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Frailty syndrome in patients with rheumatoid arthritis and the role of cardiovascular comorbidities

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Abstract

The objective of the current study was to assess the incidence and clinical features of the frailty syndrome in patients with rheumatoid arthritis (RA) as well as the role of cardiovascular disease (CVD) and cardiovascular disk factors.

Materials and methods. *Our study included 101 patients (86 women and 15 men) aged 45–81 years with confirmed RA of 8 [3; 15] year duration. Frailty syndrome was diagnosed based on the phenotype of frailty developed by Fried LP, et al (2001). We performed electrocardiography (ECG), echocardiography (echo), assessed the risk of CV mortality according to the SCORE scale, CV risk factors, the Health Assessment Questionnaire-Disability Index (HAQ-DI) functional status, nutritional status, dementia screening and calculated Charlson Comorbidity Index.*

Results. *Of all the 101 patients with RA, 41 were frail (40.6 %), 56 (55.4 %) were prefrail and 4 were not frail (4.0 %). Compared with prefrail patients, frail individuals were older (p=0.002) and had higher disease activity (p=0.03) and stage (p=0.003) of RA based on X-ray studies, were in more pain according to the visual analogue scale (VAS) (p=0.001) and had more limitations of their everyday activity according to HAQ-DI (p=0.002). In frail patients wrist dynamometry values (p=0.001) were lower and 4 m walking test time was higher (p=0.004) compared with prefrail. Frail patients were also more prone to unmotivated weight loss (p<0.001), fatigue (p<0.001) and lack of physical activity (p<0.001). However, they were at a lower risk of malnutrition (p<0.001). Frail patients with RA had higher prevalence of CVD (chronic heart failure, coronary artery disease) (p=0.008), and more pronounce left ventricular hypertrophy (p=0.004). Frail patients had higher 10-year cardiovascular mortality risk according to SCORE scale (p=0.02). The majority of these individuals were at a very high risk despite lower levels of total cholesterol compared with prefrail participants (p=0.009). Key cardiovascular risk factors in frail patients were older age, arterial hypertension, and lack of physical activity, in prefrail –hypertension and obesity.*

Conclusion. *The overall prevalence of frailty in patients with RA was 40.6 %. It is associated with older age, more severe RA, disorders of nutritional status, more everyday life limitations, CVD, and high CV risk.*

Keywords: *frailty, prefrailty, rheumatoid arthritis, cardiovascular disease.*

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Introduction

Frailty (senile asthenia) is a syndrome defined as an increased susceptibility to negative environmental factors and associated with loss of ability to self-care and adverse health outcomes [1, 2]. It's initial stage is prefrailty (preasthenia) that can further progress to frailty in the absence of any preventive measures. Frailty syndrome has emerged as a new challenge for internal medicine and is considered a consequence of age-related changes and multimorbidity. Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology characterized by a chronic erosive arthritis and systemic inflammation that causes early disability and reduction of life span [3]. RA can possibly cause accelerated aging and frailty in younger patients. According to some studies, frail patients are at a higher risk of cardiovascular disease (CVD) compared with healthy individuals [4]. On the other hand, chronic inflammation in RA accelerates atherogenesis and increases the risk of CVD [5]. As such, severe CVD is associated with frailty in RA and, at the same time, patients with RA at a higher risk of severe CV complications. Research on frailty syndrome in RA is sparse [6–10] and clinical features and the role of CVD in frail RA patients are not well studied.

The objective of this study was to investigate the incidence and clinical features of frailty syndrome in RA patients and its association with CVD and CV risk factors.

Material and methods

The study protocol was approved by the local Ethics Committee. Informed consents were obtained from all patients prior to participation.

The study included 101 patients (86 women and 15 men) with RA diagnosis according to the ACR/EULAR, 2010 criteria, aged 45–81 years (median of age was 60 years [52; 66])., who were hospitalized to Ivanovo City Hospital № 4 and Ivanovo Regional Clinical Hospital, Ivanovo, Russia. Of all patients, 50 were 60 years of age or younger. The duration of illness was from 0.5 to 40 years (median 8 years [3; 15]) and 15 patients had RA for <1 year)

Most patients (82.2 %) had seropositive RA with moderate activity (DA28, ESR 4.6 [3.7; 5.5]), stage II categorized by radiologic criteria (40.6 %), III functional class (60.4 %). 73 patients (72.3 %) were treated with methotrexate (15 [10; 20] mg/week), 19 (18.8 %) with leflunomide 20. Some patients were administered methotrexate (15 patients) or leflunomide (4 patients) together with biologic drugs. Others were administered hydroxychloroquine and sulfasalazine. 79.2 % of patients took >5 mg of corticosteroids for a prolonged period of time (>3 months). Cumulative dose of steroids was 1475 [300; 10000] mg.

Frailty syndrome was diagnosed according to Fried L. P. et al. (2001) phenotype model that included the following criteria:

Unintentional weight loss ≥4.5 kg in prior year.

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Poor endurance and energy (Fatigue Assessment Scale, FAS) (FAS≥22 points) [11].

Slowness when walking 4 m based on time to walk 4 m, male: ≥7 sec for ≤1.73 m height and ≥6 sec for >1.73 height; female: ≥7 sec for ≤1.59 m and ≥6 sec for >1.59 m.

Low grip strength measured with DK-25 dynamometer (kg-hand grip power, kgp). For men, low grip strength was considered ≤29 kgp for BMI≤24 k^2, ≤30 kgp for BMI 24.1–28 k^2, ≤32 kgp for BMI>28 k^2. For women: ≤23 kgp for BMI ≤17 k^2, ≤17.3 for BMI 23.1–26 k^2, ≤18 kgp for BMI 26.1–29 k^2, ≤21 kgp for BMI >29 k^2.

Low physical activity according to Physical Activity Questionnaire (IPAQ): for 18–39 years — <21 points, 40–65 years — <14 points, >65 years — <7 points [12].

If three or more criteria were present the patient was considered frail, one-two criteria — prefrail, none — nonfrail [13].

Nutritional status was determined using the Mini Nutrition Assessment (MNA) form: normal (≥25 points), risk of malnutrition (17–23.5 points), malnutrition (<17 points) (Guigoz Y et al., 1994). We also assessed the intensity of pain using a Visual Analogue Scale (VAS) and Health Assessment Questionnaire Disability Index (HAQ) (Bruce B. et al., 2003). We examined cardiovascular system: ECG, echocardiography, lipid profile, calculated BMI. 10-year cardiovascular mortality risk was calculated with SCORE (Systematic Coronary Risk Evaluation) scale modified by the European antirheumatic league [14]; SCORE risk was multiplied by 1.5. 10-year mortality risk was evaluated with Charlson comorbidity index (Charlson M. E. et al., 1987).

Statistical analysis was performed with Statistica 6.0 software. Results are presented as median (Me) and quartiles [Q25; Q75]. Quantitative variables were compared with non-parametric Mann–Whitney U test. Qualitative variables were compared with Chi-squared test. Correlation analysis was performed with Spearman's correlation coefficient (r). $p<0.05$ was considered statistically significant.

Results

Frailty was diagnosed in 41 patients (40.6 %), prefrailty in 56 (55.4 %) patients and 4 patients were nonfrail (4.0 %).

Frail patients were older than prefrail (Table 1). However, 14 frail patients were younger than 60 years (44–59 years). Older frail patients had higher RA activity according to DAS28 mostly due to higher levels of C-reactive protein (CRP) and worse subjective evaluation of health. More frail patients had stage III RA, III functional class. Frail patients had more intensive pain according to VAS and more loss of functional activity according to HAQ-DI.

Diagnostic criteria were also different in the study groups. Frail patients had lower values of dynamometry of the right (3 [3; 8] kgp and 8 [5; 13] kgp, p=0.001) and left wrist (4 [2.5; 7] kgp and 6.5 [4; 10] kgp, p=0.025), needed more time to walk 4 m (6.3 [5.0; 8.6] sec and 4.4 [3.4; 5.3] sec, p=0.004), more frequently lost weight unintentionally (28 vs 8 people, χ^2=29.582, p<0.001), had poor endurance and energy (39 vs 27 people, χ^2= 23.953, p<0.001) and had reduced physical activity (19 vs 0, χ^2 = 32.273, p<0.001) Reduced physical activity was associated with lower functional status according to HAQ-DI (r=0.51, p<0.05). Malnutrition risk due to reduced consumption of protein, vitamins and minerals with the same caloric intake was present in the majority of frail patients (27 vs 16, χ^2= 13.332, p<0.001).

Frail patients had higher 10-year mortality risk according to Charlson index (0 [0; 53.0]% and 53 [21; 77]%, p=0.004) due to higher comorbidity burden and older age. Comorbidities present in frail and prefrail

Table 1. **Comparison of frail and prefrail patients according to RA clinical parameters**

Parameters	Frail (n=41) Me [Q25; Q75]	Prefrail (n=56) Me [Q25; Q75]	p
Age, years	63 [55; 69]	57 [49; 65]	0.002
CRP, mg/dl	10.4 [3.2; 30.3]	7.3 [2.0; 23.1]	0.020
VAS, мм	70 [45; 88]	40 [20; 50]	0.001
DAS28 according to CPR	5.0 [4.2; 5.9]	4.4 [3.7; 4.9]	0.003
III radiographic stage, abs.	15	6	0.003
III functional calss, abs.	30	29	0.020
Pain visual self-assessment, mm	70 [50; 80]	50 [30; 60]	0.001
HAQ	2.125 [1.625; 2.5]	1.0 [0.375; 1.625]	0.002
HAQ-DI, abs.	25	6	0.035

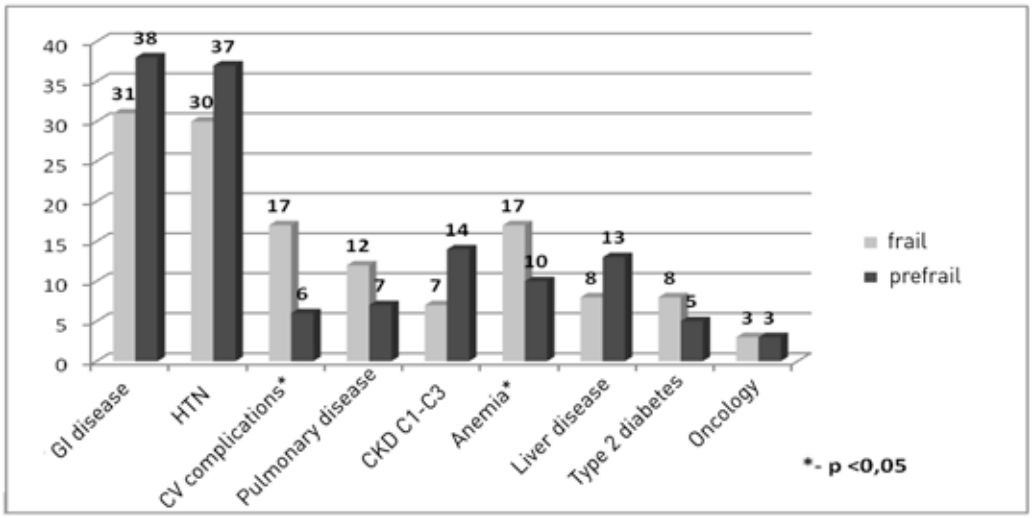

Figure 1. Comorbidities in frail and prefrail RA patients

patients are presented in Figure 1. The majority of patients from both groups had gastrointestinal diseases such as chronic gastroduodenitis, gastric and duodenal ulcers (75.6 % vs 67.9 %, p>0.05), and arterial hypertension (73.2 % vs 66.1 %, p>0.05). More frail patients had light anemia (41.5 % vs 17.9 %; p=0.025), probably due to higher RA activity.

Frail patients had higher prevalence of CVD (41.5 % vs 10.7 %, p=0.008) compared with nonfrail. CVD comorbidities in frail and prefrail RA patients are presented in Figure 2. Congestive heart failure (CHF) was the most prevalent CVD in all patients and was present in most frail patients compared with prefrail (34.1 % vs 7.1 %, p=0.010).

Frail paints had higher 10-year CV mortality according to SCORE (p=0.020). More frail patients were at a very high risk (≥10.0 %) of CV mortality compared with nonfrail (21 vs 17, p=0.04).

SCORE values correlated with age (r=0.67 and r=0.78, p<0.05), hypertension (r=0.43 and r=0.55, p<0.05), CVD (r=0.77 and r=0.58, p<0.05), CHF stage (r=0.60 and r=0.68, p<0.05), Charlson comorbidity index (r=0.70 and r=0.69, p<0.05) and was negatively associated with left ventricular ejection fraction (LVEF) (r=–0.50 and r=–0.64, p<0.05). In many prefrail patients SCORE risk correlated with LV myocardial mass index) (r=0.49, p=0.010), CRP (r=0.35, p=0.010), and was higher in slower patients (r=0.40, p=0.025) and lower dynamometry values (r=-0.34, p=0.005).

CV risk factors and some CV functional parameters in frail and prefrail RA patients are presented in Table 2.

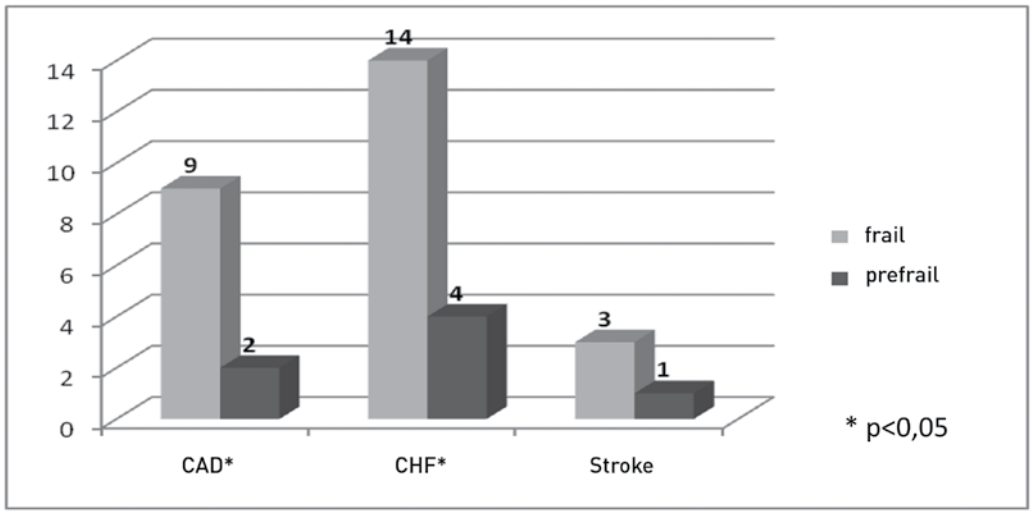

Figure 2. Cardiovascular disease in frail and prefrail patients RA

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Table 2. **Cardiovascular risk factors in frail and prefrail patients with RA**

Parameters	Frail (n=41) Me [Q25; Q75]	Prefrail (n=56) Me [Q25; Q75]	p
BMI, k^2	27.0 [23.6; 31.4]	27.4 [24.9; 31.9]	1.005
Overweight, abs	8	20	0.060
Obesity, abs.	14	21	0.085
Lack of physical activity, abs.	19*	0	0.003
Smokers. abs.	7	9	1.000
Alcohol misuse, abs.	2	0	0.070
Total cholesterol, mmol/l	4.5 [4.0; 5.4]*	5.2 [4.7; 6.0]	0.009
LDL, mmol/l	2.5 [2.2; 3.1]	3.0 [2.8; 3.4]	1.035
HDL, mmol/l	1.6 [1.2; 2.0]	1.3 [1.2; 1.7]	0.900
Hyperuricemia, abs.	3	7	0.550
SBP, mmHg	140 [130; 150]	140 [130; 150]	0.060
LVMM, ^{2}	136 [125; 164]*	120 [108; 132]	0.004
LVEF, %	58 [56; 64]	61 [58; 64]	1.150

Note. *BMI — body mass index (k^2); LDL — low-density lipoproteins (mmol/l); HDL — high-density lipoproteins (mmol/l); SBP — systolic blood pressure (mmHg); LVMM — left ventricular myocardial mass (^{2}); LVEF — left ventricular ejection fraction (%).*

Independently from the frailty phenotype most patients in both groups were overweight or obese; higher BMI values were identified in frail individuals with low physical activity (r=0.38, p=0.010). Frailty was also associated with lower total cholesterol levels (TC), unintentional weight loss (r=-0.34, p=0.005). Higher levels of TC in frailty were seen in younger individuals (r=-0.38, p=0.008) with normal nutritional status (r=0.55, p=0.002) and lower CRP (r=-0.54, p=0.040). In prefrail patients, low-density lipoprotein levels (LDL) correlated with systolic BP (r=0.73, p=0.020) and normal nutritional status (r=0.48, p=0.025). Irrespectively from baseline BP frail patients had higher LV myocardium mass index. In both groups this parameter correlated with Charlson comorbidity index (r=0.40 in frail, r=0.47 in prefrail, p=0.001). Hypertension in prefrail patients correlated with 4 m walking time (r=0.38, p=0.005).

Discussion

In accordance with the results of our previous studies that used L.P. Fried phenotype model [13], frailty syndrome was often seen in patients with RA including those younger than 60 years [6, 8]. As in our previous research, frailty prevalence in RA (40.6 %) was significantly higher than in other geriatric patients — 4–11 % [8]. In our study, prevalence of frailty was, however, higher than in the foreign studies — 15.0–23.4 % [6–9]. These differences can be due to enrollement of older patients with higher RA activity and CVD comorbidity burden. The prevalence of prefrailty was 55.4 % in RA patients, which is similar to that of patients without RA (40–55 %) [6, 13]. According to our results, frailty in RA is associated with older age, higher disease stage and activity and severe functional limitations. Frail RA patients have more motor deficits such as decreased hand drip strength, walking speed, less physical activity, and poor nutrition. Functional deficits in patients enrolled in our study are similar to the results of Andrews J. S., et al. (2017).

Frail patients with RA have higher burden of CV comorbidities that, probably, play a role in the development of this syndrome. The most prevalent comorbidities were one associated with atherosclerosis: coronary artery disease and CHF. Myocardial inflammation is also an important factor of CHF development in RA. Lack of physical activity and hypertension were the key risk factors in frail RA patients; hypertension and obesity — in prefrail. The majority of frail patients with RA had very high risk of CV mortality according to SCORE. At the same time, CV mortality in these patients wasn't associated with hypercholesterinemia. This phenomenon can be defined as «lipid paradox"»described by Myasoedova E., et al. (2011). Lipids can be paradoxically associated with CV mortality risk in RA in the presence of increased levels of proinflammatory markers when lower levels of LDL are associated with higher risk of CV mortality [15]. According to our results, CV mortality risk in frail RA patients is higher in individuals with higher disease activity and levels of CRP compared with prefrail patients. It can be supposed that an increase of anti-inflammatory cytokines that is seen both in active RA and in the presence of severe comorbidities causes LV myocardial remodeling (hypertrophy) in frail patients with RA compared with prefrail.

Limitations of this study include a small sample and an absence of control group that would include nonfrail patients with RA. However, our study was the first in Russia to describe the problem of frailty in RA. Moreover, we were the first to investigate the association between CVD and frailty in RA.

Conclusion

The prevalence of frailty and prefrailty is 40.6 % and 55.4 % in patients with RA. It can be present event in patients younger than 60 years. Prefrailty progression into frailty is associated with older age, higher disease activity and radiographic stage of RA and high burden of CV comorbidity and nutritional deficits. Frail RA patients have more physical deficits such as reduced hand grip strength, walking speed and lower functional status according to HAQ-DI. Frail RA patients also have higher burden of CV comorbidity and higher values of an absolute 10-year CV mortality risk according to SCORE with a tendency to lower levels of cholesterol ("lipid paradox" phenomenon). CV risk factors in frail patients include older age, hypertension, and lack of physical activity, in prefrail patients — hypertension and obesity.

Conflict of interest: none declared.

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