ORIGINAL RESEARCH

Assessing the multimorbid profile (CIRS) in rheumatoid arthritis. First results

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Objective: *to assess the presence and nature of multimorbidity in patients with rheumatoid arthritis (RA) and the impact of multimorbidity on disease activity.*

Patients and methods. *The investigation enrolled 117 patients (mean age, 54.8±14.8 years) with RA according to the 2010 ACR/EULAR criteria, who had been examined and treated at the V.A. Nasonova Research Institute of Rheumatology in 2018–2019. The median disease duration was 5.0 [1.5; 9.5] years; the mean DAS28 score was 5.0±1.3. Documentation and anamnesis data were analyzed with emphasis on associated diseases. The Cumulative Illness Rating Scale (CIRS) was used to assess the profile of multimorbidity.*

Results and discussion. *The patients with RA had a high index of the spectrum of multimorbidity; comorbidity was detected in 96 (82%) cases. The median number of diseases in one patient was 2 [1; 4], the mean total CIRS score was 6.7±3.3; the median value was 2.5 [1; 6]. The number of comorbidities diagnosed before using the CIRS was significantly fewer (by 48%; p<0.01) than was found in the investigation conducted. Chronic kidney disease that occurred in almost half (42.5%) of cases was most commonly undiagnosed in the cohort under study; on average, every three patients were not found to have signs of metabolic syndrome (hyperglycemia in 29% and obesity in 13.5%) and chronic hypoxia (new-onset anemia verified in 24% of cases). There was a correlation of the quantitative equivalent of multimorbidity with the clinical and laboratory measures of RA activity, including the number of painful joints (r=0.39; p<0.001), overall patient assessment (r=0.37; p=0.03), physician's global assessment of disease activity (r=0.37; p<0.01), DAS28 (r=0.42; p<0.001), CDAI (r=0.37; p<0.001), SDAI (r=0.34; p< 0.001), HAQ (r=0.34; p<0.001). The total CIRS score did not differ in patients with early- and advanced- or end-stage RA: 6.6±3.5 and 6.7±3.3, respectively (p=0.9).*

Conclusion. *A systematic screening of multimorbidity should be carried out in all patients with RA. It is advisable to use the CIRS to estimate the prevalence of multimorbidity and its consequences.*

Keywords: *rheumatoid arthritis; activity; multimorbidity; CIRS; comorbidity.*

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Nowadays the particular interest is the study of rheumatoid arthritis (RA) as part of a kind of «multimorbid disease», which includes all chronic diseases acquired during life. Multimorbidity is defined as «the coexistence of two or more chronic diseases in one person». This is a holistic concept that takes into account all potential interactions of comorbidities and their impact on patient status [1].

The relevance for a detailed assessment of the patient's multimorbid profile is due to the fact that, despite the modern achievements of rheumatology (new methods for early diagnosis of RA, scientifically based treatment strategies, including using high-tech methods), it is not always possible to achieve a pronounced improvement in the patient's condition as a whole, to maintain it functional activity and thereby significantly optimize the long-term prognosis [2–4]. The prevalence of multimorbidity in RA, according to various authors, is approximately 50–60%. [5–7] In addition, data from national registries and population studies confirm the necessity for screening and prevention of multimorbidity in chronic inflammatory rheumatic diseases (RD) in real clinical practice, which was reflected in the latest EULAR recommendations [8].

Although there are various weighted indices, each of which to one degree or another takes into account the influence of individual conditions on the analyzed parameters (life expectancy, mortality, etc.), there is still no single generally accepted standard for assessing the multimorbid profile in patients with RD, including with RA [9, 10]. The most common and cited is the Charlson comorbidity index (CCI), developed in 1989 to assess the impact of concomitant chronic diseases on mortality, the number of outpatient visits, the probability of hospitalization, and long-term financial costs [11, 12]. Unlike CCI, the Cumulative Illness Rating Scale (CIRS) proposed by B.S. Linn et al. and later modified M.D. Miller et al. [13], takes into account not only all the diseases a patient has, but also their severity. Comparative studies have demonstrated the great prognostic value of this tool [7]. CIRS allows you to evaluate the existing disease in a particular patient, both at the time of examination and in anamnesis. In addition, using this scale it is possible to detect latent chronic syndromes: hematological, metabolic, nephrological, gastroenterological, to which both doctors and patients do not always pay attention. This is due to the fact that these conditions have not been diag-

nosed, as they have not yet transformed into specific nosologies or did not require regular concomitant therapy (in addition to treating the underlying disease).

Objective of this study is to assess the presence and nature of multimorbid pathology in patients with RA and its effect on disease activity.

Subjects and methods. The study included 117 patients with a reliable diagnosis of RA (ACR/EULAR 2010), who were consistently admitted for treatment at V.A. Nasonova Research Institute of Rheumatology in 2018–2019 (tab. 1). The median (Me) duration of the disease was 5.0 [1.5; 9.5] years, and the time from diagnosis to hospitalization is 2.5 [0.1; 7.8] years. Most patients were middle-aged women (91.5%) with moderate RA activity according to the DAS28 index and high activity on the CDAI and SDAI indices, positive for the rheumatoid factor (RF) and antibodies to the cyclic citrulline peptide (ACCP). Every 5th patient at the time of inclusion in the study had extra-articular (systemic) manifestations of RA, the most common of which were rheumatoid nodules (7.5%), polyneuropathy (5.6%) and Sjogren's syndrome (5.1%).

Table 1 *Clinical and immunological characteristics of patients with RA, (n=117)*

Index	Value
Gender, n (%):	
male	10 (8,5)
female	107 (91,5)
Age, years (M±δ)	54,8±14,8
Disease duration, years, Me [25; 75 percentiles]	5,0 [1,5; 9,5]
X-ray stage, n (%):	
I	4 (3,4)
II	82 (70,1)
III	21 (17,9)
IV	10 (8,6)
DAS28, M±δ	5,0±1,3
CDAI, M±δ	24,4±11,3
SDAI, M±δ	26,6±12,3
Extraarticular manifestations, n (%)	23 (19,7)
Laboratory Markers:	
ESR according to Westergren, mm / h, M±δ	26,3±21,7
CRP, mg / l, Me [25th; 75th percentiles]	8,3 [3,4; 20,7]
IgM RF, units / ml,Me [25th; 75th percentiles]	42 [9,5; 127,8]
ATsPP, u / ml, Me [25th; 7th percentile]	73 [0,1; 216]
HAQ, M±δ	1,2±0,6
EQ-5D, M±δ	0,45±0,29

Glucocorticoids (GC) were received by 44% of patients. Me dose of HA in terms of prednisone was 5 [2.5; 10] mg / day, the duration of taking GC – 24 [6; 96] months At the time of inclusion in the study, 71% of patients used basic anti-inflammatory drugs (NSAIDs, in 50% of cases – methotrexate), 20.5% – genetically engineered biological drugs (GEBD).

To assess the quality of life of patients with RA, the EQ-5D questionnaire was used, its score averaged 0.45±0.29, and Me – 5.2 [0.08; 0.59]. Functional status was determined by HAQ, the average value of HAQ – 1.2±0.6.

Evaluation of multimorbid pathology was performed using CIRS, according to which concomitant pathology is classified according to 14 organ systems: heart; arterial hypertension – AH (only the severity of AH is taken into account, organ damage is assessed in the appropriate sections); vascular system (blood, blood vessels and cells, bone marrow, spleen, lymphocytes); respiratory system (lungs, bronchi, trachea below the level of the larynx); eyes and ENT-organs; upper gastrointestinal tract (GIT); lower gastrointestinal tract (small intestine, hernia); hepatobiliary system (liver and biliary tract); kidneys genitourinary system; musculoskeletal system and skin; central and peripheral nervous system; endocrine system; mental and behavioral disorders (documented). Identified violations, depending on the severity, were scored from 0 to 4 [7, 13]: 0 – there is no pathology affecting this system; 1 – mild pathology or pathology was in the past (cured); 2 – moderate disturbances in the system, leading to a moderate decrease in the patient's functional ability and/or for correction, which require the first line of therapy (or periodic administration of drugs); 3 – severe violations in the system that caused a significant decrease in the patient's functional ability and/or difficult to control chronic problems requiring systematic administration of drugs; 4 – disorders in the system are extremely serious, and/or requiring immediate treatment, and/or insufficiency, and/or severe organ functional failure.

The score can theoretically vary from 0 to 56, although high values are unlikely, since they suggest severe organ failure in several systems, incompatible with life. To assess the existing violations, we used the total score (the total score for each of the 14 categories), determined the total number of categories (systems) involved and the multimorbidity index (the number of categories with a score of ⩾2 points or more) [13].

For the CIRS assessment, the anamnesis of each patient was studied (with the appropriate documentation), and the main laboratory examinations used in routine clinical practice were performed: a general blood test with counting of formed elements, a biochemical blood test, including electrolytes, renal and hepatic indices, and serum iron, thyroid hormones (if you suspect a thyroid dis-

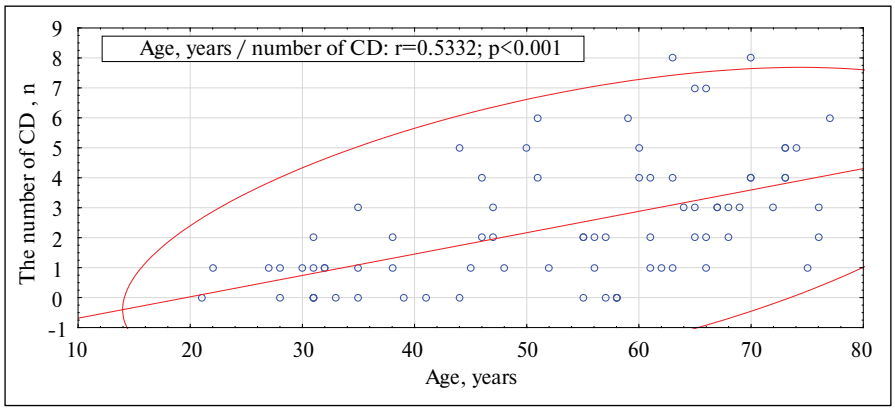

Fig. 1. *The dependence of the number of concomitant diseases (CD) on the age of patients*

ease), cholesterol, glycated hemoglobin (in the presence of diabetes mellitus, diabetes), glomerular velocity determination th filtration by MDRD and electrocardiography. CIRS were filled prior to the correction of RA therapy.

Statistical processing was performed using the Statistica program, version 10.0 (StatSoft). To describe the qualitative data, the absolute and relative frequencies (in percent) were used, the quantitative data were the mean (M) with standard deviation (?) or Me with the interquartile range [25th; 75th percentile] in the case of parameters whose distribution was different from normal. Comparison of groups was performed using t-student test. For parameters whose distribution differed from normal, when comparing two groups, the Mann–Whitney criterion was used; when comparing three or more groups, the Kruskel–Wallis criterion was used. Correlation analysis was performed according to the Spearman method. Differences were considered statistically significant at $p<0.05$.

Table 3 *Patient distribution according to CIRS value, (n=117)*

CIRS General Account	n	%
2	12	10,3
3	11	9,4
4	9	7,7
5	15	12,8
6	14	12
7	11	9,4
8	17	14,5
9	7	6
10	5	4,3
11	3	2,5
12	6	5,1
13	4	3,4
14	1	0,85
15	1	0,85
18	1	0,85

The average total score of CIRS was 6.7±3.3 points, the maximum score was 18, the minimum score was 2; The multimorbidity index is 2.5 [1; 6], the maximum number of categories with a score of ⩾2 points is 6, the minimum is 1. In the table. Figure 3 shows the distribution of patients according to the total CIRS score. It should be noted that the patient whose figure was the highest (18 points), had severe organ failure and died from acute renal failure.

The total CIRS score did not differ in patients with early (6.6±3.5) and advanced or late (6.7±3.3; p=0.9) stages of the disease.

Table 2 *Chronic pathology first detected using the CIRS index (n=117)*

Pathology	Before CIRS Examination		After a CIRS examination		Δ, %
	n	%	n	%	
Anemia	17	14,5	45	38,5	24
Hyperglycemia	6	4	39	33	29
Hypercholesterolemia	21	18	45	38,5	20
Obesity	11	9,5	27	23	13,5
Hypothyroidism	4	3,5	7	6	2,5
Lung damage	0	0	14	12	12
AH	51	44	56	48	4
CKD	0	0	50	42,5	42,5

Results. When using CIRS, concomitant pathology was diagnosed in 96 (82%) patients with RA, and Me, the number of such disorders was 2 [1; 4]. Their number ranged from 0 to 8 and increased in direct proportion to the age of the patients (Fig. 1).

The number of concomitant diseases diagnosed in patients with RA before using CIRS was significantly lower (by 48%; $p<0.01$) than the results of our study showed. Most often, the following disorders were observed in patients at the time of inclusion in the study: AH in 44%, anemia in 14.5%, hypercholesterolemia in 18%, obesity in 9.5%, thyroid disease in 11.5% (hypothyroidism criterion – in 3.5%) and diabetes – in 4%. CIRS allowed for the first time to identify chronic pathology, which is presented in table. 2. The results reflect the cautiousness of doctors regarding comorbid cardiovascular diseases in RA: only 4% of patients were diagnosed with hypertension for the first time. At the same time, before inclusion in the study, no patient with RA revealed chronic kidney disease (CKD), which occurred in almost half of the cases (42.5%). On average, every third person had no previous signs of metabolic syndrome (hyperclycemia in 29%, obesity in 13.5%) and chronic hypoxia (anemia first diagnosed was verified in 24% of cases).

Table 4 *RA activity indicators depending on the presence or absence of multimorbidity*

Index	Multimorbidity		p
	absence (n=21)	presence (n=96)	
Age, years, M±δ	45,5±10,9	57,0±14,8	<0,01
TJC28, M±δ	4,8±3,4	5,8±4,3	0,4
SJC28, M±δ	5,5±4,1	10,3±5,9	<0,01
GH, мм, M±δ	35,0±22,0	51,3±19,5	<0,01
OPR, мм, M±δ	40,5±18,4	53,9± 20,5	<0,01
CRP, mg /l, Me [25th; 75th percentiles]	18,9 [0,3; 173]	22,3 [0,3; 179]	0,3
ESR, mm /h, M±δ	20,8±15,5	27,1±19,7	0,2
ACCP, u /ml, Me [25th; 75th percentiles]	157,0 [0,1; 704,0]	137,9 [0,1; 1024,0]	0,8
RF, u /ml, Me [25th; 75th percentiles]	106,3 [9,5; 719,0]	112,9 [1,2; 1120,0]	0,5
CIRS, M±δ	3,0±1,0	7,5±0,98	<0,01

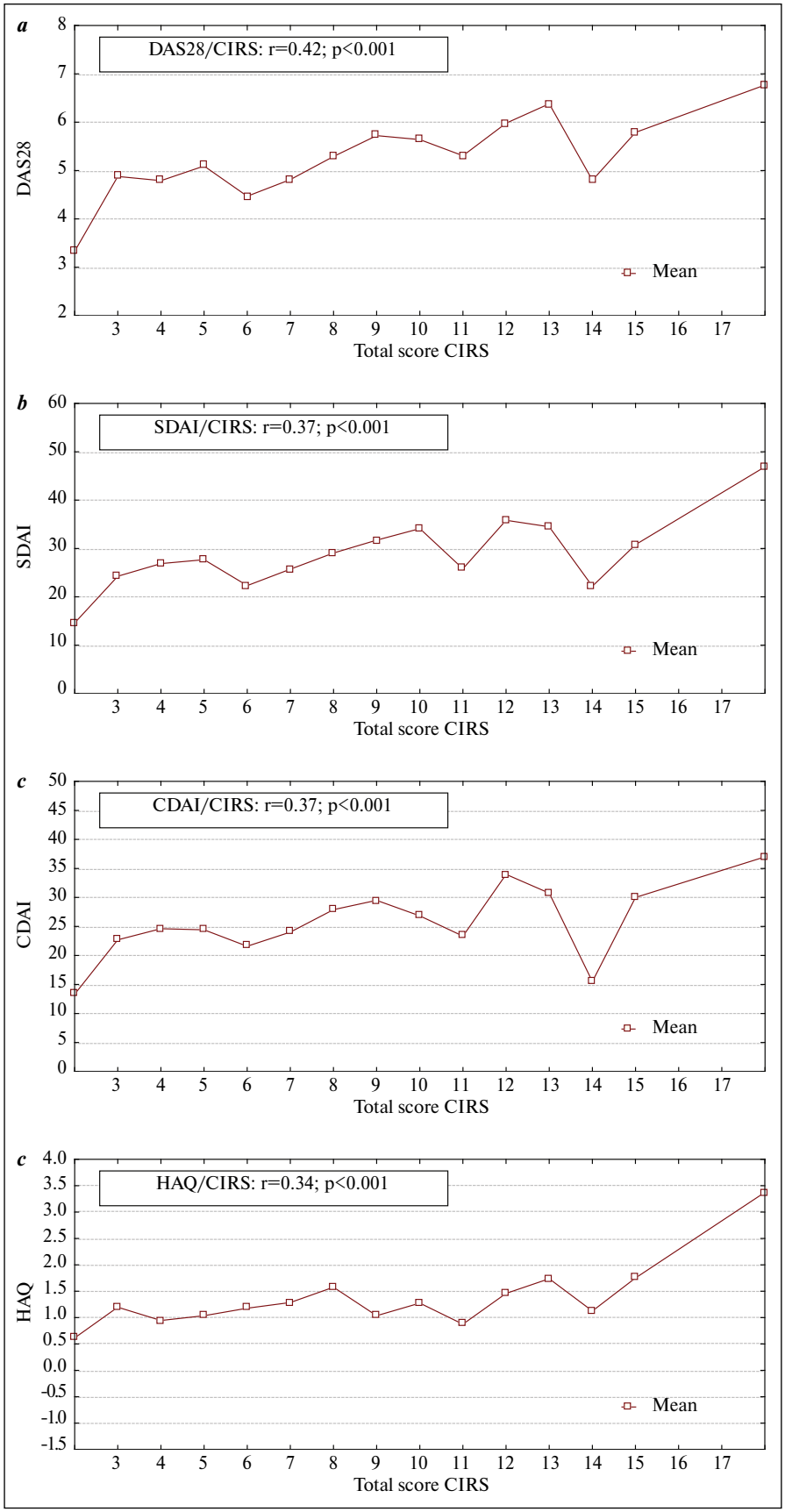

Fig. 2. *The dependence of the indices of activity of RA and HAQ on the value of CIRS*

Depending on the presence/absence of the multimorbid pathology, the patients were divided into two groups: with RA without comorbidity and with RA with comorbid disorders (Table 4). Patients with multimorbid pathology (CIRS 7.5±0.98 points) compared with the group without comorbidity were older (57 and 45.5 years respectively), had the greater number of tender joints (0–28) (TJC28), a higher overall patient rating (OPR) and a general assessment of the patient global health assement of the disease by the doctor (GH), $p<0.01$. However, such indicators of RA activity as ESR, CRP, ADC and RF levels, as well as the number of swollen joints (0–28) (SJC28) in both groups were comparable.

The CIRS index correlated with DAS28 ($r=0.42$; $p<0.001$), CDAI ($r=0.37$; $p<0.001$), SDAI ($r=0.34$; $p<0.001$) and HAQ ($r=0.34$; $p<0.001$; Fig. 2).

Discussion. Over the past decade, doctors of all specialties have increased interest in the concept of multimorbidity [6, 14, 15]. This is probably due to an aging population and the presence of multiple pathological conditions in one patient. For a rheumatologist who oversees patients with chronic systemic inflammatory diseases, multimorbidity is the rule rather than the exception.

According to the literature, the prevalence of multimorbidity among the general population is about 25% [5] and varies depending on age and assessment methods. In our study, for the first time in Russia, CIRS was used to characterize the multimorbid profile of patients with RA, which allowed us to identify not only the diseases recorded in the patient at the time of the examination, but also the risk factors for the development of multimorbidity in the long term.

In recent years, CCI has been widely used. When determining CCI in patients with RA, the number of concomitant diseases is on average 1.6 and increases with age and duration of illness [16], which is not consistent with the results of this study, in which the average number of chronic diseases per 1 patient with RA was 6.5 and the multimorbidity index is 2.5. And this is not accidental, since this technique has some drawbacks: the severity of many diseases and the presence of a number of chronic disorders prognostically important for a patient with RA, including hypertension, osteoporosis, obesity, and depres-

sion, are not taken into account when determining CCI multimorbidity [7].

When discussing the problem of multimorbidity in patients with RA, it has already become a tradition to pay attention primarily to cardiovascular diseases [16–18], which was also demonstrated in our study. At the same time, CIRS allowed us to identify previously undiagnosed CKD (both a clear disease and a latent stage of kidney damage), which in itself is a powerful risk factor for the development of any manifestation of cardiovascular disease. We have shown that, on average, every 4th patient already has, but has not yet been diagnosed, signs of metabolic syndrome and chronic hypoxia, which are not only risk factors for the development of multimorbidity, but can further aggravate the course of RA with the formation/progression of body dysmetabolism as a whole [19, 20].

To C.I. Daien et al. [21] 200 patients were included, including 157 with RA. The most common diagnosed comorbidities were hypertension (26%) and diabetes (7.5%). Screening showed that 61.5% of patients (95% confidence interval 54.6–67.9%) showed at least one previously undetected or uncontrolled disease, including diabetes (6%), hypertension (20.6%), dyslipidemia (16.1%), atherosclerosis (6.5%) and aortic aneurysm (5.5%). In our study, hypercholesterolemia was observed in 38.5% of patients, first detected in another 20%, hyperglycemia in 33%, first detected in 28%, while a reliable diagnosis of diabetes was relatively rare – in 4%, anemia – 38.5%, previously undiagnosed – 24%, obesity – 23%, first detected – 13.5% of patients. The research results confirm the need for screening for multimorbidity in chronic inflammatory rheumatic diseases, according to the recommendations of EULAR [8].

It should also be noted that the presence of multimorbidity can cause a significant distortion of the result of the assessment of inflammatory activity [18]. The search for a «therapeutic key» for suppressing the immune-inflammatory processes in RA has been carried out by rheumatologists all over the world for decades. However, despite the creation of a wide range of both NSAIDs and GEBD, more and more works have recently appeared demonstrating the insufficient effectiveness of the therapy and the preservation of the inflammatory activity of DAS28, CDAI and SDAI against the background of active treatment [22–24]. Multimorbidity can significantly affect the value of these indices, which was demonstrated in our study. Thus, with an increase in the number of concomitant diseases in patients with RA, an almost linear increase in the values of GAAD and OPR was observed, independent of the clinical and laboratory parameters of disease activity (TJC28, ESR, CRP). Multimorbidity also had a negative effect on the outcome of the assessment of the quality of life associated with health and functional status, independent of the activity of the disease. E. Loza et al. [14] noted an increase in the HAQ index simultaneously with an increase in the numerical equivalent of the multimorbid profile, which was also shown in our study.

These results dictate the need to search for the causes of this phenomenon and resolve the issue of tactics of using CIRS in patients with RA. In this case, apparently, it is necessary to take into account the presence of a relationship between the assessment of the severity of pain, including articular, and the concomitant multimorbid profile. This phenomenon has been repeatedly discussed in the literature, but it requires further study [1, 24, 25].

Conclusions. Thus, from both practical and scientific points of view, it is of interest to study the effect of multimorbidity on the activity, course, selection of adequate therapy, and therefore on the prognosis of RA. Systematic screening for multimorbidity should be performed in each patient with RA. It is advisable to use CIRS in subsequent studies to assess the prevalence of multimorbidity and its consequences. CIRS allows you to more accurately determine the contribution of each chronic disease or syndrome to the development of «multimorbid disease».

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