclerotic plaque in the carotid artery appeared as the marker of the disease. This method requires further study, creating models of other pathological conditions, and to study their interactions.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Source of Economic Support

None.

Author Contributions

This work was carried out in collaboration between both authors. Both authors read the ICMJE criteria for authorship, read and approved the final manuscript.

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