E. Lesnic[1], L.Todoriko[2], S. Ghinda[3], I. Yeremenchuk[2] THE DIVERSITY OF IMMUNE RESPONSE DISORDERS IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH DIFFERENT DRUG RESISTANCE PROFILES AND CONCURRENT SARS-COV-2 INFECTION (PART 1)

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THE DIVERSITY OF IMMUNE RESPONSE DISORDERS IN PATIENTS WITH PULMONARY TUBERCULOSIS WITH DIFFERENT DRUG RESISTANCE PROFILES AND CONCURRENT SARS-COV-2 INFECTION (PART 1)

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Abstract

Aim of the study – to evaluate the types of disorders of the adaptive, humoral and innate immune response in patients with pulmonary TB, infected with different strains of M. tuberculosis and concurrent SARS-CoV-2 infection.

Materials and methods. A prospective study included 191 newly diagnosed patients with pulmonary TB, distributed in four groups: the 1st study group (1st SG) included 80 patients with drug-susceptible TB, the 2nd study group (2nd SG) - 40 patients with primary drug-resistant TB, the 3rd study group (3rd SG) - 49 patients with MDR-TB during anti-TB treatment, and the 4th study group (4th SG) - 22 patients (11 with drug-susceptible TB and 11 with primary MDR-TB) co-infected with SARS-CoV-2. A control group (CG) consisted of 36 conventionally healthy individuals. The immune assays such as lymphocyte blast transformation tests using phytohemagglutinin and tuberculin, immunophenotyping of CD3+, CD4+, CD8+, and CD19+ cells, the nitroblue-tetrazolium reduction test on leucocytes were, assessment of immunoglobulins and antimycobacterial antibody levels in serum, evaluation of the phagocytic index and phagocytic number were conducted before the onset of the specific treatment.

Results. Clinical aspects and radiological findings indicated a more severe disease course in patients with acquired MDR-TB and those co-infected with SARS-CoV-2, supported by evidence of decreased cell-mediated and innate immunity, associated with elevated markers of humoral immune response.

Conclusions. Indices of cell-mediated and innate immunity were decreased in all patients with acquired MDR-TB and concurrent SARS-CoV-2 infection compared to those with primary MDR-TB and drug-susceptible TB, whereas humoral immunity indices were compensatory elevated.

Key words: tuberculosis, cell-mediated immunity, resistance, humoral immunity.

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РІЗНОМАНІТТЯ ПОРУШЕНЬ ІМУННОЇ ВІДПОВІДІ У ПАЦІЄНТІВ З ЛЕГЕНЕВИМ ТУБЕРКУЛЬОЗОМ З РІЗНИМИ ПРОФІЛЯМИ ЛІКАРСЬКОЇ СТІЙКОСТІ ТА СУПУТНЬОЮ ІНФЕКЦІЄЮ SARS-COV-2 (ЧАСТИНА 1)

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Резюме

Мета дослідження – визначити особливості порушень адаптивної, гуморальної та вродженої ланок імунної відповіді у хворих на легеневий туберкульоз, інфікованих різними штамами Mycobacterium tuberculosis у поєднанні з супутньою інфекцією SARS-CoV-2.

Матеріали та методи. У проспективне дослідження було включено 191 пацієнт з туберкульозом легень, яких розподілили на чотири групи. Перша досліджувана група включала 80 хворих із чутливим туберкульозом легень, друга – 40 пацієнтів з туберкульозом із первинною резистентністю. До третьої групи увійшли 49 осіб із туберкульозом із вторинною множинною лікарською стійкістю (МЛС ТБ). Четверта група включала 22 пацієнтів (11 із чутливим туберкульозом та 11 із первинним МЛС ТБ), ко-інфікованих SARS-CoV-2. Контрольна група (КГ) включала 36 умовно здорових осіб. До початку специфічної терапії всім учасникам виконували комплекс імунологічних досліджень, зокрема тести на бластну трансформацію лімфоцитів із застосуванням фітогемаглютиніну та туберкуліну, імунофенотипування клітин CD3+, CD4+, CD8+ і CD19+. Також проводили нітросиній-тетразолійний тест для оцінки відновлювальної здатності лейкоцитів, визначення рівнів імуноглобулінів та антимікобактеріальних антитіл у сироватці крові, а також аналіз фагоцитарного індексу та фагоцитарного числа.

Результати. Отримані клінічні та рентгенологічні дані вказують на важчий перебіг захворювання у пацієнтів з первинною МЛС ТБ та у пацієнтів з ко-інфікуванням SARS-CoV-2, що лабораторно підтверджується зниженням клітинного та вродженого імунітету, а також підвищеними маркерами гуморальної імунної відповіді.

Висновок. Показники клітинного та вродженого імунітету були знижені у всіх пацієнтів з набутою МЛС ТБ та супутньою інфекцією SARS-CoV-2 порівняно з хворими на первинну МЛС ТБ та чутливий туберкульоз, тоді як показники гуморальної імунної відповіді мали компенсаторне підвищення.

Ключові слова: туберкульоз, клітинний імунітет, резистентність, гуморальний імунітет.

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In 2023, an estimated 10.8 million people developed tuberculosis (TB), slightly more than in 2022, 7.5 million, with an incidence rate rising to 134/ 100,000 population [1]. Although TB-related deaths declined to 1.25 million in 2023, down from 1.32 million in 2022, 1.6 million in 2021, 1.5 million on 2020 and 1.4 million in 2019 the COVID-19 pandemic reversed years of progress, and TB is actually leading global cause of death from a single infectious agent, overpassing the deaths caused by SARS-CoV-2 infection [2]. The Republic of Moldova (RM) is among the high TB burden countries of the European region with the highest level of multidrug-resistant tuberculosis (MDR-TB) [3]. It is estimated that 33 % (30–35 %) of new TB cases in the Republic of Moldova are infected with MDR/RR-TB strains, while 60 % (56–64 %) develop drug resistance during anti-TB treatment [4]. Early diagnosis and timely initiation of appropriate anti-TB therapy based on the drug resistance profile prevent the development of resistance and improve treatment outcome [5]. Several studies indicated that COVID-19 trig-

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gers immune system activation followed by cellular exhaustion, which can reactivate latent TB foci, allowing dormant mycobacteria to mutate, develop drug resistance, and disseminate [5-7]. A study conducted during the pandemic reported poorer treatment outcomes in TB patients co-infected with SARS-CoV-2, attributed to cell-mediated immune exhaustion occurring within the first two months of infection [8]. These findings highlighted the persistence of disturbances of the immune system that require targeted pathogenic therapy to enhance disease outcomes.

The aim of the study was to assess the types and complexity of the adaptive, innate and humoral immune disorders in patients with pulmonary TB, infected with different strains of *M. tuberculosis* and concurrent SARS-CoV-2 infection**.**

Materials and methods

A prospective study was conducted involving 191 patients with pulmonary TB registered between 2019 and 2023 distributed in the 1st group (1st SG) — 80 patients with drug-susceptible TB, the 2nd study group (2nd SG) — 40 patients with primary drug-resistant TB, the 3rd study group (3rd SG) — 49 patients with acquired MDR-TB during anti-TB treatment, and the 4th study group (4th SG) — 22 patients (11 with drug-susceptible TB and 11 with primary MDR-TB) co-infected with SARS-CoV-2. A control group (CG) which included 36 conventionally healthy individuals was used for comparison. Inclusion criteria in the study were: age over 18 years, signed informed consent, microbiologically confirmed diagnosis of pulmonary TB and available drug-susceptibility test results. The patients from the 4th SG additionally had a positive antigen test for SARS-CoV-2 viral proteins from nasal or nasopharyngeal swabs and were diagnosed with mild-to-moderate COVID-19. All patients underwent clinical evaluation, chest radiography, and microbiological investigations, including Ziehl-Neelsen acid-fast staining and culture on both Lowenstein–Jensen solid media and BACTEC liquid media, GeneXpert MTB/Rif assay as well. Immunological evaluations included qualitative assessment of cell-mediated immunity using the lymphocyte blast transformation reaction (LBTR) with phytohemagglutinin (PHA) and tuberculin (PPD) antigens, while the quantitative evaluation of lymphocyte subsets was performed by flow cytometric immunophenotyping. Quantitative assessment of innate immunity was performed by calculating the phagocytic index (PI) and phagocytic number (PN), while qualitative evaluation was conducted through the nitro-blue tetrazolium (NBT) reduction test. Humoral immunity was evaluated by measuring the concentrations of immunoglobulin (Ig) classes A, G, and M, along with antimycobacterial antibodies using ELISA, and by determining the quantitative level of CD19+ cells.

Statistical analysis was conducted using SPSS version 26.0. Differences between indicators were assessed with Fisher's exact test and the nonparametric Student's t-test, considering $p<0.05$ as statistically significant. Spearman's rank correlation was used to assess the strength and direction of associations (r), with correlation strength categorized as weak for r=0.30–0.49, moderate for r=0.50–0.69, and strong for $r \geq 0.70$.

Results and discussion

Demographic characteristics. Distribution of patients by demographic characteristics showed lack of significant differences in the proportion of men and women among the study groups, with male-to-female ratios of 2.1:1 in the 1st SG (54 men [67 %] vs. 26 women [32 %]), 2.1:1 in the 2nd SG (27 men [67 %] vs. 13 women [32 %]), 1.5:1 in the 3rd SG (29 men [59 %] vs. 20 women [41 %]), and 2:1 in the 4th SG (14 men [64 %] vs. 8 women [36 %]). Distribution in age groups showed a statistical predominance of young patients (18-44 years) in the 2nd SG (25 cases [62 %] and 4th SG (17 cases [95 %] compared with 1st SG 42 [52 %] and 3rd SG 19 [39 %] (fig. 1).

Clinical-radiological assessment. Evaluation of general symptoms of active TB revealed a significantly higher prevalence of prolonged asthenia in the 3rd SG (49 cases [100 %]) and 4th SG (22 cases [100 %]) compared with the 1st SG (62 cases [77 %]) and 2nd SG (21 cases [52 %]); weight loss was also more frequent in the 3rd SG (49 cases [100 %]) and 4th SG (22 cases [100 %]) compared with the 1st SG (71 cases [87 %]) and 2nd SG (28 cases [71 %]); persistent fever was present in

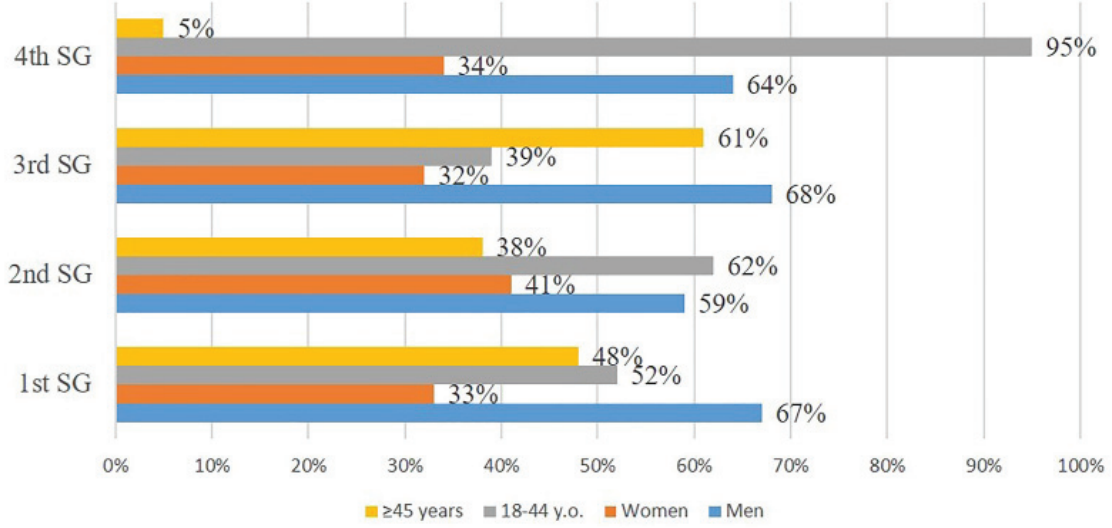

Fig. 1. Demographic characteristics

all patients of the 3rd SG (49 cases [100 %]) and in 22 cases (100 %) of the 4th SG, compared with 25 cases (31 %) in the 1st SG and 8 cases (20 %) in the 2nd SG, and was commonly associated in all patients with night sweats. So, clinical and radiological findings confirmed that TB evolution and outcome was more severe in patients from the 3rd SG and 4th SG. Radiological assessment showed that more patients in the 3rd SG (35 cases [71 %]) and 4th SG (16 cases [73 %]) exhibited all radiological severity criteria, whereas only about half of the patients in the 1st SG (44 cases [55 %]) and 1st SG (23 cases [57 %]) met these criteria (p<0.05 for both comparisons). The proportion of patients with bilateral lung involvement was significantly higher in the 3rd SG (37 cases [75 %]) and 4th SG (22 cases [100 %]) compared to the 1st SG (42 cases [52 %]) and the 1st SG (26 cases [65 %]) (p < 0.1 for both comparisons). Extensive TB involving more than three lung segments was identified in a significantly higher proportion of patients in the 3rd group (43 cases [88 %]) and 4th group (20 cases [91 %]) compared with the 1st SG (42 cases [52 %]) and the 2nd SG (20 cases [50 %]) (p <0.001 for all comparisons). Bilateral pulmonary dissemination was radiologically detected more frequently, in the 3rd SG (39 cases [80 %]) and the 4th SG (20 cases [90 %]) compared with 1st SG 14 (17 %) and the 2nd SG (24 cases [49 %]).

Immunological evaluation. Peripheral blood lymphocytes were collected and tested *in-vitro* to evaluate the adaptive (cell-mediated) immunity. For its qualitative assessment, the blast transformation reaction (RBTL) with phytohemagglutinin (PHA) showed significantly reduced lymphocyte functional activity in all study groups compared with control group (CG) (p<0.001 for all comparisons), as well more reduced in the 3rd and 4th SG compared with the 1st and 2nd SG (p < 0.001 for all comparisons), and was lower in the 4th SG compared with 3rd SG (p < 0.01).

The RBTL with PPD demonstrated decreased T-lymphocyte activity across all study groups compared with the CG (p < 0.001 for all comparisons), with lower values in the 3rd and 4th SG, compared with 1st and 2nd SG (p < 0.001 for all comparisons).

During the quantitative assessment, the proportion of CD3+ T cells, representing mature T lymphocytes and T-helper subset was decreased in all study groups compared with the CG (p< 0.001). When comparing the study groups, the lowest levels were observed in the 3rd and 4th SG compared to the 1st and 2nd SGs (p<0.001). The proportion of CD4+ T-helper cells was significantly lower all study groups compared with CG (p<0.001). When comparing the study groups, levels were reduced in the 3rd and 4th SGs than in 1st and 2nd SGs (p<0.01), with the lowest level observed in the 4th vs. 3rd SG (p<0.01). In contrast CD8+ T-suppressor cells were increased in 1st and 2nd SGs (p<0.05), and significantly decreased in the 3rd and 4th SGs compared with the CG (p<0.001), with the lowest level observed in the 4th SG. CD4+/CD8+ ratio was equal to 1 in the 1st and 2nd SGs, and increased in the 3rd and 4th SGs. The proportion of CD16+ (natural-killer) cells was reduced in all SGs compared with CG (p < 0.001) with the lowest levels in the 3rd and 4th SGs compared with 1st and 2nd SGs (p < 0.001 for all comparisons). The results demonstrated reduced adaptive immunity, more pronounced in patients with acquired MDR-TB and concomitant SARS-CoV-2 infection, due to several combined factors - lymphocytes exhaustion, inflammation, and systemic dysregulation (tab. 1).

Humoral immunity was assessed by measuring the B-lymphocyte count and the serum concentration of immunoglobulins. The proportion of CD19+ cells increased in all study groups compared with the CG (p < 0.001), with the highest level observed in the 3rd and 4th SGs compared with the 1st and 2nd SGs (p < 0.001). A negative correlation was established between the rates of CD4+ and CD19+ cells in all SGs, with stronger values in the 3rd SGs (r = 0,61; p < 0,001) and 4th SGs (r = 0,78; p < 0,001) and medium values in the 1st (r = 0,42; p < 0,01) and 2nd SGs (r = 0,56; p < 0,01). The concentration of IgA was also increased in all study groups compared with CG (p < 0.001) and the highest levels were established in the 2nd and 4th SGs vs. 1st and 3rd SGs (p < 0.001). The IgM concentration was increased in all study groups compared with CG (p < 0.001), with higher levels in the 2nd and 4th SGs vs. 1st and 3rd SGs (p < 0.001). IgG levels was elevated in all study groups compared with CG (p < 0.001) and higher levels were established in the 3rd compared to other SGs (p < 0.001). Total antimycobacterial antibodies were also increased in all study groups compared to CG (p < 0.001) with higher levels in the 3rd than in other SGs (p < 0.001) (tab. 2).

The assessment of innate immunity, measured by the number of neutrophils capable of phagocytosis, revealed a significantly reduced level in all SGs compared with the CG

Table 1

Addaptive immunity indicators (%)

Indicators	1st SG (N=80)	2nd SG (N=40)	3rd SG (N=49)	4th SG (N=22)	CG (N=36)
RBTL PHA (%)	62,8±0,7□	57,6±1,9□◊	53,7±1,7□○	47,2±1,8□●◘	79,9±1,2
RBTL PPD(%)	6,35±0,3□	4,1±0,2□◊	4,1±0,3□○	3,1±0,4□●	2,1±0,2
CD3+ (%)	63,6±0,9□	66,4±2,5□◊	46,1±1,1□○	37,3±2,1□●◘	67,9±0,5
CD4+ (%)	32,1±0,6□	34,6±1,7□◊	27,5±1,2□○●	22,4±1,13□○◘	38,3±0,6
CD8+ (%)	31,4±0,7□	32,5±1,5□◊	18,6±1,5□○●	15,9±1,2□○◘	29,6±0,7
CD4+/CD8+	1,0	1,0	1,5	1,4	1,3
CD16+ (%)	10,9±1,1	11,2±1,6	7,3±2,2□○●	7,5±1,9□	12,1±0,5

Note: applied statistical test Fisher exact test. □ — statistically significant vs. CG; ◊ — 1st vs. 2nd SGs; ○ — 1st vs. 3rd SGs; ○ — 1st vs. 4th SGs; ● — 2nd vs. 3rd SGs; ♦ — 2nd vs. 4th SGs; ◘ — 3rd vs 4th SGs.

Table 2

Humoral immunity (%)

Indices	1st SG (N=80)	2nd SG (N=40)	3rd SG (N=49)	4th SG (N=22)	CG (N=36)
CD19+ *(%)	12,8±0,5□	15,6±0,8□◊	18,6±1,1□○	16,3±0,9□○◘	9,2±0,9
IgA (g/L)**	3,6±0,8□	4,4±0,8 ◊	4,1±0,9 □	4,9±0,6□○◘	3.0±0,5
IgM (g/L)	2,5±0,3□	2,9±0,4□	2,3±0,4	3,2±0,5□○○	2.0±0,4
IgG (g/L)	18,1±0,3□	17,6±0,4 □	21,5±0,4 □○	18,1±0,5□◘	12,3±0,5
Anti-MBT antibodies (C.U.) **	4,6±0,2□	4,9±0,2□	6,2±0,3 □ ○	4,1±0,2□○♦◘	2,2±0,3

Note: * — Statistical analysis performed using Fisher's exact test; ** — Mann-Whitney test. □ — statistically significant vs. CG; ◊ — 1st vs. 2nd SGs; ○ — 1st vs. 3rd SGs; ○ — 1st vs. 4th SGs; ● — 2nd vs. 3rd SGs; ♦ — 2nd vs. 4th SGs; ◘ — 3rd vs 4th SGs.

($p < 0.001$). When comparing the SGs the lowest valued were observed in the 3rd and 4th SG compared with 1st and 2nd SG ($p < 0.001$) with more pronounced decrease in the 4th SG vs. 3rd SG.

The phagocytic index was reduced in all study groups compared with CG, with a statistically significant decrease observed only in the 4th SG compared with other SGs ($p < 0.001$). Neutrophil functional activity, assessed by the nitro-blue tetrazolium (NBT) reduction test as the percentage of NBT-positive neutrophils capable of converting NBT to formazan, was also reduced in all study groups compared with CG ($p < 0.001$), with the most pronounced reduction occurring in the 4th SG compared to other SGs ($p < 0.001$) (tab. 3).

We proposed a method for assessing the severity of immune disorders using the followinb formula: (patient's indicator/healthy individual indicator – 1) × 100. A negative result indicates an immune deficiency, while a positive result reflects hyperactivity. The degree of immune alteration is classified as follows: 1st degree (low level) for values between 1–33 %, 2nd degree (moderate level) for 34–66 %, and 3rd degree (high level) for values exceeding 67 %. The normal immune indicator values serve as the reference for this evaluation [9]. We proposed a classification of immune disorders as following: a) transient adaptive reaction (TAR), representing the general response through activation of innate and humoral immunity, corresponding to a deviation of indices from 0–16 % from the normal; b) immunodeficiency (ID), defined by a reduced capacity of the immune system to respond to antigenic stimulation and c) hyperactive response (HAR) conditioned by the significant response of the immune system. ID and HAR were further classified in the 1st degree — the indices were decreased/ increased from 17 % to 33 % from the normal range; 2nd degree — between 34 % and 66 %; 3rd degree–more than 66 %.

Table 3

Innate immunity

Indices	1st SG (N=80)	2nd SG (N=40)	3rd SG (N=49)	4th SG (N=22)	CG (N=36)
Phagocytic number (%)	71,2±0,2□	70,1±0,2□	68,9±0,3□○	63,1±0,1□○♦◘	76,9±0,9
Phagocytic index (CU)	4,4±0,3 □	4,2±0,2□	4,1±0,1 □○	3,9±0,1□○♦◘	4,6±0,8
NBT test (CU)	0,11±0,03□	0,12±0,04□	0,09±0,05□○	0,05±0,02□○♦◘	0,14±0,006

Note: * — Statistical analysis performed using Fisher's exact test; ** — Mann-Whitney test. □ — statistically significant vs. CG; ◊ — 1st vs. 2nd SGs; ○ — 1st vs. 3rd SGs; ○ — 1st vs. 4th SGs; ● — 2nd vs. 3rd SGs; ♦ — 2nd vs. 4th SGs; ◘ — 3rd vs 4th SGs.

Table 4

Complexity of immune disturbances

Indices	1st SG (N=80)	2nd SG (N=40	3rd SG (N=49)	4th SG (N=22)
	M (%)	M (%)	M (%)	M (%)
TAR	8 (10)	3 (7)	0	0
ID	72 (90)	37 (92)	49 (100)	22 (100)
Including 1st degree	30 (37)	25 (62)	2 (5 %)	2 (10)
2nd degree	33 (41)	10 (25)	14 (35)	10 (45)
3rd degree	14 (17)	5 (13)	33 (82)	10 (45)
Humoral hyperactivity	62 (77)	36 (90)	49 (100)	22 (100)
Innate resistance deficiency	51 (64)	34 (85)	49 (100)	22 (100)
Combined disorders	61 (76)	40 (100)	49 (100)	22 (100)

Assessing the immune indices of each patient, TAR was identified in 8 (10 %) from 1st SG and in 3 (7 %) patients from 2nd SG. Immunodeficiency (ID) of adaptive immunity, reflected by reduced CD4+ levels, was observed in most patients and was present in all cases from the 3rd and 4th groups. First-degree ID was significantly more frequent in the 2nd group compared with the others ($p < 0.001$), while second-degree ID occurred at a similar rate across all groups. Third-degree ID was more common in the 3rd and 4th groups than in the 1st and 2nd groups ($p < 0.001$). Humoral HAR (CD19+) was established in two-thirds of the 1st group and all cases from remaining groups. Regarding the severity of disorders: one-third of the 1st group showed 2nd-degree HAR, while all patients from the remaining groups exhibited the 3rd degree disorder. Innate resistance deficiency, assessed by the phagocytic number, was significantly more frequent in the 2nd, 3rd and 4th groups compared with the 1st group ($p < 0.001$), where all patients showed a 1st-degree disorder, while the remaining groups exhibited a 2nd-degree disorder. Combined immune disorders of all types were significantly more frequent in all groups compared with the 1st group, where only one-third of patients exhibited a combination limited to adaptive and humoral immune impairments (tab. 4).

Conclusions

Clinical and radiological findings showed a more severe course of disease in patients with acquired MDR-TB and in those co-infected with SARS-CoV-2. All study groups demonstrated reduced cell-mediated and innate immunity associated with elevated markers of humoral immunity, with a more pronounced negative immune imbalance in the groups with acquired MDR-TB and MDR-TB/SARS-CoV-2 coinfection. The severity of immune deficiencies was higher in these groups, in which all types of immune disorders were identified.

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