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Prediction of Cardiovascular Diseases in Women With Rheumatoid Arthritis

Aim	To develop prognostic models for arterial hypertension (AH) and atherosclerosis based on studying the totality and significance of traditional and disease-mediated risk factors (RFs) in women with rheumatoid arthritis (RA).
Material and methods	223 female patients with RA aged 54.9±2.1 years were evaluated at the premises of the polyclinic of the Gulla Municipal Hospital #4 (Barnaul), the «Health Center», the City Rheumatology Department of the polyclinic, and the Hospital Department in 2016–2019. Statistical analysis was performed using Excel Microsoft Office 2007, Statistica 6.0 and 10.0, and SigmaPlot 12.5 software packages. Multivariate regression analysis was used for studying the attributes influencing the development of AH and atherosclerosis in RA and for constructing predictive models. ROC analysis was used to determine the quality of the developed models. Differences were considered statistically significant at $p<0.05$.
Results	The following RFs predominating in the onset of disease were identified: traditional (hyperglycemia, obesity, increased diastolic BP (DBP), tachycardia, dyslipidemia); disease-mediated (ESR, fibrinogen, C-reactive protein (CRP), rheumatoid factor, cyclic citrullinated peptide antibodies, moderate and high DAS-28 activity), and psychosocial (stress, anxiety, depression, sleep disorders). The highest RF incidence and their combinations were determined with a RA duration of more than a year: traditional (obesity, hyperglycemia, increased systolic BP (SBP)), and decreased glomerular filtration rate; and disease-mediated (prednisolone treatment). A highly sensitive model for AH screening was developed that included a combination of RFs: disease-mediated (RA duration, CRP); traditional (improper diet, low physical activity, history of early cardiovascular diseases, increased SBP and DBP, preeclampsia and/or eclampsia, early menopause, older age, dyslipidemia); psychosocial (anxiety, depression), and a high salt-taste threshold. A highly sensitive model was developed for probable prediction of multifocal atherosclerosis in RA in women. The model includes a complex of risk factors: disease-mediated (RA activity by DAS-28, CRP, fibrinogen, ESR, dose-dependent prednisolone treatment); traditional (AH, SBP, waist circumference, heart rate, early menopause, preeclampsia and/or eclampsia, age 55 years and older, dyslipidemia); and psychosocial (sleep disorders, depression).
Conclusion	Algorithms for early prevention of AH and atherosclerosis were developed with consideration of identified predictors and proposed prediction models for women with RA.

Keywords	Rheumatoid arthritis; cardiovascular risk factors; arterial hypertension; atherosclerosis; prediction
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Introduction

PRheumatoid arthritis (RA) is the most common rheumatic disease that mainly affect working-age women and is associated with a high risk of cardiovascular diseases (CVDs) and early cardiovascular death [1]. Several studies currently define systemic inflammation in RA as a trigger of CVD progression through direct or indirect activation of existing risk factors (RFs) [2, 3]. RA was acknowledged for the first time as an independent cardiovascular RF in the current guidelines for the prevention of CVDs [4]. The existing model of cardiovascular risks in RA [5] does not capture the specific rheumatic RFs. Some authors argue about hyperdiagnosis, others about underestimating the actual risk according to this model [6]. RA is a heterogeneous disease with many characteristics; thus an individual cardiovascular prognosis should be made based on a multidisciplinary approach.

Hypertension occurs in almost 70.5% of RA cases [7–9]. High blood pressure (BP) is generally recognized cardiovascular RF, but most studies exploring the outcome [10] did not take into account individual factors and relationship with salt sensitivity as a key mechanism for the development and progression of hypertension and impaired renal filtration function. Scientific and practical interest in

Central illustration. Prediction of Cardiovascular Diseases in Women With Rheumatoid Arthritis

Study cohort
The combination and significance of traditional, disease-mediated, psychosocial risk factors in female patients with rheumatoid arthritis (RA) in the prediction model for hypertension and polyvascular disease

223 female patients with RA
(EULAR/ACR), age 54.9 ± 2.1 years
Positive serological test for RF – 52.5%
Anti-CCP Ab – 64.6 % activity according to DAS-28:
• Moderate – 17,5 %
• High – 82.5 %
Extra-articular manifestations – 46.6 %
Hypertension – 76.0 % (142.1 ± 0.2/90.9±0.4 mm Hg)
TC mmol/L – 65.3 % (6.05 ± 1.3)
LDL cholesterol – 51.6 % (3.5 ± 1.1)
GFR < 90 mL/min – 45.8 %, < 60 ≥ 44 – 11.5 %

Dyslipidemia, increased DBP, psychosocial factors, tachycardia, markers of inflammation prevail at the onset of RA.

Increased SBP, prednisolone dose, decreased GFR, obesity, hyperglycemia prevail in RA lasting more than one year.

Traditional risk factors (RSC 2017):
increased SBP and DBP; TC >4.9 mmol/L and/or LDL cholesterol >3 mmol/L, abdominal obesity (WC ≥ 88 cm), early family history of CVDs, lack of physical activity, loss of sleep (< 7 h/day), early menopause (before 45 years), HR (≥ 80 bpm), smoking (≥1 pack a day), alcohol (10 g of ethanol a day), pathologic pregnancy (preeclampsia and/or eclampsia), hyperglycemia > 6.1 mmol/L; GFR (CKD-EPI)

Additional factors:
natriuresis > 220 mmol/day, salt taste sensitivity threshold; Henkin, test strips;
duplex scanning of brachiocephalic arteries, ankle brachial index, bioelectrical impedance analysis (ABC-01 Medass)
Disease-mediated factors:
Activity assessed using the DAS-28 calculator (http://www.4s-dawn.com/DAS-28/).
X-ray of joints using the Steinbrocker method (RRA 2017)

Psychosocial factors:
HADS A and D
(8-10 = subclinical anxiety/depression).
Reeder Stress Inventory:
1–2 = severe; 2.01–3.0 = moderate; 3.01–4.0 = mild.

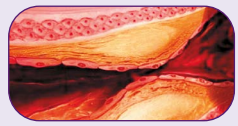
Influence of risk factors and their threshold values on the prognosis of hypertension and polyvascular disease in female patients with RA (multivariate analysis, prognostic significance for hypertension – 99.3 %; cases of atherosclerosis – 95.4 %)

For hypertension:

Age > 55 years; pathologic pregnancy, early family history of CVDs, malnutrition, TC > 5.0 mmol/L, AO > 88 cm, high STST threshold; CRP > 1.0 mg/L; DAS-28 > 3.2; stress > 3.2; depression > 8; prednisolone > 10 mg/day; RA duration > 10 years, GFR < 60 mL/min
To reduce GFR < 60 mL/min: early family history of CVDs; hypertension, TC > 6.0 mmol/L, age > 55 years; high STST; activity according to DAS-28 > 5.0; prednisolone > 10 mg/day

Additionally in the presence of RF threshold values:
determination of STST, natriuresis, bioelectrical impedance analysis, mSCORE risk, hypertension prediction model, multidisciplinary approach for the correction of risk factors and pathogenetic picture of hypertension

For polyvascular disease:



Menopause before 45 years; pathologic pregnancy, dyslipidemia (TC > 7.9 mmol/L, LDL cholesterol > 3.4); hypertension; age > 55 years; depression > 13.8; loss of sleep; prednisolone > 12 mg/day;
DAS-28 > 5.1; ESR > 53 mm/h

Exclusion of polyvascular disease if there are risk factors:
duplex scanning of BCAs, lower limb vessels, ABI, coronary angiography, mSCORE, atherosclerosis prediction model, multidisciplinary approach to risk factor correction

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this problem is due to its prevalence, insufficient knowledge of clinical and hemodynamic aspects, and as a result, the lack of a certain therapeutic and preventive strategy.

Changes in the pro-atherogenic profile of lipids and impaired transport of cellular cholesterol are the factors that contribute to the development of CVDs in RA [11–13]. Several studies showed high incidence of subclinical atherosclerosis, systemic vascular (polyvascular) lesions, but there are no prognostic models for cardiovascular complications in young people that capture individual predictors and an integrated approach to risk management in RA [14].

In view of the above, an urgent scientific task is to evaluate the role of the combination of hematological, immuno-inflammatory, and psychosocial factors in the development of CVDs and construct personalized risk prediction models in female patients with RA. Thus, the early predictors of atherosclerosis and hypertension remain unexplored, and processes are not established for the prediction and prevention of cardiovascular complications in patients of this category, which is a critical priority for cardiology.

Objective

Create prediction models for hypertension and atherosclerosis based on the combination and significance of traditional and disease-mediated risk factors in female patients with RA.

Material and Methods

Information and ethics during the study

The study was implemented under the Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Altai State Medical University (Barnaul, Russia; Minutes No. 11/12015 and the participating sites. All subjects signed the informed consent before being included in the study (Figure 1).

A total of 223 female patients with RA (mean age 54.9±2.1 years) were examined in the city outpatient clinic under N. P. Gull City Hospital No. 4 (Barnaul, Russia), rheumatology office and department, and Health Center in 2016–2019.

The inclusion criteria were female sex, age from 18 to 75 years, RA established according to the criteria of the European Anti-Rheumatic League and the American College of Rheumatology (EULAR/ACR, 2010), signed informed consent to participate in the study. The exclusion criteria were pregnancy, lactation, exacerbated and/or decompensated comorbidities, cancer, severe liver dysfunction, chronic kidney disease (CKD) stage IIIb (glomerular filtration rate (GFR) ≤44 mL/min/1.73 m^2), refusal to participate in the study (Figure 1).

Clinical characteristics of patients included in the study are provided in Table 1.

Physical examination

Traditional cardiovascular RFs (RSC 2017, ESC 2016, ESH/ESC 2017), rheumatological status and disease-mediated RFs were determined according to the criteria of RRA (2016) and EULAR (2010). RA activity was determined using the DAS-28 calculator (http://www.4s-dawn.com/DAS28/).

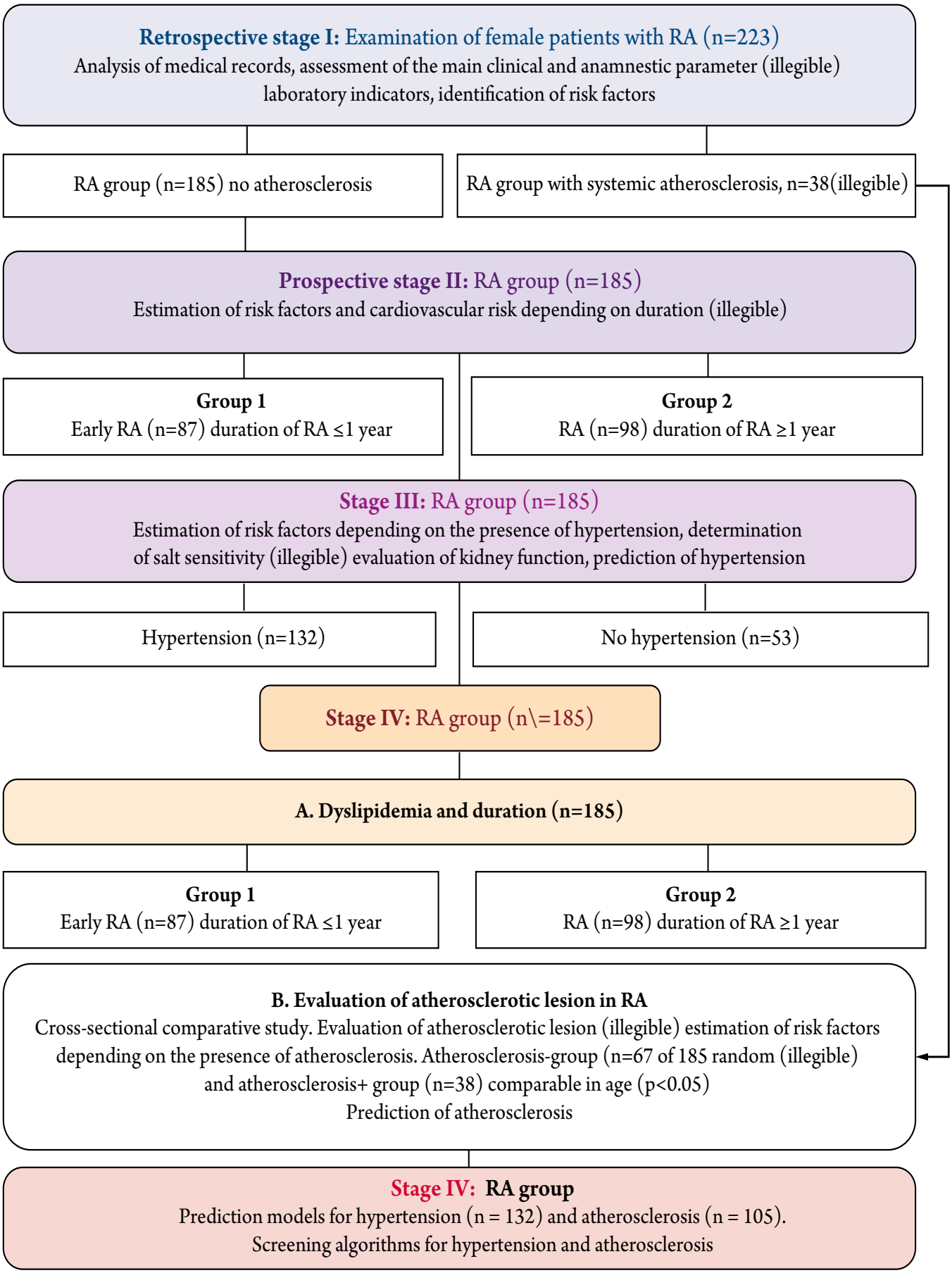
BP was measured with an Omron M2 Basic monitor with acceptable measurement uncertainty of ± 3 mm Hg (ESH/ESC 2017).

Table 1. Clinical characteristics of 223 female patients with rheumatoid arthritis

Parameter	Number of patients, n (%)	Value
Age, mean, years (M±m)	223 (100)	54.9±2.1
Extra-articular manifestations	104 (46.6)	–
Radiological stage of RA 1/2/3/4	87/48/56/32 (39.0/21.5/25.2/14.3)	–
RA functional class: I/II/III/IV	96/102/25/– (43.0/45.7/11.3/–)	–
RF seropositivity, mg/L (M±m)	144 (64.6)	72.0±6.3
Anti-CCP antibody positivity, units/mL (M±m)	117 (52.5)	4.9±0.5
Activity according to DAS-28: low/moderate/high	0/39/184 (0/17.5/82.5)	
BP, mm Hg (M±m)	170 (76)	142.1±0.2 / 90.9±0.4
Elevated TC, mmol/L (M±m)	145 (65.3)	6.05±1.3
Elevated LDL cholesterol, mmol/L (M±m)	115 (51.6)	3.5±1.1
GFR<90 mL/min/1.73 m^2 (M±m)	102 (45.8)	75.2±0.3
GFR<60 mL/min/1.73 m^2 (M±m)	27 (11.5)	53.1±0.4
Clinically apparent atherosclerosis: CVA/chronic CAD, n (%)	38 (17)	12/26 (5.3/11.6)
Disease modifying therapy		
Methotrexate, mg/week (M±m)	175 (78.5)	14.9±0.1
GCs, mg/week (M±m)	56 (25.1)	11.2±0.02
Other DMARDs	40 (17.9)	–
NSAIDs, n (%)	212 (95)	
Treatment of CVDs		
• ACE inhibitors/ARBs	44/34 (19.7/15.2)	
• Calcium antagonists	62 (27.8)	
• Diuretics	32 (14.3)	
• Beta-blockers	50 (22.4)	
• Statins	11 (5.0)	

Anti-CCP, anti-cyclic citrullinated peptide; ARB, angiotensin II receptor blocker; GC, glucocorticoid; ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug; CVA, cerebrovascular accident; RA, rheumatoid arthritis; RF, rheumatoid factor; CAD, coronary artery disease; DMARD, disease–modifying anti–rheumatic drug.

Figure 1. Study design



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Psychosocial state was assessed (HADS, Reeder Stress Inventory: 1–2 = severe stress; 2.01–3.0 = moderate stress; 3.01–4.0 = mild stress).

The cumulative cardiovascular risk was assessed using the European mSCORE scale (×1.5 for RA) (EULAR 2017). Salt taste sensitivity threshold (STST) was determined according to R. Henkin (1964) using a set of original test strips (Patent 2539014: V.P. Kulikov, A.V. Aleksentseva, 2015) Urine sodium was determined by the ion-selective method taking into account daily urine output. Increased sodium excretion was established at a level of>220 mmol/day. GFR was determined by the CKD-EPI formula (KDIGO 2017).

Duplex ultrasound scanning of the brachiocephalic arteries was performed on a Mindray DC-7 scanner. Vascular wall was examined in B-mode, blood flow was studied using pulsed and color Doppler. Intima media thickness (IMT) in the carotid bifurcation areas and in the common carotid artery areas was estimated. Ankle brachial index (ABI) was measured.

Bioelectrical impedance analysis was conducted (ABC-01 Medass device). Total volume, intra-, extra-, and intercellular fluid was determined, which should be 45–60% of body weight. This indicator is used to evaluate the severity of fluid retention in the body.

X-ray of the hand and feet joints was performed to stage RA using the Steinbrocker method (RRA 2017).

Statistical processing of the data obtained was performed in Excel Microsoft Office 2007, Statistica versions 6.0 and 10.0 (StatSoft Inc., USA), SigmaPlot 12.5 (Systat Software Inc., USA). Both absolute and relative indicators were used to assess qualitative features and were presented as the rates and percentages. The t-test and the Mann-Whitney test were used for normally and non-normally distributed variables, respectively, to determine the differences between two mean values. Significance analysis of the intergroup differences was conducted using the t-test for quantitative variables and the chi-square test for qualitative variables. Fisher's exact test (two-tailed test) was applied for the values of less than 5.

Binary logistic regression analysis was used to determine the predictors of kidney injury and hypertension. Data are presented as odds ratio (OR) for each RF, 95% confidence interval (CI), and logistic regression equation. Analysis of features affecting the development of atherosclerosis in RA was performed using multivariate regression analysis. The contribution of individual factors was reflected using Wald chi-square and standardized regression coefficient (Estimate).

Using the regression model data, ROC curves were constructed, which reflect the dependence of the number of correctly classified positive (true positive) examples on the number of incorrectly classified negative (false negative) examples. The closer this curve is to the upper left corner, the higher the predictive power of the resulting mathematical model, and vice versa, a low position of the curve shows a weak predictive power. Visual comparison of ROC curves is performed by calculating area under curve (AUC); the indicator is calculated using the numerical trapezoidal method. Thus, the greater the AUC, the greater the predictive power of the model. ROC curves are assessed using a special expert AUC scale, according to which the sensitivity and specificity of the model should be at least 85%.

The differences were considered statistically significant with $p<0.05$.

Results

Cardiovascular risk factors at the onset of RA and in RA lasting more than one year

Inflammatory activity, malnutrition, lack of physical activity, hypertension, abdominal obesity (AO), psychosocial factors, dyslipidemia are the most common factors in all patients with RA.

The groups of early RA (Group 1, n=87) and RA lasting more than one year (Group 2, n=98) were comparable for most RFs (malnutrition, lack of physical activity, AO, early history of CVDs, hyperglycemia, smoking, alcohol abuse). Traditional RF tachycardia was more common in early RA (39.2% and 25%, respectively; $p<0.05$). Markers of inflammatory activity were more common at the onset of RA (ESR by 13%, elevated CRP by 9%, rheumatoid factor by 15%, fibrinogen by 25%, anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) by 4%), high activity according to DAS-28 by 19%, and their values were higher. The incidence of dyslipidemia was high in both groups, but it was statistically significantly higher at the onset of RA, which reflects a more unfavorable blood lipid profile and increases the risk of early atherosclerosis in RA. All psychosocial factors in early RA were more common ($p<0.05$), except for mean level of stress in RA lasting more than one year ($p=0.01$).

Obesity (by 18.2%), hyperglycemia (by 11.2%), and prednisolone (by 22.5%) were more common, and its mean dose was higher in RA lasting more than one year ($p=0.05$). Hypertension was more common in advanced RA (by 28%) due to SBP, while DBP was higher in early RA (92.1±0.1 mm Hg and 88.3±0.6 mm Hg, respectively; $p=0.05$). Decreased GFR was more common by 13.2% ($p=0.02$) in RA lasting more than one year.

More than 50% of female patients in Group 1 and Group 2 faced high and very high risk of death from cardiovascular complications (58% and 75%, respectively), which is why it is necessary to identify early predictors of CVDs and take more active preventive measures (Figure 2).

Hypertension in RA

The prevalence of hypertension was high (72%), nevertheless patients were divided into groups with hypertension (n=132) and without hypertension (n=53) to identify the most significant relationship between hypertension and RA. Excessive salt intake was detected in 75% of female patients with RA. STST was higher by 32% in patients with RA and hypertension higher, mean STST was 2.6 times higher ($p<0.05$) than that in patients without hypertension. The predominance of high and moderate STST combined with hypertension in RA was 2-fold (88% in patients with hypertension, 48% in patients without hypertension; $p<0.05$). We studied natriuresis to confirm the hypothesis of salt sensitive hypertension. Natriuresis up to 200 mmol/L was detected in 65% of patients with hypertension and only 41% patients without hypertension ($p<0.05$), which may be indicative of sodium retention in hypertension. The results of body fluid analysis were higher in the group of patients with hypertension than in the group without hypertension (48.9±1.0 kg and 30.9±1.4 kg, respectively; $p<0.05$). GFR <90 mL/min/1.73 m^2 was more prevalent in the group of patients with hypertension than in patients without hypertension (57.0% and 34%; $p=0.01$), the same was true for GFR <60 mL/min/1.73 m^2 (18.0% and 5%, respectively; $p=0.01$).

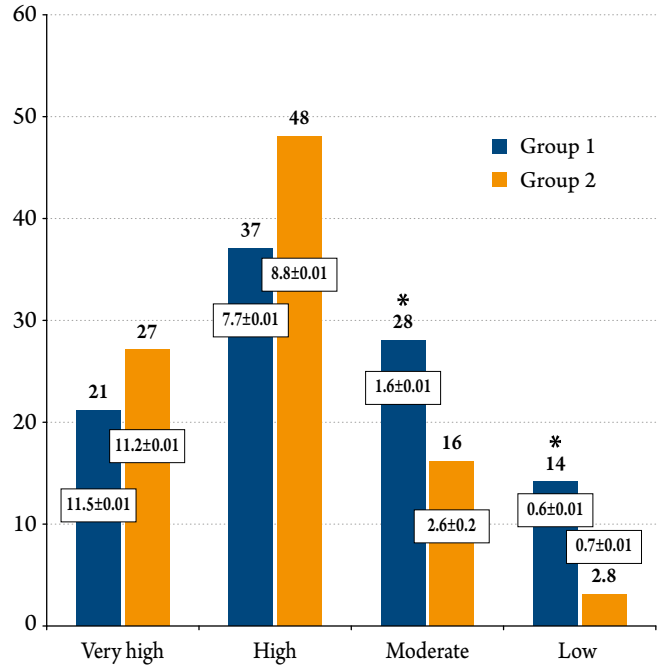
The most significant contribution of cardiovascular and disease-mediated RFs to the development of hypertension in RA was determined using univariate logistic regression method (Table 2).

Table 2. Risk factors for hypertension in RA

Risk factor	Factor grade	OR	95 % CI	p
Age	> 55 years	3.01	1.82–8.31	0.001
Early menopause	< 45 years	2.56	0.9–47.0	0.001
TC	>5.0 mmol/L	2.39	2.73–8.99	0.001
Early family history of CVDs	Yes / No	2.31	0.72–8.65	0.012
GFR	< 60 mL/min/1.73 m2	2.27	1.43–7.15	0.010
High STST	Yes / no	2.24	1.54–9.32	0.013
Malnutrition	Yes / no	2.10	1.8–41.6	0.001
History of preeclampsia and/or eclampsia	Yes / no	1.73	0.93–40.4	0.014
DAS-28	> 3.2	1.36	0.93–8.83	0.012
Reeder Stress Inventory	> 2.01	1.34	1.1–12.3	0.011
Prednisolone	>10 mg/day	1.33	1.47–11.36	0.001
HADS D	> 8	1.01	1.15–35.8	0.020
CRP	> 1.0 mg/L	1.01	1.23–26.3	0.011
Abdominal obesity, waist circumference	> 88 cm	0.96	1.05–9.43	0.012
Duration of RA	> 10 years	0.91	1.56–9.92	0.014
LDL cholesterol	Yes / no	0.82	1.3–7.5	0.033
HDL cholesterol	Yes / no	0.74	1.04–8.99	0.044

OR, odds ratio; CI, confidence interval;
STST, salt taste sensitivity threshold; RA, rheumatoid arthritis.

Figure 2. Risk of cardiovascular diseases estimated using mSCORE (%, M±m) in the study groups



* $p<0.05$ statistically significant differences between the groups of early RA (Group 1) and RA lasting more than one year (Group 2). RA, rheumatoid arthritis.

Table 3. Risk factors for GFR decrease to 45–60 mL/min/1.73 m2 in RA

Risk factor	Factor grade	OR	95 % CI	p
TC	> 6.0 mmol/L	2.19	2.20–8.31	0.001
Early family history of CVDs	Yes / no	2.11	0.49–8.21	0.012
Age	> 55 years	2.09	0.86–4.12	0.001
DBP	> 90 mm Hg	2.05	1.53–7.68	0.010
High STST	Yes / no	2.03	1.36–9.51	0.014
DAS-28	> 5.0	1.98	0.87–7.53	0.001
SBP	> 144 mm Hg	1.91	0.99–8.96	0.001
Prednisolone	>10 mg/day	1.86	1.79–9.16	0.001

RA, rheumatoid arthritis; OR, odds ratio;
CI, confidence interval; STST, salt taste sensitivity threshold.

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Table 4. Correlation between RA and risk factors in RA

Parameter	Estimate	Standard error	Wald chi-square	p (Wald)
Crossing	-34.287	13.828	6.148	0.013
Duration of RA	0.0602	0.199	0.001	0.762
Early family history of CVDs	3.662	2.485	2.171	0.014
Malnutrition	5.972	2.987	0.007	0.046
STST	3.705	2.008	3.403	0.025
LDL cholesterol (qualitative)	-5.833	4.054	2.070	0.040
HDL cholesterol (qualitative)	-3.465	1.936	3.204	0.043
Lack of physical activity	-2.662	2.522	1.114	0.029
Anxiety	1.224	1.387	0.779	0.037
Depression	7.301	3.723	3.847	0.050
Preeclampsia and/or eclampsia	-1.218	2.229	0.029	0.585
CRP (quantitative)	-0.0026	0.0208	0.015	0.901
Early menopause (<45 years)	3.757	1.924	3.813	0.051

Significant results with p<0.05. RA, rheumatoid arthritis; STST, salt taste sensitivity threshold.

Univariate logistic regression analysis (Table 3) was used to identify indicators contributing to a decrease in kidney function in female patients with RA.

Prediction model of hypertension in female patients with RA

Binary logistic regression analysis was conducted with stepwise selection of variables to account for the combined effect of factors associated with the development of hypertension in patients with RA (Table 2, Table 3). The final models included the minimum number of necessary clinically significant factors, which showed a statistically significant effect on the risk of hypertension (Table 4).

Initially, the factors associated with the development of hypertension were identified and analyzed, their significance and ability to predict hypertension in RA were determined (see Table 2 and Table 3). Then, the RFs for hypertension in female patients with RA was ranked with the appropriate coefficient, for example: + (0.0602·X1) duration of RA. Based on the values obtained, a hypertension prediction scale was developed. To identify the risk of developing hypertension, the following calculations were used, a dimensionless indicator (beta) was determined,

$$\text{Beta} = -34.287 + (0.0602 \cdot X1) + (3.662 \cdot X2) + (5.972 \cdot X3) + (3.705 \cdot X4) - (5.833 \cdot X5) + (3.465 \cdot X6) + (1.586 \cdot X7) - (3.457 \cdot X8) - 2.662 \cdot X9) + (1.224 \cdot X10) + (7.301 \cdot X11) - (1.218 \cdot X12) - (0.0026 \cdot X13),$$

where X1 is the duration of RA (years); X2 is an early family history of CVDs; X3 is malnutrition; X4 is STST; X5 is LDL cholesterol (mmol/L); X6 is HDL cholesterol (mmol/L); X7 is family history of CVDs; X8 is lack of physical activity; X9 is the presence of anxiety; X10 is the presence of depression; X11 is a history of pathologic pregnancy; X12 is CRP (mg/L); and X13 is early menopause. The quantitative indicator corresponds to a digital value, the presence of a feature was encoded in the program as 1=yes and the absence as 0=no. Beta is equal to the probability of occurrence (p) and is calculated by the formula: p= exp (beta)/(1+exp (beta)). If the resulting number is ≥ 0.5, then the probability of hypertension is increased, if it is<0.5 than the probability of hypertension is low.

The prognosis was correct for 131 of 132 patients with hypertension, the ratio of hypertension/no hypertension = 0.993 = 99.3%. Thus, the obtained mathematical model has a very high predictive value.

Dyslipidemia in RA

All subjects had polyvascular disease due to systemic inflammation in RA. Female patients with symptomatic atherosclerosis (n=38) and without symptomatic atherosclerosis (n=67) were selected to identify the most significant predictors of atherosclerosis.

Univariate regression analysis determined RFs and threshold values for atherosclerosis: use of prednisolone (OR 4.3; 95% CI 2.44–10.8), hypertension (OR 2.5; 95% CI 1.2–8.9), early menopause (OR 2.2; 95% CI 1.9–9.3), loss of sleep (OR 1.7; 95% CI 0.9–8.9), TC (OR 1.1; 95% CI 0.9–8.9), DAS-28 (OR 0.9; 95% CI 0.6–10.4], LDL cholesterol (OR 1.1; 95% CI 0.6–11.3), a decrease in HDL cholesterol (OR 0.3; 95% CI 0.2–7.9), depression (OR 0.2; 95% CI 0.1–11.6), ESR (OR 0.2; 95% CI 0.1–12.8), pathologic pregnancy (OR 0.04; 95% CI 3.4–12.3), which must be taken into account when assessing the risk of developing CVDs.

Multivariate logistic regression with stepwise selection of variables was used to assess the significance of factors in the development of polyvascular disease with the calculation

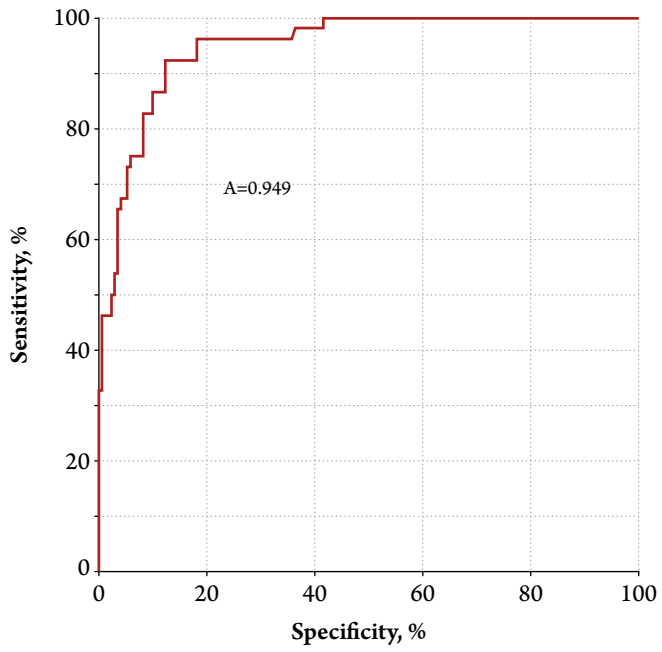
Table 5. Risk factors for polyvascular disease in RA

Predictor	Estimate	Standard error	Wald chi-square	p (Wald)
Crossing	-19.37	5.42	12.78	0.001
Age	0.15	0.04	11.46	0.001
DAS-28	0.88	0.37	5.515	0.019
AH	2.50	1.05	5.640	0.018
SBP	0.01	0.02	0.340	0.056
WC	0.01	0.04	0.013	0.721
HR	0.02	0.03	0.041	0.550
HADS D	0.26	0.11	5.680	0.022
Loss of sleep	1.74	0.62	8.031	0.005
Early menopause	2.16	0.69	9.70	0.002
History of preeclampsia and/or eclampsia	0.04	0.64	0.003	0.951
CRP	0.000	0.01	0.003	0.961
Fibrinogen	0.63	0.64	0.980	0.322
ESR	0.04	0.02	3.842	0.046
TC	1.08	0.39	7.733	0.005
LDL cholesterol	0.89	0.44	4.102	0.040
Prednisolone	4.31	1.33	10.471	0.001

HADS D, hospital anxiety and depression scale depression subscale.

of coefficients that increase the probability of the event. The model showed the predictors of atherosclerosis with multiplicative significance, increasing the risks: use of prednisolone intake – 4.3-fold (p=0.001); hypertension – 2.5-fold (p=0.018); early menopause – 2.1-fold (p=0.02); loss of sleep – 1.7-fold (p=0.05); TC – 1.0-fold (p=0.005); LDL cholesterol – 0.8-fold (p=0.04); DAS-28–0.8-fold (p=0.019). Other factors had a contribution of less than 0.3 (depression, age over 55 years, increased SBP, and waist circumference).

Figure 3. ROC analysis of prognostic significance of the model



Prediction model for polyvascular disease in RA

After standardization of the obtained predictors (Table 5) affecting the development of atherosclerosis in RA, multivariate regression analysis was used for the calculations. The contribution of individual predictors was reflected using Wald chi-square and standardized regression coefficient (Estimate).

Prediction model for polyvascular disease in RA was constructed. The probability of the event (atherosclerosis) was determined using the formula:

$$p=\exp(\text{beta})/1+\exp(\text{beta}).$$

If p ≥ 0.5, the likelihood of atherosclerosis is increased, if p<0.5, it is reduced. The presence of a feature in the program was equal to 1, the absence of the feature was 0.

Beta is the value of probability:

$$(p) = -19.374 + (0.15 \cdot X1) + (0.88 \cdot X2) + (2.50 \cdot X3) + (0.01 \cdot X4) + (0.01 \cdot X5) + (0.02 \cdot X6) + (0.26 \cdot X7) + (1.74 \cdot X8) + (2.16 \cdot X9) + (0.04 \cdot X10) + (0.000695 \cdot X11) + (0.63 \cdot X12) + (0.04 \cdot X13) + (1.08 \cdot X14) - (0.89 \cdot X15) + (4.31 \cdot X16)$$

Explanation: X1 – age (years), X2 – DAS-28 (points), X3 – hypertension, X4 – SBP (mm Hg), X5 – waist circumference (cm), X7 – HADS D score (points), X6 – HR (bpm), X8 – loss of sleep, X10 – preeclampsia and/or eclampsia, X9 – early menopause, X11 – CRP (mg/L), X12 – fibrinogen (mg/L), X13 – ESR (mm/h), X14 – TC (mmol/L), X15 – LDL cholesterol (mmol/L), X16 – use of prednisolone.

The correctness of the distribution of atherosclerosis/no atherosclerosis was 95.4%. Thus, the mathematical model of screening has a high accuracy (100%) in predicting of atherosclerosis events with a prognostic significance of 95.4%. The model is designed for 105 patients with RA and can be recommended for risk group screening, it is simple and easy to use (Figure 3).

Given the results obtained, we developed an algorithm for screening and management of hypertension, atherosclerosis, and their RFs in female patients with RA (Figure 4, Figure 5).

Multivariate regression analysis showed the influence of risk factors, which is indicative of the common origin and contribution of predictors to the development of CVDs (hypertension, atherosclerosis, decreased kidney filtration

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function), which should be taken into consideration for cardiovascular risk management in RA (Table 6).

Discussion

Despite the predominance of musculoskeletal lesions in the clinical picture of RA, mainly in young women, the main cause of death is atherothrombotic complications that develop earlier than in the general population. Studies showed that the risk of severe cardiovascular complications in RA is associated with the presence of traditional, inflammatory factors, and antirheumatic therapy [15–17]. However, the roles of psychosocial, sex-related factors [18], the duration of rheumatic disease and eating habits are not taken into consideration in the development of CVDs, especially in young women. Despite many published studies and developments, there are no prediction models for patients with RA that would establish the actual cardiovascular risk. Modified scales, such as mSCORE, do not take into account some factors: sex, psychosocial factors, and factors associated with the course of rheumatic disease [19–21]. Traditional and disease-mediated cardiovascular RFs in RA are known, but the combination of RFs for cardiovascular complications is understudied. In our study, a detailed analysis of cardiovascular RFs in women was conducted, starting with early RA (lasting less than a year), and their contribution in the later stages of RA. At the onset of RA, there is an increase in dyslipidemia, DBP, psychosocial factors (stress, anxiety, depression, sleep <7 h/day), resting tachycardia, inflammatory markers (ESR, RF, DAS-28); in RA lasting 1 year or more – obesity, hyperglycemia, increased SBP, prednisolone dose, decreased GFR.

Figure 4. Algorithm for hypertension screening and management in rheumatoid arthritis

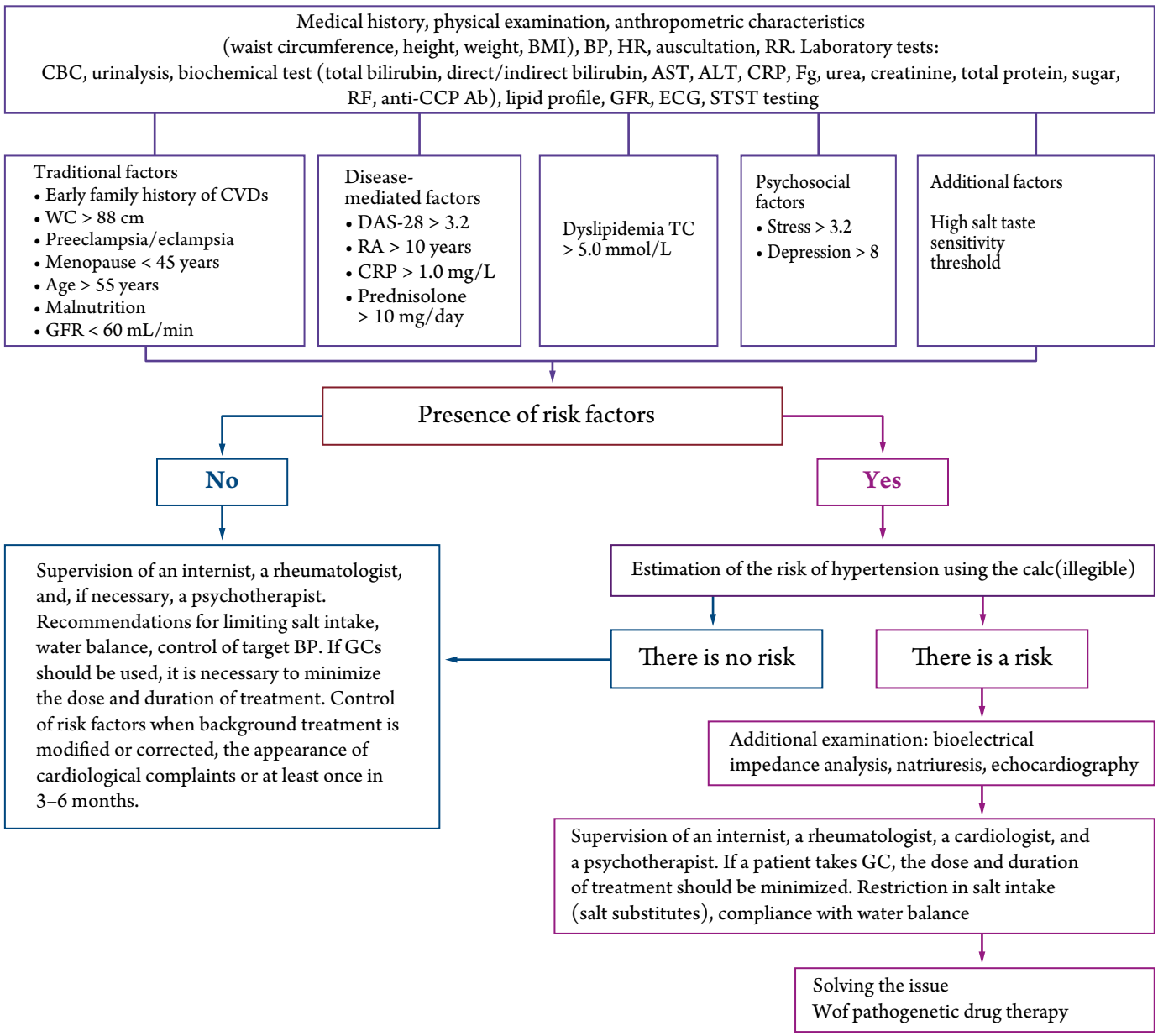
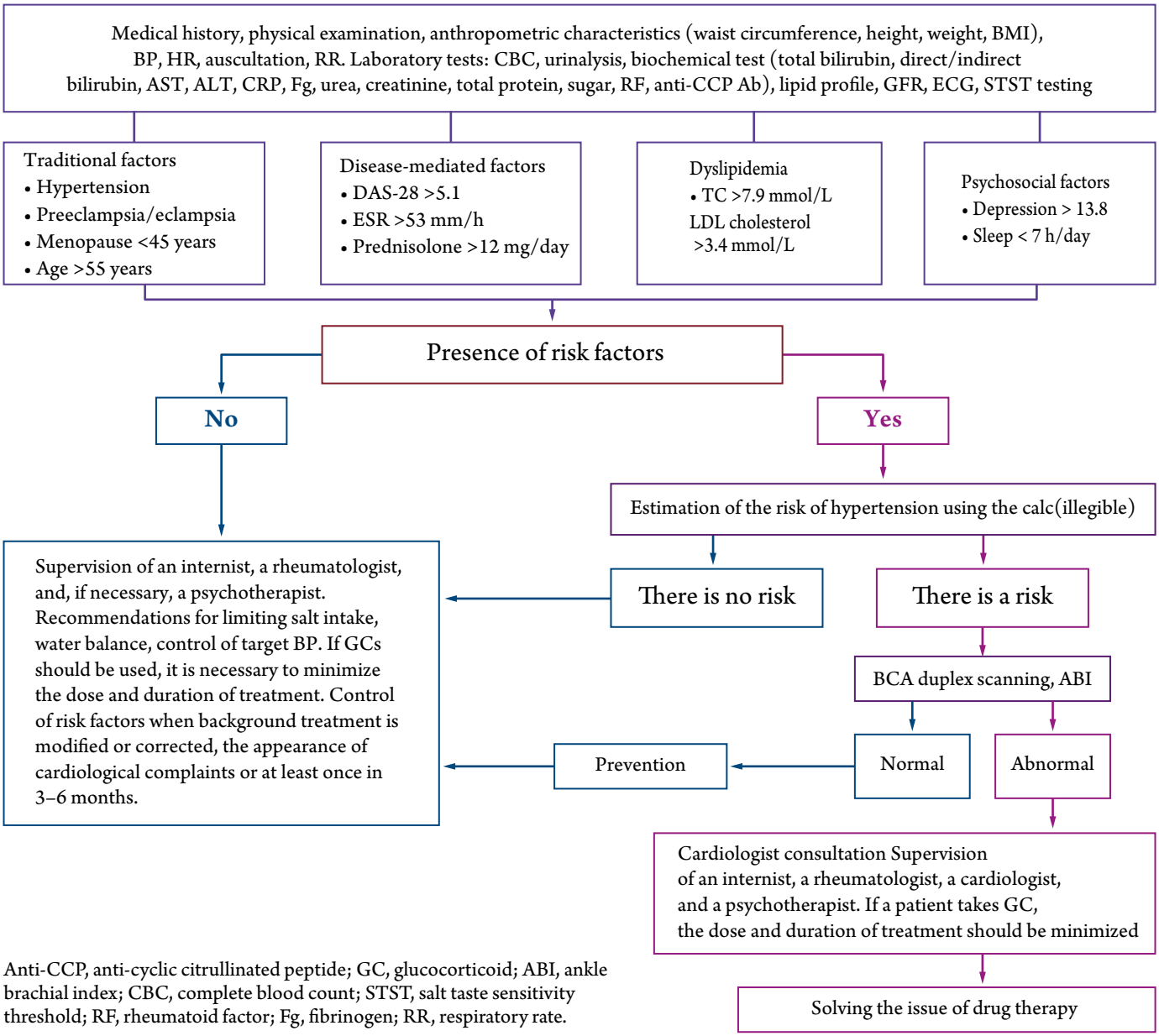


Figure 5. Algorithm for atherosclerosis screening and management in rheumatoid arthritis



Anti-CCP, anti-cyclic citrullinated peptide; GC, glucocorticoid; ABI, ankle brachial index; CBC, complete blood count; STST, salt taste sensitivity threshold; RF, rheumatoid factor; Fg, fibrinogen; RR, respiratory rate.

Female patients with RA are at cardiovascular risk, but the predictors of the transition to CVDs are not precisely defined taking into consideration the characteristics of the disease [22]. According to many researchers, autoimmune inflammation in RA is a model of atherogenesis [22, 23]. Increased blood atherogenicity is noted in rheumatoid arthritis even before the onset of articular syndrome [24–27]. Abnormal blood lipid profile at the onset of RA is comparable to that in progressive atherosclerosis. The lack of entirely clear view on the influence of factors on the development of dyslipidemia depending on the duration of RA (less or more than one year) [28–30] is an obstacle implementing strategic preventive measures during the manifestation of arthritis.

The frequent combination of high blood pressure and RA requires exploring the specifics of the developmental mechanisms and pathogenetic treatment and taking into consideration the role of salt sensitivity. Hypertension in RA is a heterogeneous disease caused by traditional and non-traditional RFs, RA is an independent RF for elevated BP. However, there is no clear idea of the complex of RFs that cause and maintain hypertension.

In our study, hypertension was also prevalent (72%) – it is volume-dependent and characterized by high STST, hyponatriuresis, and dose-dependent administration of prednisolone. Common predictors of hypertension and reduced GFR (<60 mL/min/1.73 m^2) were determined: TC; early family history of CVDs; age>55 years; high STST; activity according to DAS-28; use of prednisolone.

Atherosclerotic lesion of vessels is the main cause of death in RA [31, 32]. It was important for us to find out at what stage of RA atherosclerosis develops and what are the

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Table 6. Methods for assessing the cardiovascular risk at the onset and during RA

Generally accepted	Supported by the study results
1. Risk factors	
• Traditional • Disease-mediated • Psychosocial	Thresholds: For hypertension: age >55 years; pathologic pregnancy, early family history of CVDs, malnutrition, TC>5.0 mmol/L, OT>88 cm, high STST; CRP>1.0 mg/L; DAS-28>3.2; stress>3.2; depression>8; prednisolone>10 mg/day; duration of RA>10 years, GFR <60 mL/min/1.73 m^2. **To reduce GFR** (< 60 mL/min/1.73 m^2): early family history of CVDs; hypertension, TC>6.0 mmol/L, age>55 years; high STST; activity according to DAS-28>5.0; prednisolone>10 mg/day. **For atherosclerosis:** menopause before 45 years; pathologic pregnancy, dyslipidemia (TC>7.9 mmol/L, LDL cholesterol>3.4 mmol/L); hypertension; age>55 years; depression>13.8; loss of sleep; prednisolone>12 mg/day; DAS-28>5.1; ESR>53 mm/h
2. In dyslipidemia	
• Duplex scanning of BCAs • Duplex scanning of lower extremity vessels • Coronary angiography • ABI	• Polyvascular lesions • Localization of involved vascular systems
3. In hypertension	
• BP measurement • Medical history • Physical examination • Laboratory tests • Clinical investigations	**Additionally:** • Estimation of STST • Natriuresis • Bioelectrical impedance analysis
4. Risk prediction models	
mSCORE	**Prediction models:** • Hypertension • Atherosclerosis

AO, abdominal obesity; BCA, brachiocephalic artery; STST, salt taste sensitivity threshold; RA, rheumatoid arthritis.

contributing factors. RA is characterized by a high incidence of dyslipidemia, but TC is more common by 26% and LDL cholesterol by 12% in early RA.

The problem of a comprehensive approach to early prediction of hypertension and atherosclerosis in RA has been solved. The introduction of non-invasive methods for outpatient screening of hypertension and atherosclerosis can contribute to broadening and improving preventive recommendations, which will allow implementing a personalized and multidisciplinary approach in the management of patients and timely adjusting the RFs.

Limitations

This study was single-center and had a small sample and sex-specific boundaries.

Conclusion

Thus, the role of a combination of traditional, immunoinflammatory, psychosocial factors in the development of cardiovascular diseases was analyzed, depending on the duration of rheumatoid arthritis in female patients, and the threshold values of these factors were determined. Models for the prediction of the probability of atherosclerosis and hypertension and schemes for the prediction and prevention of cardiovascular complications in female patients of this category are presented. Further research of the presented problem in a larger patient cohort is of great theoretical and practical importance associated with the development of new approaches to the prevention and treatment of cardiovascular complications and can help improve the stratification of risk groups.

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