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## External Respiratory Function, Inflammation Markers, and Life Quality Depending on the Volume of Tuberculosis Lung Lesion

Tuberculosis is a common disease in many countries, so understanding of its impact on life quality and respiratory function as well as study of correlations of these parameters with biochemical markers of tuberculosis course and treatment effectiveness is important in evaluating new methods of treatment and prevention.

**Objective** – to investigate the relationships between the function of external respiration, the level of Human-beta-defensin-1, ferritin, interleukin-6, quality of life and the volume of tuberculosis lung lesions.

**Materials and methods.** 100 patients with pulmonary tuberculosis were included in the study. Patients were divided into groups depending on the volume of tuberculous lesions: Group 1 (n = 36) had lesions within one lung, Group 2 (n = 64) had lesions of both lungs. Examination of patients was carried out according to the current standards of providing medical care to tuberculosis patients. In addition, patients underwent determination of ferritin, interleukin-6 (IL-6), and Human-beta-defensin-1 (HBD-1) levels in the blood by ELISA test. Spirography was performed to determine the parameters of the function of external breathing. Interviews were provided using SF-36 questionnaire with the determination of the main indicators of quality of life. Statistical data processing was carried out using the Statistica 8.0.

**Results and discussion.** Comparison of spirometry parameters between groups showed significantly lower respiratory function parameters in patients with bilateral tuberculous lesions compared to patients with unilateral lesions. A decrease in external respiratory function indicators was accompanied by a corresponding significant decrease in the quality of life, which was more pronounced in Group 2. The described changes occurred against the background of a significant increase in the studied biochemical markers in Group 2 compared to Group 1. Thus, the level of HBD-1 in Group 1 was (8.11 ± 1.78) pg/ml, in Group 2 it was (30.14 ± 3.89) pg/ml (p < 0.05). Ferritin level in Group 1 was (94.19 ± 1.18) ng/ml, in Group 2 – (113.45 ± 4.77) ng/ml (p < 0.05). The level of IL-6 in Group 1 was (81.43 ± 1.14) pg/ml, in Group 2 – (103.34 ± 3.46) pg/ml (p < 0.05). When investigating the correlations between the levels of HBD-1, ferritin, IL-6 and quality of life indicators according to the SF-36 scale, reliable inverse relationships were found between all quality of life parameters and the levels of HBD-1 and ferritin. When investigating the correlations between the levels of HBD-1, ferritin, IL-6 and parameters of the function of external respiration, it was found that HBD-1 demonstrates negative reliable correlations with both volume and speed indicators (–0.24...–0.32). IL-6 shows negative relationships only in FVC (r<sub>s</sub> = –0.42) and FEV1 (r<sub>s</sub> = –0.41), however, these correlations are stronger compared to HBD-1.

**Conclusions.** An increase in the volume of tuberculous lesions of the lungs leads to a more pronounced violation of the function of external breathing and, as a result, a decrease in the patients life quality. The described changes are accompanied by an increase in the levels of HBD-1, ferritin and IL-6, which makes the studied biomarkers promising predictors of deterioration of external respiratory function and quality of life. HBD-1 and ferritin demonstrated more pronounced correlations with parameters of life quality. The investigated markers have negative correlations with indicators of both restrictive and obstructive ventilation disorders.

### Keywords

Tuberculosis, spirometry, life quality, Human-beta-defensin-1, ferritin, interleukin-6.

Tuberculosis is a common disease in many countries, so understanding its impact on quality of life and respiratory function is important when evaluating new methods of treatment and prevention [4]. Quality of life is a crucial component of health. According to the WHO's definition, health is a state of complete physical, mental, and social well-being, not merely the absence of diseases or physical defects. Furthermore, quality of life remains one of the key aspects for ensuring the effectiveness of anti-tuberculosis treatment, as it directly affects patients treatment adherence [9]. A decrease in the quality of life among patients with tuberculosis can be associated with various factors, including stigmatization, isolation, psychosocial burden, socio-demographic factors (such as age and gender), socio-economic factors (income level, education, housing availability, social support, additional costs for accessing medical care, treatment side effects, direct tuberculosis symptoms, etc.) [7]. Some factors have a double effect on the quality of life. For example, initially exacerbates the impact of stigmatization; however, in the long term, it improves the quality of life and positively influences treatment effectiveness [18]. Perhaps the most important factor that improves the life quality of tuberculosis patients is the achievement of effective treatment, since the successful completion of a course of anti-tuberculosis therapy significantly improves both physical and psychological parameters of life quality; at the same time, a noticeable improvement is observed already in the first 2 months, that is, before the end of the intensive phase of treatment [3].

The function of external breathing plays an important role in ensuring the life quality. In patients with pronounced respiratory insufficiency due to a massive tuberculous lesion, the quality of life decreases sharply and remains decreased for a long time, sometimes for a lifetime [11].

Although tuberculosis is curable, and according to WHO estimates, the effectiveness of treatment of drug-susceptible tuberculosis is 85 % [20], respiratory dysfunction of various degrees of severity is observed in about half of those who have successfully completed treatment [12, 13]. The polymorphism of lung lesions in tuberculosis (cavity formation, fibrosis, infiltrates and their combination) leads to diversity in the manifestations of ventilation disorders [5, 8]. Respiratory dysfunction is caused by direct mycobacterial damage, but worsens due to the immune response of the host organism [13]. Later, respiratory insufficiency can lead to more serious diseases, such as Chronic Obstructive Pulmonary Disease (COPD) [1].

Considering the fact that the deterioration of the function of external breathing, as well as a decrease

in the quality of life in patients with tuberculosis, occur gradually, but have a protracted course, an urgent question is the establishment of relationships between these parameters and biochemical markers of the tuberculosis course and effectiveness of tuberculosis treatment.

**Objective** – to investigate the relationships between the function of external respiration, the level of Human-beta-defensin-1, ferritin, interleukin-6, quality of life and the volume of tuberculosis lung lesions.

## Materials and methods

100 patients with pulmonary tuberculosis were included in the study. Patients were divided into groups depending on the volume of tuberculous lesions: Group 1 (n = 36) had lesions within one lung, Group 2 (n = 64) had lesions of both lungs.

Examination of patients was carried out according to the current standards of providing medical care to tuberculosis patients. In addition, patients underwent determination of ferritin, interleukin-6 (IL-6), and Human-beta-defensin-1 (HBD-1) levels in the blood by ELISA test on an empty stomach. Spirometry was performed to determine the parameters of the function of external breathing.

Interviews were provided using SF-36 questionnaire with the determination of the main indicators of quality of life. Quality of life measures included: PF (physical functioning), RP (role physical functioning), BP (bodily pain), GH (general health), VT (vitality), SF (social functioning), RE (role emotional functioning), MH (mental health).

Statistical data processing was carried out using the Statistica 8.0 software environment using descriptive statistics, Mann–Whitney coefficient and Spearman correlation coefficient ( $r_s$ ).

## Results

Comparison of spirometry parameters between groups showed significantly lower respiratory function parameters in patients with bilateral tuberculous lesions compared to patients with unilateral lesions as expected, as shown in Table 1.

A decrease in external respiratory function indicators was accompanied by a corresponding significant decrease in the quality of life, which was more pronounced in Group 2 (Table 2).

The described changes occurred against the background of a significant increase in the studied biochemical markers in Group 2 compared to Group 1. Thus, the level of HBD-1 in Group 1 was ( $8.11 \pm 1.78$ ) pg/ml, in Group 2 it was ( $30.14 \pm 3.89$ ) pg/ml ( $p < 0.05$ ). Ferritin level in Group 1 was ( $94.19 \pm 1.18$ ) ng/ml, in Group 2 – ( $113.45 \pm 4.77$ ) ng/ml ( $p < 0.05$ ). The level of IL-6 in Group 1 was

(1.43 ± 1.14) pg/ml, in Group 2 — (103.34 ± 3.46) pg/ml ( $p < 0.05$ ).

When investigating the correlations between the levels of HBD-1, ferritin, IL-6 and quality of life indicators according to the SF-36 scale, reliable inverse relationships were found between all quality of life parameters and the levels of HBD-1 and ferritin. More pronounced connections were found with physical functioning ( $r_s = -0.43$  for HBD-1 and  $r_s = -0.42$  for ferritin), social functioning ( $r_s = -0.41$  for HBD-1 and  $r_s = -0.43$  for ferritin), role-emotional functioning ( $r_s = -0.41$  for HBD-1 and  $r_s = -0.35$  for ferritin) and patients overall assessment of their health ( $r_s = -0.43$  for HBD-1 and  $r_s = -0.38$  for ferritin). The relationship with the level of bodily pain was the lowest ( $r_s = -0.23$  for HBD-1 and  $r_s = -0.26$  for ferritin). At the same time, IL-6 showed only weak negative correlations with the level of general health ( $r_s = -0.26$ ) and mental health ( $r_s = -0.28$ ). The obtained data are presented in Table 3.

When investigating the correlations between the levels of HBD-1, ferritin, IL-6 and parameters of the function of external respiration, it was found that HBD-1 demonstrates negative reliable correlations with both volume and speed indicators (from  $-0.24$  to  $-0.32$ ). IL-6 shows negative relationships only in forced vital capacity ( $r_s = -0.42$ ) and forced expiratory volume in 1 sec ( $r_s = -0.41$ ), however, these correlations are stronger compared to HBD-1. That is, an increase in the levels of HBD-1 and IL-6 is associated with the occurrence of both obstructive and restrictive disorders of the function of external respiration. On the other hand, ferritin did not demonstrate reliable correlations with external respiratory function indicators. The obtained results are presented in Table 4.

**Table 1. Comparison of spirometry parameters between groups depending on the volume of tuberculosis lung lesions**

Spirometric parameter	Group 1	Group 2
IRV, l	1.79 ± 0.18	1.35 ± 0.09
FVC, l	3.76 ± 0.23	3.08 ± 0.17
FEV <sub>1</sub> , l	3.27 ± 0.23	2.62 ± 0.14
PEF, l/sec	5.74 ± 0.49	4.48 ± 0.28
FEF <sub>25</sub> , l/sec	5.34 ± 0.49	4.04 ± 0.29
FEF <sub>50</sub> , l/sec	4.34 ± 0.39	3.43 ± 0.26

Note. IRV — inspiratory reserve volume; FVC — forced vital capacity; FEV<sub>1</sub> — forced expiratory volume in 1 sec; PEF — peak expiratory flow; FEF<sub>25</sub> — forced expiratory flow 25 %; FEF<sub>50</sub> — forced expiratory flow 50 %;  $p < 0.05$ .

**Table 2. Comparison of quality of life parameters between groups depending on the volume of tuberculous lung lesions, point**

Parameters of life quality	Group 1	Group 2
PF	63.06 ± 2.78	44.52 ± 3.19
RP	31.25 ± 5.67	18.25 ± 3.68
GH	22.39 ± 2.32	12.87 ± 1.78
VT	20.28 ± 2.51	11.98 ± 1.86
SF	55.76 ± 2.66	39.88 ± 3.00
MH	40.39 ± 1.89	30.00 ± 1.58

Note.  $p < 0.05$ .

## Discussion

Today, the efforts of the anti-tuberculosis treatment are focused to a greater extent on the implementation of etiotropic therapy and to a lesser extent on the elimination of the symptoms of tuberculosis in order to overcome the epidemic and economic problems caused by the disease. Instead, little attention is paid to the psychosocial aspects of the

**Table 3. Correlations between the levels of HBD-1, ferritin, IL-6 and parameters of life quality according to the SF-36 scale**

	PF	RP	BP	GH	VT	SF	RE	MH
HBD-1	-0.43	-0.38	-0.23	-0.43	-0.32	-0.41	-0.40	-0.30
Ferritin	-0.42	-0.35	-0.26	-0.38	-0.36	-0.43	-0.35	-0.30
IL-6	—	—	—	-0.26	—	—	—	-0.28

Note.  $p < 0.05$ .

**Table 4. Correlations between the levels of HBD-1, IL-6 and parameters of external respiratory function**

	VC	IRV	FVC	FEV <sub>1</sub>	PEF	FEF <sub>25</sub>	FEF <sub>50</sub>	FEF <sub>75</sub>
β-defensin-1	-0.31	-0.30	-0.32	-0.32	-0.25	-0.25	-0.27	-0.26
IL-6	—	—	-0.42	-0.41	—	—	—	—

Note. IRV — inspiratory reserve volume; FVC — forced vital capacity; FEV<sub>1</sub> — forced expiratory volume in 1 sec; PEF<sub>25</sub> — peak expiratory flow; FEF<sub>25</sub> — forced expiratory flow 25 %; FEF<sub>50</sub> — forced expiratory flow 50 %; FEF<sub>75</sub> — forced expiratory flow 75 %;  $p < 0.05$ .

disease, the issues patients life quality, which, nevertheless, are closely related to the functional capabilities of a person in the long term [6]. This issue is gaining special relevance with the spread of resistant forms of tuberculosis, as their treatment is often longer, associated with a greater number of side effects and unwanted phenomena, as well as with a lower patients quality of life [16, 19].

In the course of the study, it was found that an increase in the volume of tuberculosis lesions of the lung tissue leads to a deterioration of the function of external breathing according to the mixed type and, as a result, to a decrease in the life quality, which is especially reflected in the parameters of physical and social functioning, general health and vital activity. These disorders are accompanied by an increase in the levels of HBD-1, ferritin, and IL-6, which allows us to consider these biomarkers not only as predictors of the effectiveness of tuberculosis treatment [16], but also as prognostic markers of impaired external respiration and decrease in the quality of life of patients.

Biochemical markers of the course of tuberculosis [16] are most closely related to functional parameters of quality of life, namely physical, role, and emotional functioning. Also, a sensitive parameter of life quality, which decreases with an increase in pro-inflammatory markers, is the patient's own assessment of his state of health. HBD-1 and ferritin demonstrated more pronounced correlations with quality of life, while for IL-6 only trends toward correlation were found, which had low reliability, suggesting a lower specificity of this marker.

The obtained data are consistent with the study by M. Bauer et al., in which it was found that the functional indicators of life quality are primarily and most affected, and even a month after the start of effective anti-tuberculosis therapy, when the severity of tuberculosis symptoms decreases, and self-assessment of the state of health improves, functional indicators of the quality of life remain significantly decreased [2].

One of the key aspects of improving the quality of life of tuberculosis patients is the restoration of respiratory function. The study of A.F.S. Amaral et al. [1] showed that respiratory rehabilitation programs aimed at restoring ventilation function during and after tuberculosis had a positive effect on patients quality of life.

Violation of the ventilation function in patients with tuberculosis is a consequence of the interaction between direct damage to the lower respiratory tract by *Mycobacterium tuberculosis* and the immune response of the host [13]. These processes lead to a decrease in the elasticity of the airways, their destruction, destruction of the muscular compo-

nents of the walls of the bronchi, damage to the lung parenchyma and vascular network, and ultimately to damage to both ventilation and perfusion in the respiratory system [17]. Factors such as drug resistance of the causative agent, repeated episodes of the disease and late diagnosis of tuberculosis, as well as the presence of bad habits, in particular smoking, increase the severity of respiratory disorders [6, 12].

We obtained results that indicate that the studied markers have negative correlations with both restrictive and obstructive ventilation disorders. Correlations with FVC and FEV<sub>1</sub> were most reflected, i. e. the higher the levels of HBD-1 and IL-6, the lower the forced vital capacity of the lungs and bronchial patency. It should be noted that HBD-1 showed correlations with other indicators of respiratory function, which makes it a more sensitive marker, while ferritin showed no reliable correlations with spirometry parameters at all. Stronger correlations between the level of IL-6 and parameters of FVC and FEV<sub>1</sub> (compared to HBD-1) can be explained by the fact that IL-6 is the first (along with IL-1 $\beta$ , TNF- $\alpha$  and IL-12) to be produced by immune cells in response to direct contact with *M. tuberculosis*, therefore, this marker begins to work first and is the most sensitive, and its excessive production in the future leads to increased fibrosis and the formation of severe residual changes [10].

Although an effective immune response is the key to successful eradication of the TB pathogen, a violent inflammatory response in the granuloma with excessive production of cytokines, including HBD-1, interleukins, and TNF- $\alpha$ , induces excessive production of enzymes, particularly matrix metalloproteinases, that contribute to the destruction of lung tissue and deterioration of respiratory function [15]. This fact explains the relationship between the high level of the studied markers of the course of tuberculosis and low indicators of respiratory function.

Several years after the end of antituberculosis treatment, disorders of respiratory function in the future can lead to the formation of chronic respiratory diseases with chronic shortness of breath and cough, therefore, early prediction of respiratory function disorders with the aim of timely respiratory rehabilitation against the background of effective antituberculosis therapy will prevent the development of these delayed complications and improve the quality of life and functionality of patients in the future [14].

## Conclusions

Enlargement of the volume of tuberculous lesions of the lungs leads to a more pronounced violation of the function of external breathing and, as a result, a decrease in the patients life quality. The described

changes are accompanied by an increase in the levels of Human-beta-defensin-1, ferritin, and interleukin-6, which makes the investigated biomarkers promising predictors of deterioration of external respiratory function and quality of life. Human-beta-defensin-1 and ferritin demonstrated more pronounced correlations with parameters of life quality. Biochemical markers of the course of tuberculosis are most closely related to functional

parameters of quality of life, namely physical, role, and emotional functioning. The studied markers have negative correlations with indicators of restrictive and obstructive ventilation disorders. Higher levels of Human-beta-defensin-1 and interleukin-6 are accompanied by lower forced vital capacity of the lungs and bronchial patency. Ferritin did not reveal any reliable correlations with spirometry parameters.

**No conflict of interests.**

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## Функція зовнішнього дихання, маркери запалення та якість життя залежно від об'єму туберкульозного ураження легень

Туберкульоз — поширена хвороба у багатьох країнах, тому розуміння його впливу на якість життя та функцію дихання, а також зв'язок цих показників з біохімічними маркерами перебігу й ефективності лікування туберкульозу має важливе значення для оцінки нових методів лікування та профілактики.

**Мета роботи** — дослідити зв'язок між функцією зовнішнього дихання, рівнем β-дефензину-1, феритину, інтерлейкіну-6, якістю життя та об'ємом туберкульозного ураження легень.

**Матеріали та методи.** У дослідження було залучено 100 пацієнтів із туберкульозом легень. Пацієнтів розподілили на дві групи відповідно до об'єму туберкульозного ураження: група 1 (n = 36) — ураження в межах однієї легені, група 2 (n = 64) — ураження обох легень. Обстеження пацієнтів проводили згідно зі стандартами надання медичної допомоги хворим на туберкульоз. Додатково методом імуноферментного аналізу визначали рівень феритину, інтерлейкіну (ІЛ)-6 та β-дефензину-1 у крові натще, проводили спірографію для визначення показників функції зовнішнього дихання, а також анкетування за опитувальником SF-36 із визначенням основних показників якості життя на початку лікування та через 60 днів. Статистичну обробку даних проводили за допомогою програмного середовища Statistica 8.0.

**Результати та обговорення.** Порівняння спірометричних показників між групами очікувано показало статистично значущо нижчі параметри функції зовнішнього дихання у пацієнтів з двобічним туберкульозним ураженням порівняно із пацієнтами з одnobічним ураженням. Зниження показників функції зовнішнього дихання супроводжувалося відповідним зниженням якості життя, більш вираженим у групі 2. Зміни відбувалися на тлі статистично значущого підвищення досліджуваних біохімічних маркерів у групі 2 порівняно з групою 1: рівень β-дефензину-1 у групі 1 становив у середньому  $(8,11 \pm 1,78)$  пг/мл, у групі 2 —  $(30,14 \pm 3,89)$  пг/мл ( $p < 0,05$ ), феритину — відповідно  $(94,19 \pm 1,18)$  і  $(113,45 \pm 4,77)$  нг/мл ( $p < 0,05$ ), ІЛ-6 —  $(81,43 \pm 1,14)$  та  $(103,34 \pm 3,46)$  пг/мл ( $p < 0,05$ ). При дослідженні кореляційних зв'язків між рівнями β-дефензину-1, феритину, ІЛ-6 та показниками якості життя за опитувальником SF-36 встановлено статистично значущі обернено пропорційні зв'язки між усіма показниками якості життя і рівнями β-дефензину-1 та феритину. Дослідження кореляційних зв'язків між рівнями β-дефензину-1, феритину, ІЛ-6 та показниками функції зовнішнього дихання виявило, що β-дефензин-1 має статистично значущі обернено пропорційні зв'язки як з об'ємними, так і зі швидкісними показниками ( $r_s = -0,24 \dots -0,32$ ), ІЛ-6 — лише із форсованою життєвою ємністю легень ( $r_s = -0,42$ ) та об'ємом форсованого видиху за першу секунду ( $r_s = -0,41$ ), але ці кореляційні зв'язки є сильнішими порівняно з β-дефензином-1.

**Висновки.** Збільшення об'єму туберкульозного ураження легень призводить до виразнішого порушення функції зовнішнього дихання і, як наслідок, — до зниження якості життя пацієнтів. Ці зміни супроводжуються підвищенням рівня β-дефензину-1, феритину та ІЛ-6, тому зазначені біомаркери є перспективними предикторами погіршення функції зовнішнього дихання та якості життя. Сильніші кореляції з показниками якості життя продемонстрували β-дефензин-1 та феритин. Досліджувані маркери мають обернено пропорційні зв'язки із показниками як рестриктивних, так і обструктивних вентиляційних порушень.

**Ключові слова:** туберкульоз, спірометрія, якість життя, β-дефензин-1, феритин, інтерлейкін-6.

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### ДЛЯ ЦИТУВАННЯ

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