ORIGINAL INVESTIGATIONS

Indicators of rheumatoid arthritis disease activity. An association with a patient's psychological status

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Objective: *to study of the relationship between psychological factors and indicators of rheumatoid arthritis (RA) disease activity in patients who have been followed up for a long time after initiation of treat-to-target therapy.*

Patients and methods. *The investigation enrolled 38 RA patients (29 women and 9 men) aged 33 to 80 years (mean age, 56.5Ї}12.5 years) with a mean disease duration of 6.0Ї}0.9 years. All the patients underwent clinical examination; the following parameters were recorded: patient global assessment; physician's global assessment; pain visual analogue scale (VAS), by measuring in millimeters; number of painful joints (NPJ), and number of swollen joints (NSJ). The investigators determined functional status with the Health Assessment Questionnaire (HAQ), quality of life with the 36-Item Short Form Health Survey questionnaire (SF-36), the nature of pain by the painDETECT questionnaire (PDQ), and the presence of anxiety and depression with the Hospital Anxiety and Depression Scale (HADS). The patients also filled out the Resilience (Res) Questionnaire (RQ) and the General Self-Efficacy ((GSE) Scale. Disease activity was evaluated by DAS28, CDAI, and RAPID3 scores.*

Results and discussion. *RA disease activity was high in 4 patients, moderate in 21, and low in 9, and 4 patients had DAS28 remission. The average scores of RQ, its individual components, and GSE scale were comparable with the corresponding population scores for this age group. The patients who had RQ scores below the average group ones were noted to have significantly higher scores of patient global assessment; physician's global assessment, NPJ, NSJ, CDAI, and RAPID3 than in those who had moderate and higher RQ scores. The similar trend was traced for individual Res components, such as involvement (INV), control (CONT), and risk acceptance (RA). However, the revealed differences in these indicators failed to reach statistical significance. There was no correlation between the measures of inflammatory activity and the result of GSE. The patients with subclinical and clinical anxiety and depression had significantly lower RQ, INV, and CONT scores than those who did not have anxiety or depression, whereas RA and GSE did not differ significantly in these groups. There was a significant positive correlation of Res, INV, and CONT with the quality of life, as assessed by SF-36. The findings suggest that low RQ scores can decrease the efficiency of the therapy performed (due to the patient's poor compliance), on the one hand, and can corrupt the result of inflammatory activity assessment (due to the impact on a patient's perception of his/her illness), on the other hand.*

Conclusion. *The findings may suggest that there is a need to assess the psychological status of a patient when determining the level of RA disease activity.*

Keywords: *rheumatoid arthritis; activity rating; psychological status; vitality; self-efficacy.*
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Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints, the main manifestations of which are persistent arthralgias and progressive functional insufficiency [1]. Persistent autoimmune inflammation that develops in RA can also be accompanied by stiffness, weakness, fatigue, and the formation of irreversible joint changes [2]. Many patients have serious comorbid diseases in addition to RA, which can significantly worsen their condition [3].

More active use of synthetic traditional disease modifying anti-rheumatic drugs (DMARD), widespread introduction of genetically engineered biologic drugs (GMBD) and targeted DMARD into clinical practice can significantly increase the effectiveness of anti-rheumatic therapy [4]. Modern principles of RA treatment suppose the earliest possible prescription of DMARD and, first of all, methotrexate (MT), regular patient supervision, assessment of the dynamics of inflammatory activity with the help of quantitative methods, and timely correction of therapy taking into account its efficacy and tolerability. It is believed that this approach should provide a stable remission or low activity of the disease [5].

At the same time we have to clarify the concepts of remission and low activity of the disease, which now lack clear definition. When specialists try to determine the level of inflammatory activity and the effectiveness of therapy, they generally take into account laboratory parameters, joint count and those parameters that the patients evaluate by themselves. But even the dynamics of acute-phase reactants, which is supposed to be one of the most objective criteria, does not allow us to reliably assess the result of

treatment, since modern drugs such as interleukin 6 and Janus-kinase inhibitors can affect the results of laboratory tests to a greater extent than the clinical manifestations of the disease [6]. Joint count also does not always adequately characterize the patient's existing disorders.

Therefore, the parameters that reflect the opinion of the patient are of great importance for assessing the level of RA activity. However, in some cases, there is a discrepancy between the values of objective signs of inflammation and the assessment given by the patient [7]. This inconsistency may be due to imperfect objective parameters, as well as incorrect assessment of the patient, who does not always manage to differentiate the influence that chronic arthritis has on his health and factors that do not have a direct connection with inflammation. Meanwhile, to choose an adequate anti-rheumatic therapy, it is very important to determine correctly the level of inflammatory activity of the disease.

The presence of chronic changes in the musculoskeletal system and accompanying disorders has a powerful psychological impact on the patient and can cause the formation of a persistent negative emotional background, which contributes to the development of depression [8]. In turn, psychological status can have a significant impact on the patient's perception of existing disorders. The patient's assessment of his condition is an important component of quantitative methods for determining inflammatory activity, which are used to choose an appropriate drug therapy.

Current recommendations for RA treatment require the mandatory use composite disease activity measures to monitor the activity of RA and evaluate the effectiveness of therapy, but none of them is considered preferable [9]. According to EULAR experts, a mandatory component of the activity index is the joint count, which usually includes tender joint count (TJC) and swollen joint count (SJC) [10]. To date, three validated indexes that meet this requirement are widely used (DAS28, SDAI, and CDAI). The key components of each of them are patient global assessment (PGA) and TJC. The values of these parameters can be significantly affected not only by the inflammatory process, but also by central sensitization and psychological characteristics of the patient. Meanwhile, the relationship of traditional signs of inflammatory activity with the psychological status of the patient has not been studied well enough.

Table 1 *Clinical characteristics of patients*

Parameter	Value
Age, years, M±δ	56,5±12,5
Gender, female/male n	29/9
Duration of the disease, years M±δ	6,0±9,0
RF+ n	36
ACCP+ n	37
PGA mm on VAS M±δ	33,0±20,1
Pain mm on VAS M±δ	17,4±12,8
PhGA mm on VAS M±δ	28,8±15,9
SJC M±δ	2,6±2,7
TJC M±δ	4,7±3,3
ESR mm/h M±δ	17,4±12,8
DAS28 M±δ	3,8±1,1
CDAI M±δ	13,5±9,1
RAPID3 M±δ	8,3±5,9
HAQ M±δ	0,61±0,53
Body mass index kg/m^2 M±δ	26,1±5,3

The objective of this investigation was to study the relationship between psychological factors and signs of RA activity in patients who were observed for a long time after the appointment of therapy, which was carried out according to the treat to target strategy.

Material and methods

Our study included patients who were observed for a long time in the framework of REMARKA program. The target group consisted of 29 women and 9 men aged 33 to 80 years (average age 56.5±12.5 years) with a disease duration of an average of 6.0±0.9 years (table 1). At the beginning of observation, all patients had high inflammatory activity, and the duration of RA did not exceed 3 years. All patients were prescribed methotrexate (MT) subcutaneously at 10 mg/week with a rapid escalation of the dose to 20–30 mg/week. In cases when remission or a 17-point reduction in SDAI was achieved after 3 months, MT therapy was continued. If the treatment was not effective enough, a biological drug was added to the treatment. In case the first biologic drug was not effective enough, it was replaced with a second one with different mechanism of action. With the development of persistent remission, it was possible to cancel biologic, and continue treatment with MT. In the case of an exacerbation after the cancellation of biologic, therapy with the same drug was resumed.

The current study included patients who were prescribed such treatment at least 5 years ago. All patients underwent a clinical examination, PGA, physician global assessment (PhGA), assessment of pain in mm on a visual analog scale (VAS), TJC, SJC were registered. Functional status was assessed using the HAQ questionnaire, quality of life by SF-36, pain character by painDETECT, and presence of anxiety and depression by HADS. Patients also filled in Hardiness Survey (HS) and overall self-efficacy (SEF) questionnaires. Disease activity was assessed by DAS28, CDAI, and RAPID3. All patients signed an informed consent to participate in the study.

Statistical processing was performed using the Student's t-test and Spearman's correlation coefficient. The data are presented as the mean and standard deviation (M±δ).

Results

33 of 38 patients had advanced stage and 5 had late stage of RA. 36 patients were positive for rheumatoid factor (RF), 37 – for anti-cyclic citrullinated peptide antibodies (ACCP). 22 patients had 1, 16 – 2, and 1 – 3 functional class.

At the time of examination, 9 patients received MT and adalimumab (ADA), 2 – MT and certolizumab pegol (CP), 1 – leflunomide (LF) and ADA, 1 – LF and abatacept (ABT). In 11 patients monotherapy with MT, in 3 – with LF, in 2 – with sulfasalazine, in 1 – with AD, in 1 – with ABT and in 1 – with CP

was performed. 4 patients did not receive DMARD. 8 patients were treated with glucocorticoids.

Most patients had moderate or low disease activity (table 2).

13 patients had subclinically or clinically expressed anxiety (HADS>8), 4 – subclinically or clinically expressed depression (HADS>8). In 14 patients, the painDETECT questionnaire revealed probable or definite symptoms of neuropathic pain. 24 patients did not have these symptoms. The average values of HS and its individual components – – commitment (CMT), control (CT) and challenge (CLN) – were comparable with the corresponding population indicators for this age group (table 3). Overall SEF score for the group was 29.8±5.9 (in the population 31.3–33.2±4.6).

Patients with a lower-than-average HS had significantly higher values of PGA, PhGA, SJC, TJC, CDAI, and RAPID3 than those with an average or higher HS level (table 4). A similar trend was observed for individual components of HS. However, differences in these components did not reach statistical significance. We did not find any connection between inflammatory activity indicators and the result of the overall SEF assessment.

There was a significant inverse correlation between HS, CMT and CT indicators and the severity of anxiety and depression according to HADS (table 5). At the same time, we did not observe a significant assosiation of CLN and SEF with the values of anxiety and depression.

In the presence of subclinically and clinically expressed anxiety and depression, the HS, CMT and CT were significantly lower than in their absence, while the CLN and SEF in these groups did not differ significantly (Fig. 1, 2). The presence of neuropathic pain was also associated with a significant decrease in the HS, CMT and CT in the absence of significant differences in the CLN and SEF (Fig. 3)

We observed a significant positive correlation of HS, CMT, and CT with quality of life, which was evaluated by SF-36 (table 6). These parameters correlated with almost all SF-36 scales. At the same time, we were unable to find a significant association of CLN, SEF with the severity of anxiety and depression on HADS, as well as with the quality of life.

Table 2 *Activity of the disease, n*

Activity	Index		
	DAS28	CDAI	RAPID3
High	4	7	9
Moderate	21	13	13
Low	9	17	7
Remission	4	1	9

Table 3 *Hardiness in the group of RA patients and in the General population*

Parameter	RA M±δ	General population M	
Age, years	56,5±12,5	>35	<35
Hardiness	81,2±21,7	79,8	85,2
Commitment	37,8±9,3	36,6	38,0
Control	27,7±8,8	27,6	29,8
Challenge	17,0±8,1	15,5	17,3

Table 4 *Assosiation of hardiness and its components with inflammatory activity indicators. M±δ*

Parameter	Hardiness		Commitment		Control		Challenge	
	⩾81	<81	⩾38	<38	⩾28	<28	⩾17	<17
Pain mm	27,4±14,5	45,3±24,1**	30,9±18,2	40,8±23,7	28,2±14,6	42,1±24,2*	32,5±17,0	39,3±25,1
PGA mm	26,0±16,9	40,8±21,0*	29,2±20,6	36,8±19,5	28,2±17,4	36,9±21,8	32,3±19,7	33,6±21,3
SJC	1,7±1,8	3,6±3,2*	2,0±2,3	3,2±3,0	1,8±1,8	3,2±3,2	2,9±3,2	2,3±3,1
TJC	3,6±2,3	6,0±3,9*	4,0±3,0	5,5±3,6	3,7±2,0	5,6±4,0	5,1±3,7	4,4±3,0
PhGA mm	24,0±14,0	34,1±16,7*	25,5±15,9	32,1±15,7	25,8±14,2	31,1±17,2	28,9±16,0	28,6±16,4
CDAI	10,4±6,3	17,1±10,5*	11,4±8,1	15,6±9,7	10,9±6,4	15,7±10,5	14,1±9,6	12,9±8,7
RAPID3	5,6±3,5	11,3±6,7**	6,5±4,8	10,1±6,6	5,5±3,8	10,6±6,5**	7,6±5,4	9,0±6,5
DAS28	3,5±0,8	4,1±1,3	3,7±1,0	3,8±1,3	3,5±0,8	4,0±1,3	3,8±1,1	3,7±1,2
HAQ	0,47±0,50	0,77±0,53	0,51±0,55	0,72±0,50	0,52±0,51	0,69±0,55	0,57±0,53	0,65±0,64

* – p<0,05, ** – p<0,01

Table 5 *Association of psychological factors with the severity of anxiety and depression according to HADS (Spearman correlation coefficient)*

Parameter	Anxiety	Depression
HS	-0,749**	-0,615**
CMT	-0,799**	-0,630**
CT	-0,698**	-0,539**
CLN	-0,310	-0,246
SEF	-0,237	-0,153

** – p<0,01

Discussion

Currently, we are not able to assess the activity of RA relying only on objective indicators. By themselves, they do not allow us to measure the severity of the patient's inflammatory changes confidently. Therefore, the parameters that are evaluated with the patient's participation are of great importance for determining the level of RA activity. These include pain, PGA, TJC, functional status assessment, and PhGA. Values of these parameters can be influenced not only by the severity of inflammatory changes in the joints, but also by the patient's perception of the disease.

Approximately 30% of RA patients have persistent pain, fatigue and functional disorders in spite of low values of objective signs of inflammation [11]. This discrepancy shows the need for a more detailed assessment of the patient's status, which will allow doctors to take into account the influence of additional factors that are not directly related to the patient's existing inflammatory changes. One of the most significant factors is the psychological status of the patient. The presence of a chronic disease with an uncertain prognosis and accompanied by persistent pain syndrome often leads to the development of anxiety and depressive disorders, which correlate with the activity of the disease and are usually considered as comorbid pathology [12].

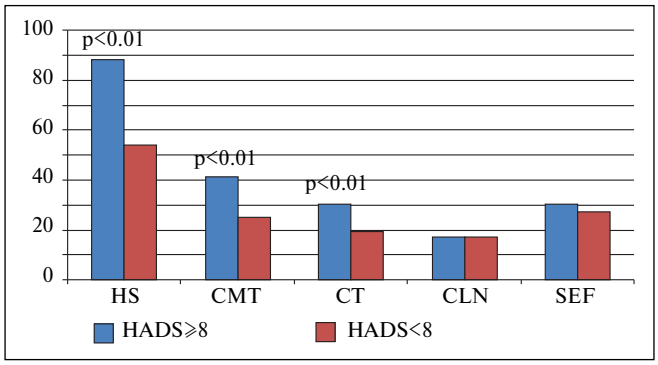

Fig. 1. *Relationship of psychological factors to the assessment of anxiety severity by HADS*

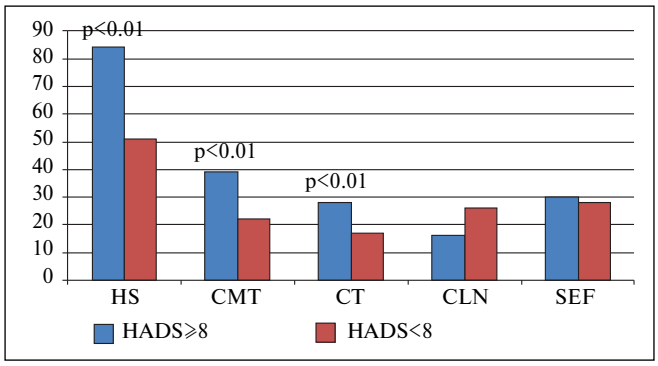

Fig. 2. *Relationship of psychological factors to the assessment of depression severity by HADS*

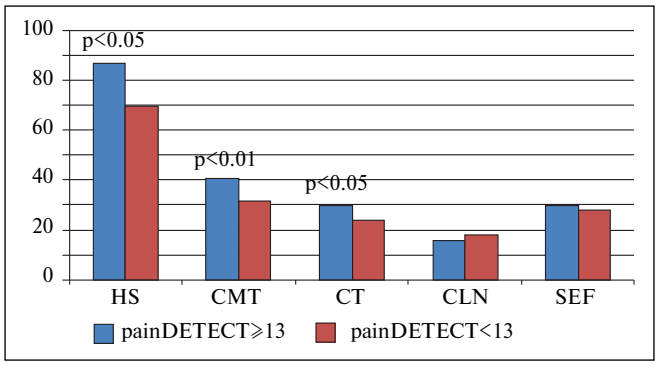

Fig. 3. *Relationship of psychological status factors with the presence of signs of neuropathic pain*

The severity of psychological distress, which was assessed using questionnaires describing the patient's level of anxiety and depression, was one of the key factors determining PGA value in RA [13]. At the same time, the probability of anxiety and depression itself is largely determined by the psychological characteristics of the patient. For example, Ryan S. and McGuire G. [14] examined 317 RA patients using questionnaires describing pain, anxiety, depression, pain catastrophization, pain self-concealment, autonomy, relatedness, and competence. The authors showed that greater relatedness was associated with less depression, and greater autonomy was a predictor of less severe anxiety.

The study of the patient's HS may be essential for understanding the psychological characteristics of the patient. HS can be defined as a system of beliefs about oneself, about the world, and about one's relationship with the world [15]. Its application value is determined by the role it plays in dealing with stressful situations. HS is considered a key personal component that mediates the impact of stressful factors on somatic and mental health, as well as on the success in all fields.

It is customary to distinguish three relatively autonomous components of the HS: CMT, CT, and CLN. The value of each of them prevents the emergence of internal tension in stressful situations. CMT characterizes a person's confidence that involvement in what is happening gives him the maximum chance to find something meaningful and interesting for him. CT is the belief that the struggle allows you to influence the result of what is happening. CLN is a person's belief that everything that happens to him contributes to his development. HS components are formed in childhood and adolescence. Later, they can be developed with special training.

The HS test is an adapted Hardiness Survey that was developed by Salvatore Maddi [15]. It was translated into Russian and validated in the Russian population. With the help of this questionnaire a clear inverse relationship was found between the severity of HS components and the probability of developing a serious disease within a year after the occurrence of a stressful situation. With low severity of all three components of HS, the probability of disease was 92.5%, with a high level of one of the components – 71.8%, with a high level of two components – 57.7%, with a high level of all three components – 1.1% [16]. HS is particularly important in severe and terminal diseases [17]. For such patients, it helps them to adapt effectively to their condition and to avoid despair and feeling of helplessness.

In populational studies HS was the same for men and women and did not depend on education, but it decreased slightly with age [15]. In our group of RA patients, the values of HS and its individual components were comparable with the population values for the corresponding age group. This sug-

Table 6 *Assosation of psychological factors with the quality of life of RA patients*

Parameter	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
HS	0,372*	0,504**	0,384*	0,527**	0,780**	0,513**	0,410*	0,759**	0,375*	0,690**
CMT	0,350*	0,476**	0,321	0,530**	0,760**	0,525**	0,486**	0,805**	0,335*	0,740**
CT	0,367*	0,504**	0,387*	0,548**	0,779**	0,489**	0,361*	0,734**	0,424**	0,651**
CLN	0,027	0,188	0,155	0,078	0,302	0,192	0,078	0,284	0,030	0,240
SEF	0,026	0,056	0,143	0,252	0,213	0,188	0,025	0,401*	0,052	0,261
Anxiety	0,030	0,011	-0,124	-0,041	0,142	0,054	0,014	-0,056	-0,057	-0,016
Depression	0,100	-0,013	0,008	-0,008	0,050	-0,066	0,087	-0,037	0,016	-00,71

* – p<0,05, ** – p<0,01, PF – physical functioning, RP – role physical, BP – bodily pain, GH – general health, VT – vitality, SF – social functioning, RE – role emotional, MH – mental health, PCS – Physical Component Summary, MCS – Mental Component Summary.

gests that the mere presence of chronic inflammatory joint disease for 5–6 years did not have a significant impact on the HS. At the same time, we observed a significant relationship between HS and disease activity signs. Thus, in patients who had a lower-than-average HS in the group, the values of PGA, SJC, TJC, CDAI and RAPID3 were significantly higher than in patients with higher levels of HS.

A similar relationship can also be observed for individual components of HS. Reduced values of CMT and CT were associated with a significant increase in inflammatory activity signs. This connection may be due to various reasons. On the one hand, low HS is associated with low resistance to stressful situations. It can negatively affect the patient's perception of their disease and cause an overestimation of the existing discomfort. On the other hand, low HS may be associated with less perseverance whet the patient has to deal with drug availability issue, irregular visits to hospital and inaccurate adherence to medical recommendations.

In favor of this assumption is the fact that HS affected not only the parameters that the patient himself estimates, but also the SJC, which is an objective indicator of inflammatory activity. Low HS also served as a prerequisite for the development of anxiety and depression. Our patients with subclinical and clinical signs of anxiety and depression had significantly lower HD than in the absence of these signs. In turn, anxiety and depression can significantly affect the value of inflammatory activity signs and, above all, the PGA. Thus, Challa N. V. et al. found a link between PGA and the severity of anxiety and depression [13]. Our patients also had a significant correlation of PGA with signs of anxiety and depression, which were evaluated using the HADS questionnaire. At the same time, we observed a significant inverse correlation of HS with the HADS anxiety and depression score.

In addition, low HS was associated with the presence of signs of neuropathic pain, which may be due to the development of neurological pathology or central sensitization. We did not perform a neurological examination and therefore cannot completely rule out the presence of neurological disorders in our patients. However, there were no obvious signs of tunnel syndromes during objective examination, and the presence of polyneuropathy in this group is unlikely, since its development is associated with vasculitis due to high inflammatory activity [18]. Meanwhile, in our patients, neuropathic pain was usually observed against the background of moderate or low RA activity. Only 2 out of 14 patients with neuropathic pain had high disease activity according to DAS28. Therefore, the most likely cause of its occurrence is central sensitization. The data we have obtained suggest that a reduced HS may contribute to the formation of such changes.

We also observed a significant correlation of HS and its individual components with the quality of life of patients, which was evaluated by SF-36. HS correlated with all the scales of SF-36, and this dependence may be due to both the patient's perception of their disease, and higher inflammatory activity, which was recorded at low values of HS.

Another tool for assessing the psychological status of the patient, which was analyzed in this study, is the overall SEF test. The concept of SEF was developed by A. Bandura, who defined it as a person's confidence that he or she can perform a certain task and get the desired result [19]. SEF is considered to be the main driving force for the development of motivation and psychological well-being. A high SEF facilitates the decision-making process and is associated with a greater willingness to take risks. Low SEF levels are associated with depression, anxiety, and helplessness. Martinez-Calderon, J. et al. [20], who analyzed 11 investigations evaluating SEF in RA, reported that in 4 out of 5 studies a higher level of SEF was associated with a lower intensity of pain, in 3 out of 4 studies high SEF was associated with more favorable functional status, and in 3 studies a significant correlation of SEF with the quality of life of patients was observed.

The overall SEF scale was developed by Schwarzer R. and Jerusalem M. [21]. Later it was translated into Russian and validated in the Russian population [22]. In our group of patients, SEF, as well as HS, was comparable to the populational level. However, unlike the case of HS, we could not find a significant association of SEF with signs of inflammatory activity, anxiety, depression, and quality of life of patients. It is possible that this result will be due to the relatively small number of patients included in this study. At the same time, it should be noted that even in such a small sample, we observed a clear connection between HS and key signs of inflammatory activity, the severity of psychological distress and the quality of life of patients.

Currently, signs of inflammatory activity, which are evaluated with the participation of the patient, are one of the main com-

ponents of quantitative methods for determining the activity of RA. The patient's perception of their disease can have a significant impact on the outcome of their assessment. At the same time, the discomfort that the patient experiences depends not only on the existing inflammatory changes, but also on a number of other factors. In this paper, we evaluated the status of patients who were prescribed active anti-rheumatic therapy in a timely manner at an early stage of RA in full compliance with current recommendations for the treatment of this disease. In the course of follow-up in real clinical practice, most of them did not achieve a stable decrease of inflammatory activity to the target level (remission or low activity).

Our results suggest that one of the significant factors determining the lack of effectiveness of therapy may be a low level of HS in patients, which does not allow them to effectively adapt to a stressful situation. We observed a significant relationship between HS and its individual components with the main signs of inflammatory activity and the quality of life of patients. In addition, low HS was also a predictor of anxiety, depression, and neuropathic pain. The obtained data suggest that a low HS may on the one hand reduce the effectiveness of the therapy (due to insufficient patient performance), and on the other hand distort the result of inflammatory activity evaluation (due to the influence on the patient's perception of their disease).

Conclusion

Thus, further research is needed to develop recommendations to evaluate psychological factors which can influence the effectiveness of treatment and the assessment of inflammatory activity.

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