Cardiovascular risk estimation in young patients with ankylosing spondylitis: A new model based on a prospective study in Constanta County, Romania

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Abstract. Cardiovascular (CV) risk assessment charts are useful in establishing a patient therapeutic plan, but the most commonly used charts have essential limitations when applied to special populations. Our aim was to determine whether the Systematic Coronary Risk Evaluation (SCORE) chart underestimates the CV risk in young patients with ankylosing spondylitis (AS) and to promote the necessity of new risk assessment models. We conducted a prospective study in Constanta County, Romania including 70 consecutive patients ≤50 years of age, previously diagnosed with AS, without a history of established CV disease, diabetes mellitus and chronic kidney disease. We estimated the CV risk using SCORE based on total cholesterol, applied for a high-risk population, such as the Romanian population. Estimation of CV risk was also conducted with the relative risk (RR) chart, considering the following variables: Smoking, systolic blood pressure and total cholesterol. The majority of patients (n=46, 65.71%) had low risk according to the SCORE chart and only 24 (34.28%) were found to have moderate CV risk; none of them with high or very high CV risk. Ten patients (21.74%) of the 46 who were considered to have a low risk based on the SCORE system presented with carotid plaques. Twelve patients (50%) of the remaining 24 with moderate CV risk were found to have carotid plaques. According to 2016 'European Society of Cardiology' (ESC) guidelines, 22 of all 70 patients were at high/very high CV risk due to the presence of carotid plaques. Comparing the RR chart with carotid plaque detection, only 4 out of 30 (13.3%) patients with RR=1 had carotid plaques; the frequency was higher in those with RR>1. Our results attested that the SCORE system underestimates the risk in patients with carotid plaques. Carotid ultrasound provided a more heightened sensitivity of the RR chart. C-reactive protein (CRP) >3 mg/dl is associated with RR>1, making this chart a better CV risk predictive system in this particular category of patients.

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Introduction

'The best way to predict the future is to create it.' Abraham Lincoln Ankylosing spondylitis (AS) represents a chronic inflammatory disease with incompletely known etiology, which usually affects young men. It progresses to significant disabilities due to skeletal disorders which include: Reduced spinal mobility, peripheral joint injuries and extra-articular damage (including visceral lesions) resulting in decreased quality of life and labor productivity among these patients (1). Although the pathogenesis of AS remains incompletely elucidated, the currently accepted hypothesis is that AS develops through complex interactions between immune-mediated mechanisms and genetic conditions, environmental factors, microbial infection and endocrine disorders (2).

Various reviews and meta-analyses report that AS is associated with a 1.5- to 2-fold higher mortality rate by comparison with the general population, mostly linked to cardiovascular (CV) complications (3).

The 'European Society of Cardiology' (ESC) clinical practice guidelines on CV disease prevention recommend using the Systematic Coronary Risk Evaluation (SCORE), as a predictive model to estimate the 10-year risk of fatal CV disease (mortality from myocardial infarction, stroke, aortic aneurysm or others), including the following variables: Age,

sex, total cholesterol, smoking status and systolic blood pressure levels-age having the most significant impact in this model (4).

Although risk assessment tools can be useful aids for physicians in establishing a patient therapeutic plan, the 'SCORE' presents with certain significant limitations in its ability to identify high CV risk patients when applied to the population under 50 years of age, thus impeding them from the initiation of primary prevention (5,6). Pharmacological intervention, especially statin therapy, used to reduce CV risk is indicated only among those considered to be at high risk of CV events; thus, a large proportion of young AS patients can be neglected (7,8).

The 2016 ESC guidelines proposed the use of a relative risk (RR) chart rather than the traditional SCORE model in patients younger than 50 years. Unlike the SCORE, the RR estimates the relative, not absolute risk, showing the likelihood of developing a fatal CV disease in an individual with traditional CV risk factors compared to another that does not have any risk factors (4,9). This fact constitutes a central point of concern in AS, a disease associated with early atherosclerosis characterized by oxidative stress and inflammation (10,11).

We propose the use of additional tools, such as carotid intima-media thickness (evaluated by ultrasound) (12); conduction abnormalities on ECG (13); aortitis (14), aortic valve disease (15), cardiomyopathy or myocardial dysfunction (16) (in particular an abnormal relaxation pattern of the left ventricle) that can be diagnosed by transthoracic echocardiography (TTE).

There is also recent evidence that C-reactive protein (CRP) plays an important role in the immune response and is a possible marker of vascular inflammation and vessel damage-causing ischemic heart disease (IHD) (17).

Thus, the aim of the study was to determine whether the classic risk charts may underestimate the CV risk in young patients with AS and also to promote the necessity of new risk assessment models and methods to achieve primary prevention of CV disease in this population.

Patients and methods

Our study included 70 consecutive patients ≤50 years of age (range, 35-50 years) of both genders, living in rural and urban areas, previously diagnosed with AS according to the 1984 modified New York criteria (18). All subjects were Romanians, and they were assessed over a 4-year period (January 2016 to December 2019) at the Constanta County Emergency Hospital. Exclusion criteria were patients diagnosed with IHD, cerebrovascular disease (CVD), heart failure (HF), peripheral artery disease (PAD), diabetes mellitus (DM) and chronic kidney disease (CKD).

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (http://www.basdai.com), Bath Ankylosing Spondylitis Functional Index (BASFI) (http://basdai.com/BASFI.php) and Ankylosing Spondilitis Disease Activity Score (ASDAS) (https://www.asas-group.org/instruments/asdas-calculator/) were calculated in order to evaluate function and disability; these scores are routinely used in clinical practice to measure the disease activity in AS patients.

We calculated the CV risk by using the SCORE system based on total cholesterol (TC) alone, applied for the high-risk population, such as the Romanian population. Estimation of CV risk was also conducted with the RR chart score, considering the following variables: Smoking, systolic blood pressure and total cholesterol values (Fig. 1). Both CV risk assessment systems are included in the 2016 ESC guidelines and are used to facilitate risk estimation in apparently healthy individuals (4).

This study also included the prevalence of the most common extra-articular manifestations in AS, such as uveitis, inflammatory bowel disease and psoriasis (Table I).

Statistical analysis. Data analysis was performed by using IBM SPSS Statistics version 23 (IBM Corp). The procedures used were: Descriptive statistics, parametric statistical tests (independent sample t-test), non-parametric statistical tests [Chi-square test of the association, with the evaluation of odds ratio (OR)], adjustments for accounted variables. The significance level used in the analysis (P-value) was 0.05. Continuous variables were reported as mean ± standard deviation (SD) or median [interquartile range (IQR)] and categorical variables as a number of patients (percentage). 'Receiver operating characteristic' (ROC) curve [with 95% confidence interval (CI)], area under the curve (AUC) and Youden index values were used to assess the sensitivity, specificity, percentage of correctly classified patients, for each CV risk model and the significant risk factors.

Results

The main demographics, clinical and ultrasound features of the study group are summarized in Table I.

There was a significant statistical difference between sex distributions among the study group, with male domination (77.1%) with the age of onset peaking in the second and third decade of life (mean age, 32.34 years) (Table I).

The majority of patients (n=46, 65.71%) had a low risk according to the SCORE chart, and only 24 (34.28) were found to have moderate CV risk; no patients presented with high or very high CV risk.

A total of 10 patients (21.74%) of the 46 considered at low risk based on the SCORE system had carotid plaques. A total of 12 patients (50%) of the remaining 24 patients with moderate CV risk were found to have carotid plaques (Table I).

Based on 2016 ESC guidelines, patients were considered to have high/very high CV risk if the SCORE was ≥5 (none in our study group) or if they had carotid plaques assessed with ultrasounds.

According to the definition, 22 of all 70 patients were at high/very high CV risk because of the presence of carotid plaques.

On the contrary, when we compared the RR chart score with the presence of carotid plaque, we found that only 4 of 30 (13.3%) patients with RR=1 had carotid plaques, and we observe that the frequency was higher in those with RR>1 (18 of 40, 45%) (Table II).

The area under the ROC curve (A=0.930) was greater than A^0=0.5; the calculated probability associated with A was P<0.0001 (<α=0.05), and Youden index J=0.7500. Under

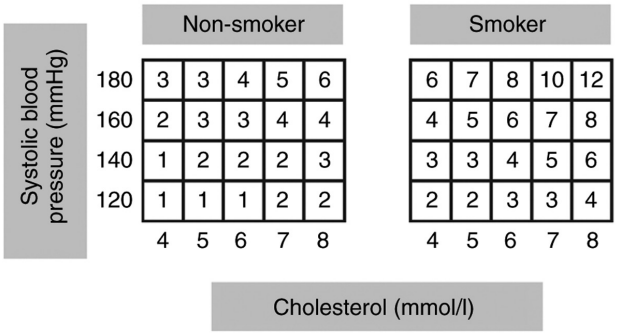

Figure 1. Relative Risk (RR) Chart based on the European Society of Cardiology (ESC) 2016 guidelines (4).

these conditions, we can appreciate that the relative risk (RR) has the ability to distinguish between the two groups-the presence or absence of carotid plaques (sensitivity=90%, specificity=85.00%, associated criterion RR>2) (Fig. 2).

The area under the ROC curve (A=0.755) was greater than A_0=0.5; the calculated probability associated with A was P<0.0001 (<α=0.05), and Youden index J=0.5567. Under these conditions we can conclude that the relative risk has the ability to distinguish between the two groups CRP >3 mg/dl or ≤3 mg/dl (sensitivity=71.79%, specificity=83.87%, associated criterion >2) (Fig. 3).

The area under the ROC curve in the case of RR (A_{RR}=0.764) differed significantly from the area under the ROC curve in the case of SCORE (A_S=0.627); the difference between the area=0.137 and P=0.0160 (<α=0.05). Under these conditions, we can appreciate that the RR variable has the ability to distinguish better between the two groups (CRP >3 mg/dl vs. CRP ≤3 mg/dl) than the SCORE variable (Fig. 4).

According to our results, the SCORE system underestimates the risk in the case of the patients with carotid plaques. In contrast, the sensitivity of the RR chart was higher (90%) if the carotid ultrasound was performed in young AS patients, with a high sensitivity (85%). Moreover, RR>1 is associated with CRP>3 mg/dl, making this chart a better CV risk predictive system.

The relative risk (RR) chart score, the value of CRP >3 mg/dl at the period of disease diagnosis throughout the performance of carotid ultrasound can establish the presence of high/very high cardiovascular risk.

Discussion

There is growing evidence that atherosclerosis represent an inflammatory disease (19). The role of inflammation in the development of heart disease has only recently been recognized (20). Inflammatory rheumatic disorders can be considered a 'natural experiment' in the interaction between chronic inflammation and cardiovascular (CV) disease (21). This interaction could elucidate the fundamental mechanisms by which inflammation accelerates the development of atherosclerosis and the onset of CV disease (22).

Although the best-documented condition remains rheumatoid arthritis, evidence shows that individuals suffering from ankylosing spondylitis (AS) and psoriatic arthritis also have an increased risk of developing CV disease (23,24). Extra-articular manifestations of AS, such as uveitis, inflammatory bowel disease, cardiovascular, pulmonary or renal involvement may vary in frequency and severity (25,26), but among the visceral manifestations, the CV damage has particular importance, as it influences the evolution and prognosis of the disease (27).

Table I. Main epidemiological, clinical and ultrasound features of the AS group.

Variable	AS group (N=70)
Men/women, n (%)	54 (77.1)/16 (22.9)
Age at diagnosis (years), mean ± SD	32.34±5.34
Disease duration (years), median (IQR)	16.30 (4.00-27.00)
Rural/Urban, n (%)	18 (25.7)/52 (74.3)
Early ill health retirement, n (%)	33 (47.1)
BASDAI, mean ± SD	5.05±2.11
BASDAI >4, n (%)	32 (45.7)
BASFI, mean ± SD	4.36±1.96
ASDAS-CRP, mean ± SD	3.25±0.99
ASDAS-ESR, mean ± SD	3.36±1.02
Syndesmophytes, n (%)	48 (68.6)
Extra-articular manifestations, n (%)	39 (55.71)
Inflammatory bowel disease, n (%)	12 (17.1)
Psoriasis, n (%)	7 (10)
Uveitis, n (%)	20 (28.6)
HLA-B27 positive, n (%)	55 (78.6)
CRP >3 mg/l at time of diagnosis, n (%)	55 (78.6)
ESR, mean ± SD - at time of diagnosis	30.40±16
Therapy, n (%)	
NSAIDs >20 days/month	25 (35.7)
Biologic treatment	43 (61.4)
Corticosteroids	14 (20)
History of classic CV risk factors, n (%)	
Current smokers	31 (44.3)
Have ever smoked	11 (15.7)
Obesity	22 (31.4)
Hypercholesterolemia	14 (20)
Hypertension	11 (15.7)
Family history of CV disease	28 (40)
Carotid plaques	22 (31.4)
Diastolic dysfunction - grade I	27 (38.6)
Aortic regurgitation (grade II-IV)	14 (20)
SCORE-TC, n (%)	
Low (<1%)	46 (65.71)
Moderate (≥1 and <5%)	24 (34.28)
High (≥5 and <10%)	0
Very high (≥10%)	0

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation; IQR, interquartile range; CV, cardiovascular; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

Table II. Relative risk (RR) chart score-presence of carotid plaques.

	Frequency	Percentage	Carotid plaques n (%)
RR=1	30	42.86	4 (13.3%)
RR>1	40	57.14	18 (45%)
Total	70	100	22

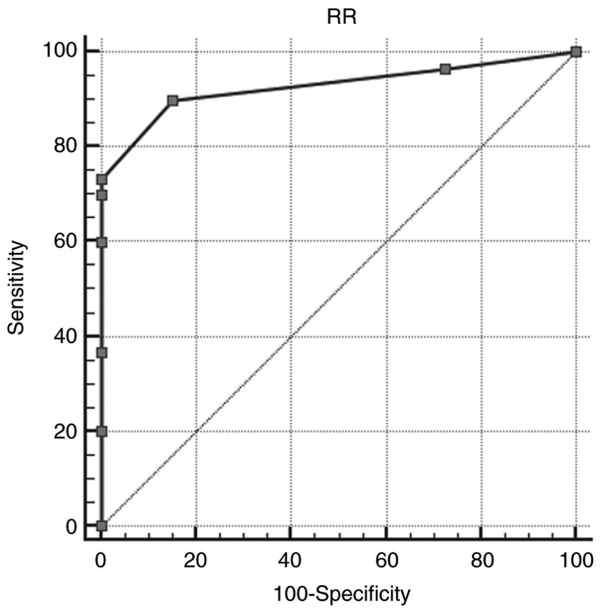

Figure 2. ROC curve regarding the relation between Relative Risk (RR) and carotid plaque.

The socioeconomic impact of AS is represented by the prevalence of the disease (~1% of the adult population) (28), the onset at a young age (20-40 years) in the most productive period of life, the rapidly progressive ankylosis and disability that result in the retirement of almost 5% of patients in the first year after diagnosis. A high rate of early ill health retirement [33 (47.1%)] in our population confirms the importance of early diagnosis and prevention of these young patients (29).

Cardiovascular morbidity is elevated in AS patients, with an increased prevalence of CV disease in all stages of atherogenesis, from endothelial dysfunction to carotid thickening and/or plaque and even to acute myocardial infarction or stroke (30). In addition, even after adjusting for traditional CV risk factors, the CV risk burden persists, being attributed to a pro-inflammatory state of AS (31,32).

Prediction of CV risk is an extremely important aspect of CV prevention. Even though significant developments have been made in recent years, risk scores for primary prevention need to be improved, especially in patients under 50 years of age, and new prediction models need to be developed and validated (33). There is a divergence in knowledge for both primary and secondary prevention concerning the risk of CV events in young patients with AS (34,35), either on the short or on the long term, especially in different age groups and genders (36).

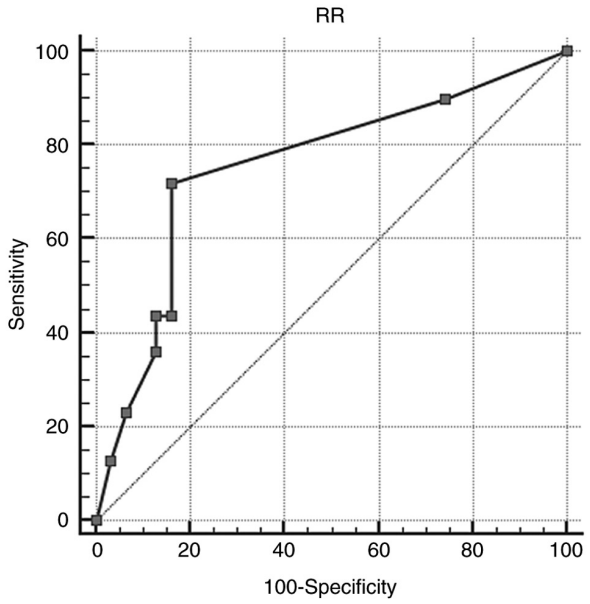

Figure 3. ROC curve regarding the relation between Relative Risk (RR) and C-reactive protein (CRP).

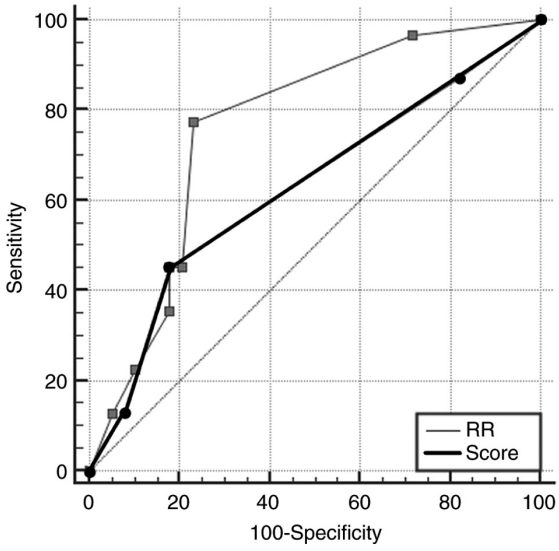

Figure 4. Comparison of ROC curves related to Relative Risk (RR) or Systematic Coronary Risk Evaluation (SCORE) in the case of patients with C-reactive protein (CRP) >3 mg/dl.

Risk estimation is not an exact science since the different combinations of risk factors interact in complex ways; they vary as a person ages (especially the predisposing factors that aggravate independent factors) (37,38). The models and charts used are only approximations to reality and must be interpreted in light of the physician's knowledge and experience (39).

In the present study, we aimed to assess whether the most used system to assess CV risk, the Systematic Coronary Risk Evaluation (SCORE) chart, may underestimate the absolute risk of developing a fatal CV disease in the case of patients under 50 years of age, previously diagnosed with AS. We concluded that RR was superior to SCORE when trying to identify young patients with high CV risk; in this regard AS patients with RR>1 were almost four times more

likely to have subclinical atherosclerosis than those with RR=1 (45 vs. 13.3%), making them at high risk. The effect of additional risk factors such as CRP and intima-media thickness (IMT) need to be considered. Their contribution to absolute CV risk estimations for patients with AS is important.

Our study exhibited that most of the AS patients do not exhibit the traditional CV risk factors used by the standard score charts. Yet, many of them are at high risk of developing CV disease, when we consider other parameters such as CRP levels or carotid plaques. Thus, the present study contributes to a deeper understanding of CV risk in AS, allowing the development of innovative patient-specific CV risk models.

To conclude, the present research pointed out that there is still a growing need for the improvement of CV risk prediction models suited for young patients with chronic inflammatory diseases. The effect of the additional risk factors such as CRP and IMT need to be considered. In this respect, further studies need to be carried out by clinical researchers together with statisticians and epidemiologists.

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Availability of data and materials

Data used in the current original study are available in the patients' archive files, Constanta County Emergency Hospital, Romania. Any further information regarding the present study is available from the corresponding author upon reasonable request.

Authors' contributions

MI, APSu and IM designed the study and collected data from the recruited cases. PI and VA analyzed the data and performed the statistics. APSt and IRP analyzed and wrote the Results and Discussion sections and performed the literature review, prepared the manuscript, translated it and managed all the correspondence for publishing. All authors read and approved the final manuscript for publishing.

Ethics approval and consent to participate

This non-interventional study was approved by the local Ethics Commission of Constanța County Emergency Hospital, Romania (no. 32/06.09.2018).

Patient consent for publication

Not applicable.

Competing interests

There are no competing interests regarding the authors of this research.

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