Cardiometabolic Risk Calculation in the Assessment of Cardiometabolic Risk Profiles

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Abstract – **Numerous factors, together labelled as cardiometabolic risk (CMR), increase chances for developing cardiometabolic diseases. CMR estimation has a crucial role in the early prevention and enables the prompt treatment to prevent disease progression and complications. For this purpose several calculators and scoring systems were created, all based on similar, but not the same, input variables. CMR calculators are usually based on various statistical procedures and are result of previously conducted studies. Artificial neural network (ANN) is a method of artificial intelligence that has been recently applied for assessment of CMR in an easy, non-invasive and cheap way.**

Keywords **– Cardiometabolic Risk, Assessment, Risk Calculators, Artificial Neural Networks.**

1. Introduction

Health prevention programs should be capable of making a large in degree of contribution to the control of diseases and conditions associated with both adverse health outcome and high cost of care [1]. In Serbia, the most common diseases are those known as chronic non-communicable diseases. Chronic non-communicable diseases are caused by the interaction of many environmental and socio-economic factors with the biological response of the human body. They are gaining importance because greatly depend on the common risk factors and in more than 70% are preventable [2]. Mass non-communicable diseases include cardiovascular diseases, malignant tumors, diabetes mellitus, obesity, chronic obstructive pulmonary disease, musculoskeletal diseases etc. [3]. Cardiovascular diseases (CVD) are the leading cause of death in most developed and developing countries, thus representing one of the most significant health and medical problem over the world. The survey shows that about 20% of the world population suffers of some form of CVD. In the United States annually, CVD kills about 5.5 million people and in Europe approximately 3.2 million. According to the World Health Organization (WHO) in 2020, 25 million people will die as a result of CVD [4].

The global cardiometabolic risk (CMR) is defined as probability of developing a type 2 diabetes mellitus and CVD (coronary heart disease and stroke) [5] within a defined period of time, taking into a account numerous risk factors simultaneously. Also known as metabolic syndrome or insulin resistance syndrome, it includes the following disturbances: abdominal obesity, atherogenic dyslipidemia, high blood pressure, insulin resistance, proinflamatory and prothrombotic state [6]. In addition to mentioned conditions, development of cardiovascular and metabolic disorders are influenced by other factors such as tobacco use, physical inactivity, inadequate nutrition, age, gender and genetic predisposition. Relationship between cardiometabolic syndrome and increased risk for developing some of the CVD has been already demonstrated by large multicentric studies. Namely, PROCAM study showed that the risk for developing coronary heart disease is twice as high in men with metabolic syndrome compared to those without the metabolic syndrome [7]. Also, this study proved that women with metabolic syndrome have a 85% chance to develop ischaemic heart disease. The prevalence of cardiometabolic syndrome is different in some parts of the world, for example, in America the incidence is 24% while in Iran that number is much higher-43% [8]. Data from our area show that the frequency of cardiometabolic syndrome in the population of Novi Sad is 13.62% [9].

2. General features of cardiometabolic risk

The diagnosis of cardiometabolic syndrome is established when at least three of the following five risk factors are present.

Abdominal obesity. Obesity is one of the leading disease of modern civilization and in the last two decades has obtained pandemic proportions. Visceral adiposity (fat deposition around internal organs) plays a major role in the development of unfavourable cardiometabolic risk profile and is associated with increased cardiovascular morbidity and mortality [10]. As the first method for diagnosis of obesity, the calculation of Body Mass Index (BMI) is recommended:

$$BMI[kg/m^2] = \frac{BW[kg]}{BH[m] \cdot BH[m]}$$

However, this parameter cannot distinguish fat mass from lean, and therefore other anthropometric indicators are suggested for the assessment of fat distribution. One of the proposed cardiometabolic risk indicators is WHtR (proportion of waist circumference and body height) is founded to be a better risk indicator of CMR, compared to BMI. [11]. By using artificial neural networks, Kupusinac et al. concluded that obese persons with the WHtR ≥ 0.578 have increased risk of hyperglycemia [12].

Atherogenic dyslipidemia is primarily characterized by elevated serum concentrations of tryglicerides and reduced HDL-cholesterol. A low level of HDL cholesterol is responsible for the development of atherosclerosis of the blood vessels in a way that reduces the antioxidant and antiatherogenic processes [13].

If the *high blood pressure* persists high over time, it can damage heart muscle and lead to atheromatous plaque buildup. It is important to note that high blood pressure is present in most individuals with the metabolic syndrome and is strongly associated with obesity and insulin resistance.

Insulin resistance is an important factor that contributes to the development of cardiometabolic diseases. The presence of insulin resistance leads to lipid disorders, atherosclerosis and hypertension, followed by glucose intolerance and diabetes. In fact, insulin resistance is the first step in development of diabetes mellitus.

Proinflammatory state. Adipose tissue releases proinflammatory cytokines such as C-reactive protein (CRP), fibrinogen, interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α) which together lead to complications of obesity and metabolic syndrome.

Prothrombotic state is expressed with a high concentration of plasminogen activator inhibitor-1 (PAI-1), fibrinogen, prothrombin and coagulation factors (VII, IX, X) [14].

3. CMR calculators

Many years ago, it became clear that it is necessary to timely identify people with cardiometabolic risk profile and thus initiate proper treatment (lifestyle modification and/or pharmacological treatment) in order to prevent cardiovascular and metabolic diseases. In this regard, as a result of large conducted researches, different scoring systems well-known as CMR calculators were created to predict global CMR. However, the structure of CMR calculators has changed over time but they all have the same goal - practical application in clinical practice. In addition, they are usually in form of software applications available to estimate CMR and they are based on statistical methods. These calculators have gradually adapting to advances in medicine, with understanding the complex pathogenesis of cardiometabolic disorders, as well as the progress of computer technology and statistical methods. Nowadays, about one-third of health plans and guidelines recommend at least 1 of the risk assessment tools to estimate CMR. [1]. In the text that follows we will describe CMR calculators that are commonly used for clinical and research purposes with special emphasis on artificial neural networks (ANN) as a potential tool in detection of people with CMR profiles.

Most of the primary guidelines in the United States are using *Framingham risk score* (FRS) for estimating 10-year risk of having a heart attack [15]. This tool was designed for adults aged 20 and older who do not have heart disease or diabetes, and includes following variables: age, gender, cholesterol (total and HDL), systolic blood pressure and smoking. At first, multivariate logistic regression was used to calculate cumulative risk but today FRS is a model based on Weibull probability distribution [16] and has been received for widespread use around the world. However, there are numerous reports indicating that FRS derived charts are systematically overestimating risk, in particular for cardiovascular heart diseases in different population settings [17]. This is understandable if we know that epidemiology of cardiometabolic disorders represents variously in different populations, so FRS have been tested in British population where FRS was found to be significantly overestimate the absolute coronary risk [19]. The same conclusion was arrived from Liu J et al. after evaluating Framingham risk functions in a large Chinese population [20].

In addition to mentioned factors, the *Reynolds Risk Score* uses novel information from two other risk factors - high sensitivity CRP (a measure of inflammation) and genetic risk, in order to increase accuracy of risk prediction of having a heart attack and stroke in the next 10 years. In derivation of novel risk prediction algorithms they used Cox proportional hazards model and discrimination and calibration (how close are the predict and actual risk) to assess the predictive accuracy [20]. This calculator is applicable to both sexes, as well as for healthy persons without diabetes.

Further, in 2001 *UKPDS* Risk Engine was published including the additional parameters specific to diabetes: duration of diabetes and glycaemic control (HbA1c) [21]. This is a type 2 diabetes specific calculator based on 53.000 patients years of data from the UK Prospective Diabetes

Study. It provides risk estimatation and 95% confidence intervals for:

- Non-fatal and fatal coronary heart disease
- Fatal coronary heart disease
- Non-fatal and fatal stroke
- Fatal stroke

This calculator takes into account the following data: current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol levels. UKPDS Risk Engine represents a computer simulation model and it has been used in a range of research and clinical implication worldwide.

In attempt to design risk scoring system that will be applicable in European population, in 2003 scientists have developed *SCORE* project (Systematic Coronary Risk Evaluation) [22]. The project is based on data collected from 12 European cohorts with 205 178 participants, in link with Third Joint Task Force. They created risk charts based on total cholesterol and total cholesterol/HDL ratio, predicting 10-year risk of fatal cardiovascular disease in population at high and low risk. The lack of this project is that it estimate only fatal CVD, and do not evaluate the total CVD risk [23].

DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe Study Group) equation was made after performing DECODE study which involved 14 cohorts, including data from more than 2000 individuals with diabetes. This model is focused on fasting glucose concentration and/on glucose tolerance state, predicting the risk of fatal cardiovascular events [24].

The *PROCAM* scoring system was developed based on the 10-year follow-up of the Prospective Cardiovascular Münster study and represents a simple scoring scheme for calculating the risk of acute coronary events (fatal or nonfatal myocardial infarction or acute coronary death) [25]. Namely, in this study 8 variables were used: age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of myocardial infarction, diabetes mellitus and triglycerides.

4. Artificial neural networks (ANN)

Over the last 10 years, a new kind of technical solution known as Artificial neural networks (ANN) was found as a replacement or alternative to standard statistical methods on which are based previously mentioned risk calculators [26]. Artificial neural network is a method of artificial intelligence that simulates how the human brain solves their problems [27]. Such systems implement human reasoning and decision-making system to test certain variables, thus suggesting output, in this case the risk. They consist of artificial neurons that are based on the functioning of those which are biological [28]. ANN are based on the structure of the human brain and as well as the brain, they can recognize certain patterns, manage data, and most importantly, they can learn [28]. The ability to learn, which is not associated with conventional risk calculators, proves it´s flexibility and efficacy. As for the man himself, experience is important for ANN [29].

How does it work? The artificial neural network is actually a type of artificial intelligence that uses non-linear mathematical model. The neural network takes into account the previously solved problems to create a system of conclusions. These conclusions are not certain but logarithmic network using the examples. As already mentioned, ANN consists of a layers of neurons. The most commonly used ANN model (so called multilayer perceptron) is composed of input, hidden and output layer. Input layer is generated by neurons that can receive the characteristics of a particular problem. The hidden layer neurons receive data from input and is associated with output layer by weights [30]. Hidden layers between input and output are able to learn to identify the output of the totally new input [28]. Input neurons are first multiplied with a weightening factor that determines the extent to which each input affects the output and weighted inputs are summed to include the transfer that results in neural output. Controlled during the training phase, the data set is presented in ANN with the correct outputs that are available. By first the ANN is trained randomly, initializing the connection between weight network and comparing the output with the known responses. Then the process is repeated and the network changes the connection between weights so that errors of output are minimized. Therefore, the neural network is used for prediction [30].

ANNs are used to solve very complex problems especially when it comes to non-linear models or when the mechanism underlying the problem is not yet known [27]. The ANN should be superior to the standard statistical approach, because they automatically calculate arbitrary nonlinear relationships between the dependent and independent variables and all the possible interactions between the dependent variables. Standard statistical techniques require additional modeling to reach this flexibility, which takes time. In addition, the ANN does not require explicitly declared dispersion. [26]. There are hundreds of different models that are considered as ANN since the first neural models that have tried to implement McCulloch an Pitts on 1943 [31]. However, there are few that deal specifically with calculating CMR.

Recently, Vos et al. used data from the aforementioned studies named PROCAM to obtain neural network for the prediction of CVD events [17]. They concluded that prediction through ANN is superior to conventional logistic regression, but external confirmation still has not happened. Ionnas et al. used two ANN based methods for the analysis of the available data and have received that ANN based methods are promising predictive models that can be used globally [32]. Their results showed that the ANNs and their hybrids may offer useful analysis for the determination of complex diseases. In particular, they dealt with obesity and its complex etiology and identification of genetic variations and/or factors related to diet contributing to this variability. Very recently, Stokic E et al. estimated SAD (Sagittal abdominal diameter) low-limits for the adverse metabolic profile, based on ANN [33]. As inputs variables, they used: gender, age, BMI, systolic and diastolic blood pressures, HDL-, LDL-, and total cholesterol, tryglicerides, glycemia, fibrinogen and uric acid. Further, Chai-Cheng et al. used ANN and multivariate logistic regression models to try to obtain rapid identification of metabolic syndrome in patients on SGA therapy (Second generation antipsychotics) without using biochemical parameters (only anthropometric and demographic data) [30]. It is known that metabolic syndrome is very important adverse effects of this drugs, so after the study they concluded that ANN are very good noninvasive tool for screening large number of people.

5. Conclusion

Accuracy in estimation of cardiovascular risk is an essential part of the preventive medicine and clinical practice. As a target of public health prevention, CMR risk assessment should adapt to new challenges in medicine and mathematics. Artificial neural network could provide an effective, noninvasive and easy way to select persons with increased CMR, so additional studies in this field are required.

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