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Quality of Life and Physical Working Capacity in Pulmonary Sarcoidosis

Abstract

Objective To study the quality of life (QOL) and physical working capacity (PWC) in patients with pulmonary sarcoidosis. **Materials and methods.** Eighty patients with pulmonary sarcoidosis were examined (mean age 35 (39; 45) years), including 43 men (53.8 %) and 37 women (46.3 %). The duration of sarcoidosis was 3 (2; 4) years. Seventy-five percent of patients had pathologically proven sarcoidosis. All patients completed the SF-36 questionnaire; physical examination, chest computed tomography, spirometry and cardiopulmonary exercise testing (CPET) were conducted. PWC was determined according to the peak oxygen uptake (VO$_2$ peak) via CPET. **Results.** Thirty-six point three percent of patients had reduction of QOL (psychological and physical components of health). The most significant decrease of QOL was noted on the scale "general health" — 67 (47; 77) scores, "mental health" — 72 (54; 84) scores and "vitality" — 72.5 (50; 82.5) scores. Female patients (p=0.008) over 40 years of age (p=0.044) with clinically significant symptoms (p=0.012) and comorbidities (p=0.049) had a lower QOL. Patients with high or low QOL did not have differences in radiology stages, laboratory test results and lung function parameters. The female sex (OR 3.26, 95 % CI 1.15–9.23; p=0.026) and the clinical manifestations of sarcoidosis (OR 3.63, 95 % CI 1.06–15.47; p=0.041) were the independent factors of low QOL. Pulmonary sarcoidosis patients with exercise intolerance had the most significant reduction of the physical (p=0.037) and psychological components of health (p=0.033). **Conclusion.** Factors of QOL reduction in patients with sarcoidosis were female sex and clinically significant pulmonary sarcoidosis. In patients with low QOL, CPET can be used to determine the PWC and mechanisms of its reduction. The presented diagnostic algorithm will optimize the choice of therapy for patients with sarcoidosis.

Key words: pulmonary sarcoidosis, quality of life, physical exercise, cardiopulmonary exercise testing

DV — due value, QOL — quality of life, CPET — cardiopulmonary exercise testing, FEV$_1$ — forced respiratory volume in 1 sec, sGCS — systemic glucocorticosteroids, FVC — forced vital capacity, PWC — physical working capacity, VO$_2$ peak — peak oxygen uptake, SF-36 — SF-36 Questionnaire (Short Form Medical Outcomes Study 36)

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Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas with the activation of T-cells, excessive release of chemokines, proinflammatory cytokines, and damage to various organs [1].

Sarcoidosis more frequently affects respiratory organs (up to 95 %) and has diverse clinical manifestations. There is a high proportion of patients with an asymptomatic (up to 70 %) and/or benign course of sarcoidosis in which spontaneous remission is observed within 2 years from the onset of the disease. However, sarcoidosis can become chronic, and its progressive course may result in the development of permanent functional disorders that compromise the quality of life (QOL) and limit the physical working capacity (PWC) of patients [1].

Investigating the QOL is one of the essential tools to assess the subjective state of a patient. QOL is a multifaceted concept and covers the assessment of all areas of human activities. Modern medicine uses a narrower concept of "health-related quality of life", i. e., the assessment of parameters associated and not associated with the disease that make it possible to establish how the disease and treatment affect the patient's psychological and emotional state, and social status. QOL depends on the patient's ability to perform basic physiological functions, pain, and subjective perception of well-being, health or illness. QOL assessment tools include general and specific questionnaires [2]. It was shown that determining the patients' QOL in combination with other examination methods is of major clinical relevance and may be used to assess the treatment efficacy in different chronic diseases, including sarcoidosis [3].

Sarcoidosis affects the patients' psychophysiological state and self-perceived health status, irrespective of the severity of its symptoms. Studies on this issue show a reduction in the overall QOL level, as well as decreased physical and mental well-being, independence and social relationships scale scores [3, 4].

Currently, the study of physical working capacity (PWC) of sarcoidosis patients and the identification of its relationship with QOL is of particular interest. Marcellis R. G. et al. (2011) demonstrated that the QOL level in patients with sarcoidosis (assessed using the WHO questionnaire (WHOQOL-BREF)) varied depending on muscle strength (6-minute walk test, dynamometry of lower and upper extremity muscles) [5]. Pilzak K. et al. (2018) defined the relationship between the QOL in patients with sarcoidosis, as assessed using SF-36 Questionnaire (Short Form Medical Outcomes Study 36), and 6-minute walk test results [6]. The authors of the study noted that the PWC level was associated not only with QOL, but also with everyday physical activities [7].

Other studies used a more informative diagnostic technique to assess the PWC in patients with sarcoidosis, i. e., cardiopulmonary exercise testing with gas analysis (CPET). In particular, the PWC level determined by the peak oxygen uptake (VO_2 peak) dropped 20–30 % of the due values (DV) in patients with sarcoidosis, including those without pulmonary dysfunction. In addition, exercise tests reveal cardiac rhythm disorders, ventilation-perfusion ratio changes, enhanced alveolar-arterial oxygen pressure gradient and diminished breathing reserve in patients with sarcoidosis [1, 8, 9], which may affect the QOL as well.

Despite available literature data showing the reduced QOL and PWC in patients with sarcoidosis [7, 10], the relevance of these studies is limited. This is due to the small number of patients examined (30 to 200), non-homogeneous clinico-radiological phenotypes of sarcoidosis, use of different questionnaires for assessing the QOL and exercise tests for determining the PWC (6-minute walk test, treadmill test, isometric exercise testing, CPET) [2, 7, 10, 11]. Therefore, the objective of this study was to acquire additional knowledge and information about QOL and PWC characteristics in pulmonary sarcoidosis patients.

Materials and methods

The open-label, one-time, observational, comparative study was conducted at the City Clinical

Hospital No. 38 (Nizhny Novgorod). Eighty sarcoidosis patients aged 21 to 64 years (35 (29; 45) years) were examined. The male to female ratio was 1:0.9 (males — 43 (53.8 %); females — 37 (46.3 %)). The disease duration was 3 (2; 4) years. Sixty (75 %) patients had histologically confirmed diagnosis. The inclusion criteria were as follows: pulmonary sarcoidosis diagnosed in accordance with the Federal Guidelines of sarcoidosis diagnosis and treatment [1], age of 18–65 years, patient's consent to participate in the study. The exclusion criteria: PWC-limiting acute respiratory diseases and severe chronic non-contagious diseases at the time of examination (NYHA II–IV chronic heart failure, II–III degree chronic respiratory failure, decompensated forms of diabetes mellitus, cancer).

Clinical symptoms, potential risk factors, pulmonary sarcoidosis onset features (acute or chronic course), extrapulmonary sarcoidosis manifestations, comorbidities, administration of systemic glucocorticosteroids (sGCS) were assessed in all patients.

QOL was assessed using the non-specific SF-36 questionnaire, comprising of 36 questions and 8 scales. The scales in the questionnaire are combined into two cumulative measures of "Physical Health" and "Mental Health". Physical Health includes the following scales: Physical and Role-Physical Functioning, Pain Scale, General Health; and Mental Health includes the scales of Psychological Health, Role-Emotional Functioning, Social Functioning, and Vitality. The scores are assessed cumulatively from 0 to 100 points. The higher each score, the better the QOL according to that parameter.

The comprehensive study of pulmonary function parameters and CPET with gas analysis was conducted using Quark COSMED (Italy) in compliance with the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards [12, 13]. Among spirometric parameters, forced vital capacity (FVC), forced respiratory volume in 1 sec (FEV1), modified FEV_1/FVC index, peak volumetric flow rate and mean forced expiratory flow rate from 25 to 75 % of FVC were assessed. The exercise testing used the incrementally increasing protocol, individually pre-adapted in such a way to ensure that the testing lasted 8 to 12 minutes [12]. The following CPET parameters were assessed: VO_2 peak and oxygen uptake at the anaerobic threshold (VO_2 AT, %), maximum exercise, respiratory rate, respiratory volume, minute ventilation, breathing reserve (BR), heart rate, oxygen pulse (VO_2 to heart rate ratio, ml/beats/min), expired CO_2 and O_2 left expiratory tension ($PetCO_2$ and $PetO_2$, mm Hg), ventilation equivalent for CO_2 (Ve/VCO_2). In addition, diagnostically significant electrocardiogram (ECG) changes were analyzed.

The study was conducted in accordance with the Good Clinical Practices and the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the Biology and Biomedicine Institute of the National Research State University of Nizhny Novgorod named after N. I. Lobachevsky (Protocol No. 33 dated 28.02.2019). All subjects signed the voluntary informed consent.

Statistical processing of the findings was performed using R 3.5.2 software. Quantitative data were presented as a median and interquartile interval: Me (Q_1 — 25th quartile; Q_3 — 75th quartile), and qualitative data — as absolute and percentage values. The Mann-Whitney U-test was used to compare the quantitative data; the Fisher exact test — for nominal variables with two categories; the likelihood-corrected Chi-Squared test ($\chi2$) — for nominal variables with more than two categories. The variables were classified by the k-means cluster analysis. Multivariate analysis was carried out using binary logistic regression. Null hypothesis of no statistically significant differences was discarded at $\rho<0.05$.

Results

At the first stage, the comprehensive assessment of QOL was performed for all patients. Findings of the questionnaire (SF-36) survey in pulmonary sarcoidosis patients showed that the QOL parameters were different from 100 % "ideal" health: Physical Health scores — 79.1 (63.9; 90.3), and Mental Health scores — 76.2 (55.9; 87.8).
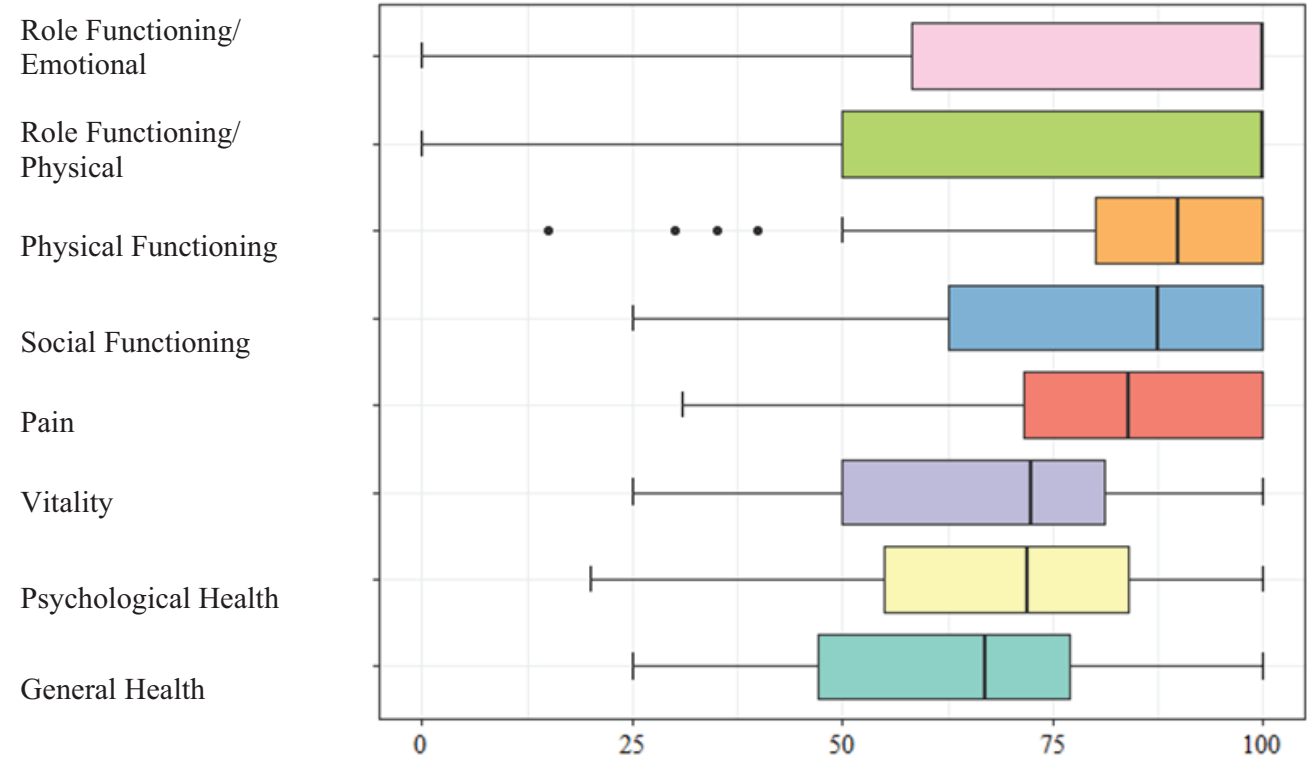
Figure 1. *QOL scores in patients with pulmonary sarcoidosis, taking into account the scales studied (SF-36 Questionnaire)*
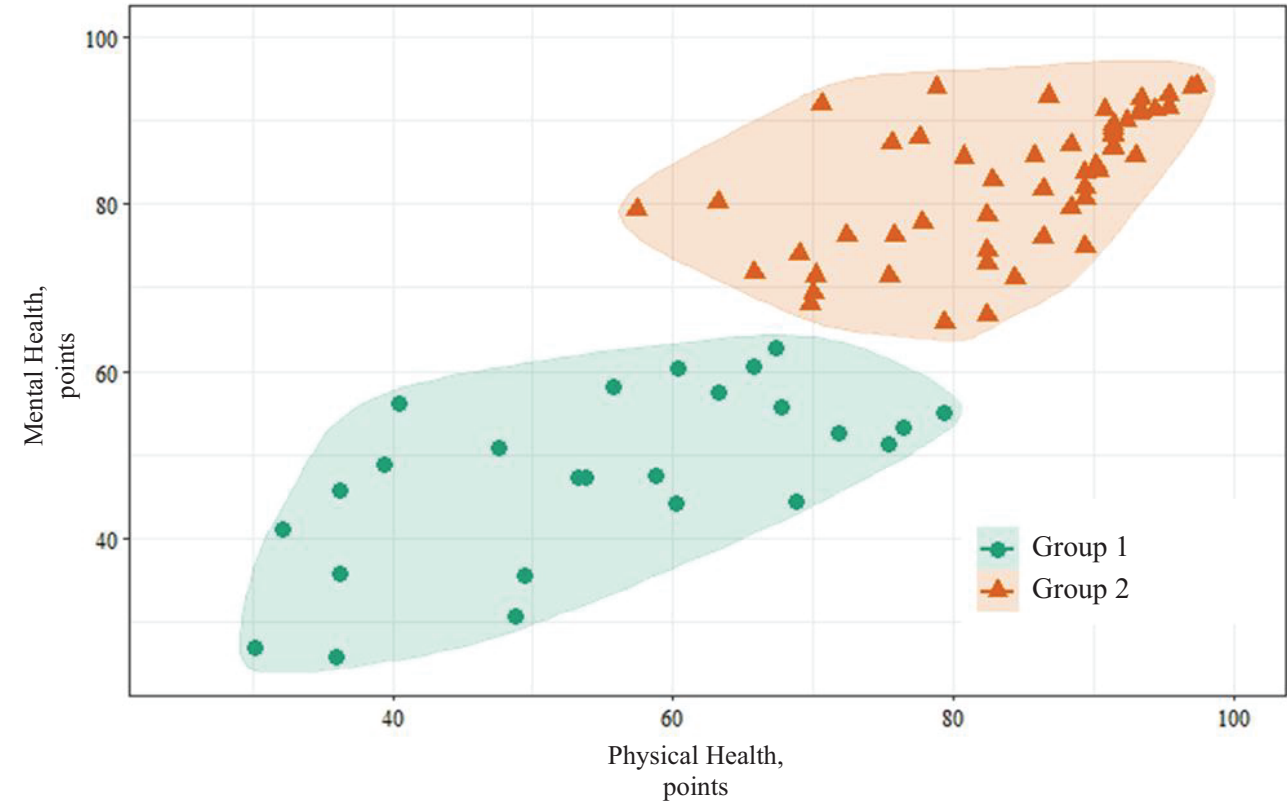

Figure 2. *Scatter diagram for health indicators that determine the QOL level in patients with sarcoidosis (k-means cluster analysis)*

There were no statistically significant differences between the health indicators analyzed ($p=0.211$). We noted the high QOL scores according to the Role Physical (100 (50; 100)) and Emotional Functioning scales (100 (50; 100)). The dramatic drop in QOL scores was observed on the General Health (67 (47; 77)), Psychological Health (72 (54; 84)) and Vitality scales (72.5 (50; 82.5)) (Figure 1).

To identify groups in the analyzed patient population based on the similarities and differences in the QOL parameters, the k-means cluster analysis was applied in the study. Two variables — Physical and Mental Health — were used as clustering criteria. Based on the clusters obtained, two groups of patients were identified on a provisional basis: Group 1 (n=26) — patients with reduced QOL, Group 2 (n=54) — patients with high QOL (Figure 2).

In Group 1, the median values for both health indicators did not exceed 60 points (Physical Health — 55.7 (40.2; 67.5) points, Mental Health — 48.1 (41; 55.9) points). Mental Health in this group of patients was significantly lower than Physical Health ($p=0.039$). In Group 2, the median values of Mental Health (85.1 (76.1; 93) points) and Physical Health (87.6 (77.8; 91.4) points) exceeded 80 points and have no differences between each other ($p=0.224$).

Patients with high QOL were younger (34.5 (29; 40) years) than those with low QOL (40.5 (32; 50) years) ($p=0.044$). Differences between the groups were determined by gender as well (Table 1).

Table 1. *Comparative characteristics of patients with pulmonary sarcoidosis depending on the QOL level*

Parameter		Group 1 (n=26)	Group 2 (n=54)	p
Age, years		40.5 (32; 50)	34.5 (29; 40)	0.044
Males/females		8 (30.8) / 18 (69.2)	35 (64.8) / 19 (35.2)	0.008
Disease duration, years		3 (2; 5)	3 (1; 4)	0.37
Radiographic stages	1	3 (11.5)	7 (13)	$\chi2=0.566$, df=2, $p=0.754$
	2	21 (80.8)	45 (83.3)	
	3	2 (7.7)	2 (3.7)	
Extrapulmonary manifestations		5 (19.2)	5 (9.3)	0.28
Acute and subacute onset		1 (3.8)	5 (9.3)	0.658
Asymptomatic course		4 (15.4)	25 (46.3)	0.012
Fatigue		19 (73.1)	10 (18.5)	<0.001
Cough		18 (69.2)	23 (42.6)	0.033
Dyspnea		10 (38.5)	4 (7.4)	0.001
Comorbidities		10 (38.5)	9 (16.7)	0.049
sGCS, including in past medical history		11 (42.3)	14 (25.9)	0.198
RBC, $*10^{12}$/l		4.5 (4.3; 4.87)	4.8 (4.5; 5.12)	0.099
WBC, $*10^9$/l		6.3 (6; 7.1)	6.4 (5.3; 7.3)	0.861
Hemoglobin, g/l		140 (133; 149)	145 (138; 157)	0.123
PLT, $*10^9$/l		217.5 (204; 241)	225 (204; 259)	0.622
Erythrocyte sedimentation rate, mm/hour		9 (4; 13)	5 (3; 13)	0.204

Note: data are presented as median and quartiles (Me (Q1; Q3)) or absolute and percentage values (n (%)), p — statistical significance of differences between the groups; χ2 — chi-square; df — degree of freedom

Group 1 was dominated by females, while Group 2 had more males ($p=0.008$). Respondents with low QOL more frequently reported fatigue ($p<0.001$), cough ($p=0.033$) and dyspnea ($p=0.001$), and Group 2 was characterized by prevailing asymptomatic course of sarcoidosis ($p=0.012$). There were more comorbidities among the patients in Group 1 ($p=0.049$), of which 77.7 % were cardiovascular diseases. The analyzed groups of patients were comparable by the incidence of extrapulmonary manifestations, disease duration, radiographic stages of pulmonary sarcoidosis, and sGCS administration. Complete blood counts in patients with pulmonary sarcoidosis were normal and showed no differences between the groups.

In most cases, respiratory function parameters at rest in the examined patients were normal (>80 % DV) and comparable between the groups (Table 2).

Mild FVC reduction was diagnosed in three cases (1 patient in Group 1, and 2 patients in Group 2; $p=1$), mild obstructive disorders (FEV1 60–80 % DV) — in 7 patients (1 patient in Group 1, and 6 patients in Group 2; $p=0.418$).

To identify QOL-affecting factors, binary logistic regression analysis was performed using direct and reverse step-by-step inclusion of variables, for which the differences between the groups were revealed. Based on the analysis results, it was established that only the female sex (OR 3.26, 95 % CI 1.15–9.23; $p=0.026$) and clinically

Table 2. Pre-test spirometry parameters in patients with pulmonary sarcoidosis depending on the QOL level

Parameters	Group 1 (n=26)	Group 2 (n=54)	p
FVC, DV %	101.5 (98; 108)	103.5 (97; 114)	0.488
FEV_1, DV %	96.5 (92; 105)	99 (88; 107)	0.886
FEV_1/FVC	0.82 (0.77; 0.86)	0.79 (0.76; 0.84)	0.265
PEF, DV %	85.5 (77; 100)	94.5 (86; 106)	0.077
MEF25-75, DV %	88 (58; 98)	79 (64; 98)	0.7

Note: data are presented as median and quartiles (Me (Q1; Q3)); PEF — peak expiratory flow; MEF25-75 — mean forced expiratory flow rate from 25 to 75 % of FVC; p — statistical significance of differences between the groups

Table 3. CPET parameters in patients with pulmonary sarcoidosis depending on the QOL level

Parameters	Group 1 (n=26)	Group 2 (n=54)	p
Maximum exercise, W	122.5 (100; 125)	182.5 (130; 220)	<0.001
VO_2 peak, ml/min	1,632.9 (1,242.7; 1,943)	2,222.1 (1,692.8; 2,828.7)	<0.001
VO_2 peak, ml/min/kg	21.2 (18.1; 26.5)	29.2 (22.4; 33.3)	<0.001
VO_2 peak, DV %	82 (72.5; 93.5)	85 (77; 94)	0.494
Respiratory rate, movements/min	32.2 (27.9; 35.1)	33 (28.4; 39.5)	0.355
Respiratory volume, l	1.6 (1.3; 2.5)	2.2 (1.8; 2.7)	0.002
Minute ventilation, l/min	49.8 (43.6; 66.2)	77.5 (61.2; 93.6)	<0.001
CO_2 left expiratory tension, mm Hg	38 (34; 40)	39 (35; 42)	0.506
Oxygen pulse, ml/beats/min	10.4 (8.6; 11.6)	12.7 (10.1; 16.5)	0.012
Breathing reserve, %	49 (44; 64)	49 (37; 57)	0.149

Note: data are presented as median and quartiles (Me (Q1; Q3)); p — statistical significance of differences between the groups
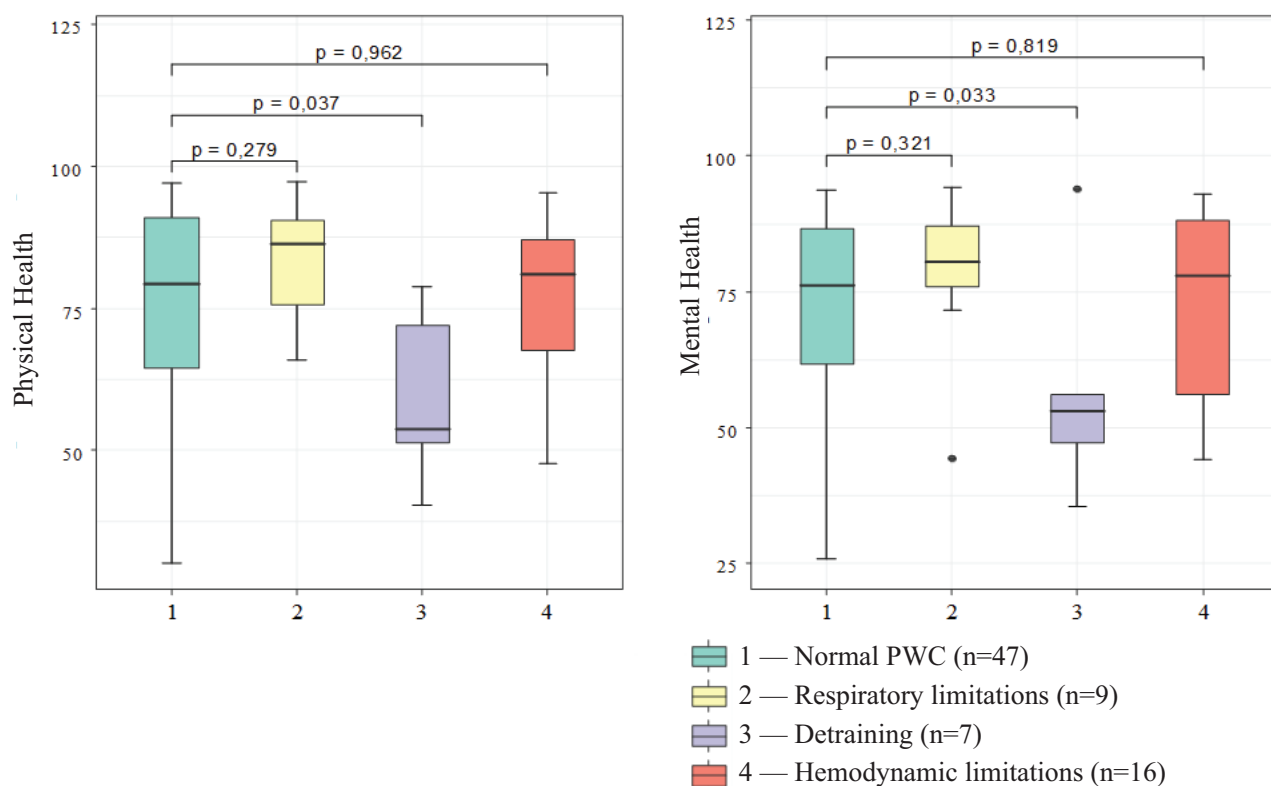
Figure 3. Quality of life parameters in patients with pulmonary sarcoidosis depending on types of functional limitations (n=79)

significant manifestations of sarcoidosis (OR 3.63, 95 % CI 1.06–15.47; ρ=0.041) were independent factors for higher probability of QOL reduction. In other cases, no statistically significant impact of the variables was identified (ρ>0.05).

At the second stage, the comparative analysis of CPET parameters was performed. Patients in Group 1 showed a statistically significant reduction in maximum exercise (ρ<0.001), VO_2 peak (ml/min and ml/min/kg) (ρ<0.001), respiratory volume (ρ=0.002), minute ventilation (ρ<0.001) and oxygen pulse (ρ=0.012) as compared to Group 2. VO_2 peak reflected in DV % was comparable in both groups (ρ=0.494) (Table 3).

In order to clarify the impact of the reasons for PWC reduction on the QOL in pulmonary sarcoidosis patients, the exercise testing results were analyzed in accordance with the American Thoracic Society recommendations [12] with the aim to identify leading limiting pathophysiological mechanisms.

Depending on functional limitation types, the following groups were formed: patients with normal PWC (n=47), detrained patients (n=7), persons with hemodynamic (n=16) and respiratory abnormalities (n=9). In one patient, PWC reduction was related to obesity (this patient was disregarded in the analysis).

Figure 3 shows the QOL comparison results (Physical and Mental Health) for sarcoidosis patients with normal PWC and various functional limitations based on the exercise testing. It should be noted that the lowest Physical and Mental Health was reported in detrained persons versus other analyzed groups (ρ<0.05). Moreover, detrained patients with pulmonary sarcoidosis had lower QOL scores according to the Physical (ρ=0.009) and Social (ρ=0.025) Functioning scales, Role-Physical (ρ=0.03) and Emotional (ρ=0.011) Functioning scales as compared to patients with normal PWC.

Discussion

The QOL of a patient assessed by the questionnaire survey is a subjective diagnostic tool, but is still important for a doctor. This is mainly because not only laboratory and instrumental health indicators are important for every patient, but also the sense of well-being in respect of the physical, mental and social aspects. In this study, 63.7 % of respondents with pulmonary sarcoidosis had a high QOL score according to the key parameters of the SF-36 Questionnaire. This score was probably related to specific features of the enrolled patients (more frequently — with asymptomatic course (36.3 %) or minimum clinical manifestations, rarely — with extrapulmonary damages (12.5 %) and impaired pulmonary ventilation at rest (8.7 %), lack of "honeycomb" changes in lung parenchyma according to the high-resolution computer tomography).

This study found no significant differences in the QOL depending on the incidence of extrapulmonary manifestations of sarcoidosis, while there were opposite results in the available literature [14]. This is probably related to the localization and severity of extrapulmonary damages. It is known that the QOL is significantly compromised by cardiac sarcoidosis due to the high risk of life-threatening complications and side effects of high doses of sGCS [15], as well as visual organ and nervous system damages that may lead to permanent functional impairments. Only mild systemic manifestation of skin changes (non-granulomatous erythema nodosum) was observed in the study population of pulmonary sarcoidosis patients.

The reduction of QOL in patients with sarcoidosis may be considerably due to comorbidities and concomitant conditions, the number of which increases with age. According to A. A. Vizel et al. (2018), the incidence of comorbidities in sarcoidosis patients over 55 years old is higher than 70 % [16]. In this study, a comorbid condition was reported in every fifth patient and was associated with low QOL.

The study findings made it possible to identify relevant factors affecting the reduction of QOL in patients with sarcoidosis: female sex and clinically significant symptoms, which in some cases is consistent with findings of foreign authors [17, 18].

The maximum exercise and VO_2 peak (ml/min/kg) based on the exercise testing in patients with low QOL were substantially lower than in the group with retained QOL. The results may be related to the prevailing number of female patients in Group 1, in whom VO_2 peak (ml/min/kg) is consistently lower than in males. This fact has been confirmed by the lack of significant differences in VO_2 peak (DV %) between the groups, when the patient's sex, age, height and weight were taken into account, and this demonstrates that the PWC was comparable between the groups. Similar results and their justification are provided by Pilzak K. et al. (2018) [6].

The ability to do physical exercise depends not only on the somatic musculature status, but also on the coherence of the cardiorespiratory system, which supplies oxygen to tissues [12, 13]. In this paper, the comparative appraisal of QOL in patients with sarcoidosis was performed for the first time, taking into account PWC, as assessed in the standardized exercise testing, as well as depending on the limiting mechanism. This approach to the QOL analysis in pulmonary sarcoidosis patients with reduced PWC and various functional limitations revealed that subjective health assessment is least in detrained patients. These data suggest that active physical exercise in patients with sarcoidosis may positively affect the QOL. Some evidence of the positive impact of respiratory muscle exercise using respiratory exercisers with inspiratory pressure increase for 30 minutes twice a day for 6 weeks, including on the QOL in patients with sarcoidosis, was provided in the study conducted by Karadallı M. N. et al. (2016) [19].

Conclusion

The study results for the QOL in patients with pulmonary sarcoidosis demonstrated the reduction in this health indicator in 32.5 % of cases. The deterioration of QOL was related to reductions

in both mental and physical health. The QOL-decreasing factors for sarcoidosis patients were the female sex and clinically significant progress of the disease.

The CPET with gas analysis in sarcoidosis patients revealed that the PWC decreased in patients with pulmonary sarcoidosis due to various reasons: cardiorespiratory system disorders, weak peripheral musculature, ventilation limitations. At the same time, it was shown that the subjective QOL assessment by patients with sarcoidosis was primarily affected by detraining.

Thus, the QOL investigation and monitoring in patients with sarcoidosis is a valuable cost-effective tool to identify groups of patients, including those with paucisymptomatic progress and retained functional capacity of lungs at rest, for whom it is appropriate to perform CPET with gas analysis in order to diagnose latent PWC limitations and determine its reduction mechanisms. Such a diagnostic algorithm can optimize the selection of therapy for patients with sarcoidosis.

Author Contribution

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L. B. Postnikova (ORCID ID: https://orcid.org/0000-0002-8509-7133): article concept and design, text editing, final manuscript approval

V. A. Kostrov: collection of clinical materials

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N. I. Kubysheva: text writing and editing

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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