THE IMPACT OF TUBERCULOSIS ON THE DEVELOPMENT OF IMMUNE RESPONSE TO SARS-COV-2

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Given the fact, that adaptive immune response is important for control and elimination of viral infections causing human diseases, estimation of adaptive response to SARS-CoV-2 is extremely important. The neutralizing antibodies and $CD4^+$/$CD8^+$ T cells contribute to the SARS-CoV-2 control. Tuberculosis remains the leading cause of mortality among bacterial infections all over the world. Currently, treatment of tuberculosis is complicated by the COVID-19 co-infection. The aim of the study was to investigate the formation of neutralizing antibodies against SARS-CoV-2 and $CD4^+$ and $CD8^+$ T cells specific for SARS-CoV-2 in patients with pulmonary TB. The levels of neutralizing antibodies against SARS-CoV-2 and the amount of T cells specific for SARS-CoV-2 were estimated at two time points (3 and 6 months after COVID-19) in patients diagnosed with pulmonary tuberculosis (69 individuals: 33 females and 36 males aged 18–70 years). Patients without tuberculosis (35 individuals: 25 females and 10 males aged 18–70 years) who had undergone COVID-19 served as the control group. The study showed equal levels of SARS-CoV-2 neutralizing antibodies in both groups 3 months after COVID-19. The levels of antibodies decreased 6 months after COVID-19 compared to the levels reported 3 months after the disease in both groups. The antibody levels were significantly lower in the group of patients with TB ($p = 0.01$). The amount of SARS-CoV-2 specific T cells was lower in TB patients 6 months after COVID-19 ($p < 0.001$) compared to the control group. Thus, TB co-infection reduces the specific immune response to SARS-CoV-2 6 months after COVID-19.

Keywords: COVID-19, tuberculosis, immunologic memory, $CD4^+$ T lymphocytes, IgG

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ВЛИЯНИЕ ТУБЕРКУЛЕЗА НА ФОРМИРОВАНИЕ ИММУННОГО ОТВЕТА К SARS-COV-2

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С учетом того, что адаптивный иммунный ответ важен для контроля и устранения вирусных инфекций, вызывающих заболевания у людей, крайне важна оценка адаптивного ответа на SARS-CoV-2. Нейтрализующие антитела и Т-лимфоциты $CD4^+$/$CD8^+$ способствуют контролю SARS-CoV-2. Туберкулез до сих пор остается главной причиной смерти среди бактериальных инфекций в мире. На данный момент лечение туберкулеза осложнено коинфекцией COVID-19. Целью работы было исследовать образование нейтрализующих антител против SARS-CoV-2 и специфичных для SARS-CoV-2 Т-клеток $CD4^+$ и $CD8^+$ у пациентов с ТБ легких. Уровни нейтрализующих антител к SARS-CoV-2 и количество специфичных к SARS-CoV-2 Т-клеток оценивали в двух временных точках (через 3 и через 6 месяцев после перенесенного COVID-19) у больных с диагнозом туберкулез легких (69 человек: 33 женщины и 36 мужчин от 18 до 70 лет). В контрольную группу вошли пациенты, перенесшие COVID-19 без туберкулеза (35 человек: 25 женщин и 10 мужчин от 18 до 70 лет). В результате исследования были зарегистрированы одинаковые уровни нейтрализующих антител к SARS-CoV-2 в обеих группах через 3 месяца после перенесенного COVID-19. Уровни антител снизились в двух группах через 6 месяцев после COVID-19 по сравнению с 3 месяцами. Уровень антител был достоверно ниже в группе больных ТБ ($p = 0,01$). Количество SARS-CoV-2-специфичных Т-клеток было ниже у больных ТБ через 6 месяцев после перенесенного COVID-19 ($p < 0,001$) по сравнению с контрольной группой. Таким образом, коинфекция ТБ снижает специфический иммунный ответ против SARS-CoV-2 через 6 месяцев после перенесенного COVID-19.

Ключевые слова: COVID-19, туберкулез, иммунологическая память, Т-лимфоциты $CD4^+$, IgG

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The ongoing tuberculosis (TB) epidemic was undoubtedly negatively affected by the redistribution of health services during the COVID-19 pandemic. The acute form of COVID-19 and TB may co-occur, and the rate of such co-infection may be underestimated in the regions where the prevalence of TB is high. The prior or current TB is a risk factor of death from SARS-CoV-2. The T-cell response to Mtb can be modulated by SARS-CoV-2, as demonstrated in ex vivo studies of blood cells from individuals with acute infection. In contrast, the activation of innate and adaptive immunity in the presence of concomitant TB may impair the immune response to SARS-CoV-2 and increase inflammation. Although animal studies and epidemiologic data suggest that BCG may protect against SARS-CoV-2, vaccine efficacy has not been confirmed in several large clinical trials [1].

The COVID-19 pandemic has created new problems for patients with pre-existing respiratory infections. Of particular concern is the interaction between COVID-19 and TB, the combination of which presents a challenging clinical landscape [2]. Both respiratory infections are characterized by hyperintense inflammation with high levels of pro-inflammatory cytokines, including TNF, IL6, and IL1. These released cytokines and chemokines attract the immune cells that enhance the pro-inflammatory response and contribute to tissue damage. The data obtained underscore the severity of this interaction, showing that concurrent or sequential lung infection with COVID-19 and TB exacerbates respiratory symptoms and markedly reduces lung function [3].

It has been shown that TB can affect the severity of COVID-19 due to impaired immunity and chronic pneumonia [4]. Dysregulated immune responses are observed in patients with active TB, which can impair the immune response to COVID-19 and result in a more severe disease. In addition, COVID-19 can reactivate latent TB in patients with a history of the disease, further exacerbating the severity of symptoms [5, 6]. Comparison of patients with TB and COVID-19 with the patients having pneumonia showed that 22% of surveyed patients with TB had mild-to-moderate clinical forms of the disease, while other 78% developed more severe COVID-19 forms [7].

The novel coronavirus disease (COVID-19) led to the high morbidity and mortality rates [8]. The adaptive immune response plays an important role in controlling the majority of viral infections. The most important basic components of the adaptive immune system are B cells (as a source of antibodies) and T cells ($CD4^+$ and $CD8^+$). Given the fact that adaptive immune responses are important for control and elimination of almost all viral infections causing human diseases, and both adaptive immune responses and the immunological memory play a key role in developing the vaccine-induced immunity, it is extremely important to understand the adaptive responses to SARS-CoV-2. SARS-CoV-2 specific antibodies as well as $CD4^+$ and $CD8^+$ T cells are produced by the host in response to viral infection [9–11]. Antibodies and T cells play a defensive role in the fight against viral infections. However, the role and importance of each adaptive immunity component vary depending on the type of viral infection. The relationship between the neutralizing antibodies, memory T cells and COVID-19 severity seems to be complex. High titers of neutralizing antibodies are associated with severe disease and possibly extrafollicular B cell responses [12, 13], while memory T cells specific for SARS-CoV-2 show variable associations depending on the study [14–17]. IgG and $CD4^+$ T cells against SARS-CoV-2 antigens are detected in blood of almost all patients having a history of COVID-19. It has been shown that the intensity of Spike-specific $CD4^+$ T-cell response correlates with the Spike IgG levels [9, 16, 18]. However, some individuals have detectable $CD4^+$ T cells against SARS-CoV-2 despite low or negative IgG test results. 1–10% of people infected with SARS-CoV-2 experience this situation [19–21].

The study was designed to evaluate the duration of persistence of cellular and humoral immunologic memory to SARS-CoV-2 in the context of TB co-infection.

METHODS

Patients

A total of 120 people (59 males and 61 females) aged 18–70 years (average age 40 ± 15 years) were included in the study. Inclusion criteria: Healthy individuals (15 persons) — Individuals with no history of COVID-19 and TB; Individuals who had had COVID-19 within 3 months prior to inclusion in the study (without a history of TB) (16 persons); Individuals who had had COVID-19 within 6 months prior to inclusion in the study (without a history of TB) (19 persons); Patients treated at the Central Tuberculosis Research Institute between August 2021 and February 2022 for pulmonary TB who had received COVID-19 within 3 months prior to enrollment in the study (31 people); Patients treated at the Central Tuberculosis Research Institute between August 2021 and February 2022 for pulmonary TB who had received COVID-19 within 6 months prior to enrollment in the study (38 people).

All patients diagnosed with pulmonary TB were prescribed therapy taking into account *M. tuberculosis* drug resistance and individual drug tolerance. Diagnosis of TB in all patients in the study was performed with the use of the BACTEC MGIT 960 (BD; USA) in accordance with the manufacturer's recommendations [22]. All the samples that tested positively were stained by Ziehl-Neelsen and assessed by microscopy in order to identify acid-fast bacteria. Biomaterial was further assessed using the PCR-based method.

All patients enrolled in the study had a history of mild to moderate COVID-19. No patients with severe COVID-19 were enrolled in the study.

Exclusion criteria: age under 18 years; pregnancy; history of diabetes mellitus, polyvalent allergy, bronchial asthma, systemic autoimmune disease, active infection; decompensated chronic heart failure; acute myocardial infarction; continuous intake of corticosteroids.

The study involved the use of peripheral blood samples obtained from the patients and healthy individuals enrolled.

Determination of T cells specific for SARS-CoV-2 antigens

A total of 8 mL whole venous blood was collected from patients on test day. Sodium heparin was used as an anticoagulant. Peripheral blood mononuclear cells were isolated using a Ficoll gradient at a density of 1.077 g/cm^3 (PanEco; Russia). The TigerTest® SARS-CoV-2 kit (GENERIUM; Russia) was used to determine the number of T cells specifically responding to SARS-CoV-2 viral antigens according to the manufacturer's instructions. The S6 Ultra reader (CTL; USA) was used to enumerate spots corresponding to $CD4^+$/$CD8^+$ T cells secreting IFNγ.

Determination of IgG antibodies to the SARS-CoV-2 antigen

A total of 5 mL of whole venous blood was collected from each patient enrolled. Serum was then used for ELISA. The SARS-CoV-2 IgG ELISA kit (FSBI "NMRC for Hematology", Ministry of Health of the Russian Federation) was used for

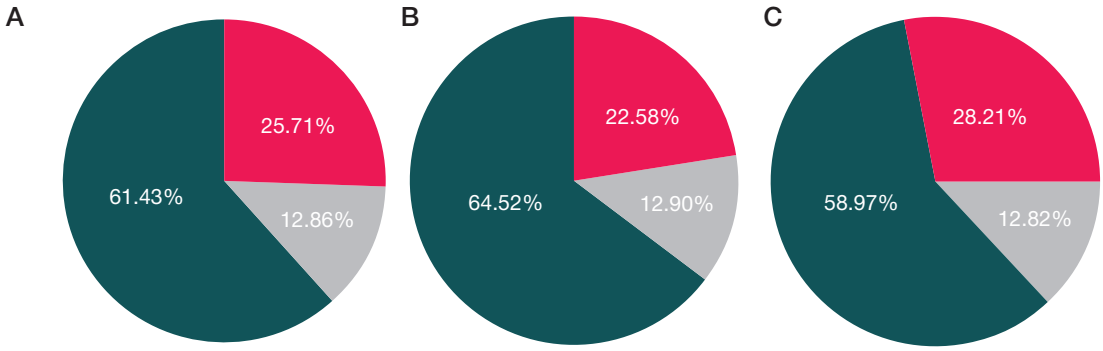

Fig. 1. Distribution by TB process among groups of pulmonary TB patients included in the study. **A**. All the patients diagnosed with pulmonary TB that were included in the study. **B**. Patients diagnosed with pulmonary TB, who had had COVID-19 within 3 months before inclusion in the study. **C**. Patients diagnosed with pulmonary TB, who had had COVID-19 within 6 months before inclusion in the study. Red sector of the diagram — patients with destructive TB; green sector of the diagram — patients with infiltrative TB; gray sector of the diagram — patients with disseminated TB

semi-quantitative determination of IgG to SARS-CoV-2 antigen in serum by solid-phase enzyme-linked immunosorbent assay according to the manufacturer's recommendations. Optical density was measured using the Sunrise™ microplate reader (TECAN; USA).

Statistical analysis

Statistical processing was performed using GraphPad Prism 8.4.3 (GraphPad Software; USA) with Mann-Whitney and χ^2 tests.

RESULTS

Characteristics of enrolled individuals

The study involved 69 individuals (33 females and 36 males) treated in the Central Tuberculosis Research Institute and having a history of COVID-19 within 3 months (31 individuals: 15 females and 16 males; average age 38 ± 15 years) and 6 months (38 individuals: 18 females and 20 males; average age 39 ± 15 years) before enrollment in the study as the experimental groups. The majority of patients had infiltrative TB (up to 64%), up to 28% were patients with destructive pulmonary TB, and 12.9% were patients with disseminated TB (Fig. 1A–C). All the patients were prescribed chemotherapy considering the M. tuberculosis drug resistance and individual drug tolerance. Bacteremia was observed in 58% and 47% of patients with a diagnosis of TB who had COVID-19 up to 3 and 6 months prior to study entry, respectively.

Thirty-five individuals (25 females and 10 males) who had undergone COVID-19 up to 3 months (16 individuals: 14 females and 2 males; mean age 48 ± 13 years) and 6 months (19 individuals: 11 females and 8 males; mean age 40 ± 14 years) prior to enrollment and had no history of TB were included as comparison groups.

Healthy individuals (15 people (7 females and 8 males; average age 49 ± 14 years)) having no history of TB and COVID-19 were included in the study as negative controls.

Determining IgG against the SARS-CoV-2 antigens

In the first phase of the study, we compared the presence and titers of specific IgG against the SARS-CoV-2 antigens in patients from different groups. In the group of patients 3 months after COVID-19, active TB had no effect on the presence of specific IgG. No significant differences between these groups were revealed (Fig. 2).

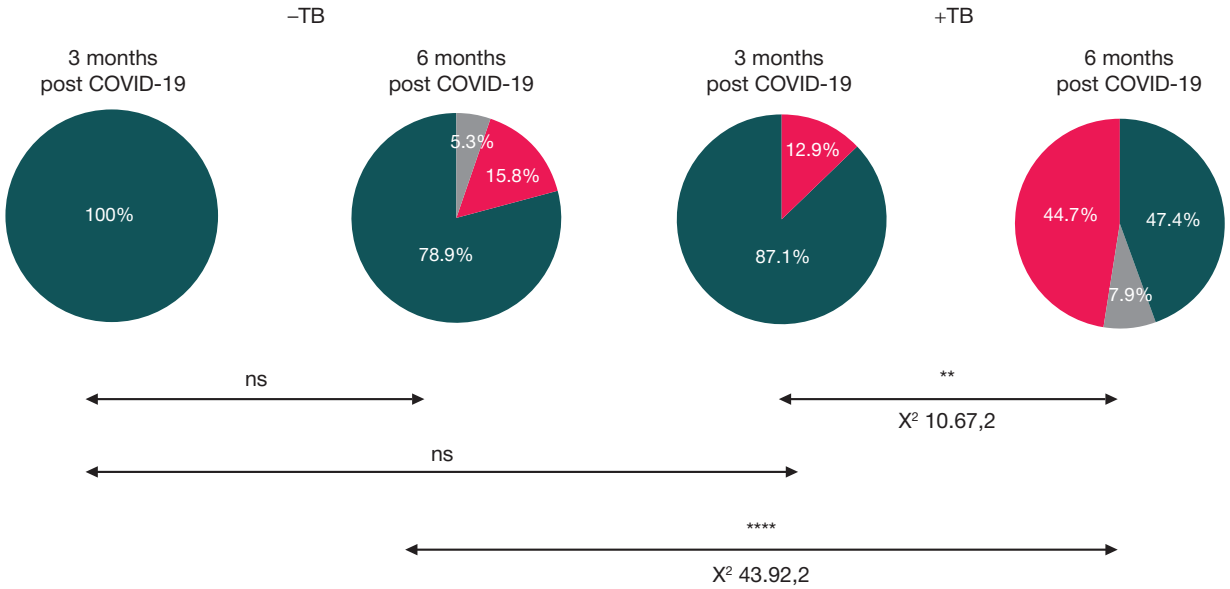

Fig. 2. Differences in serum levels of IgG to SARS-CoV-2 antigens in individuals who had COVID-19 within 3–6 months prior to enrollment, had no history of pulmonary TB (–TB), and were diagnosed with active pulmonary TB (+TB). Green sector of the diagram — patients testing positive for IgG to the SARS-CoV-2 antigens; gray sector of the diagram — patients with indeterminate results of the test for IgG to SARS-CoV-2 antigens; red sector of the diagram — patients testing negative for IgG to the SARS-CoV-2 antigens. ns — non-significant differences; ** — $p < 0.01$; **** — $p < 0.0001$

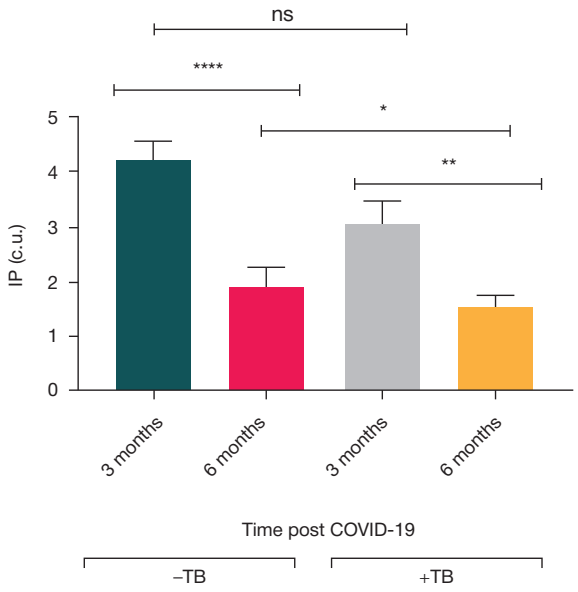

Fig. 3. Titers of IgG to SARS-CoV-2 antigens in blood serum of individuals who experienced COVID-19 within 3-6 months prior to enrollment, had no history of pulmonary tuberculosis (–TB), and were diagnosed with active pulmonary tuberculosis (+TB). Data are presented as a positivity index (PI) calculated according to the manufacturer's recommendations. ns — non-significant differences; * — $p < 0.05$; ** — $p < 0.01$; **** — $p < 0.0001$

Significant differences were observed when comparing the presence of IgG to SARS-CoV-2 antigens in the groups of patients who had a history of COVID-19 within 6 months prior to enrollment in the study. There were also significant differences in the percentage of patients testing positive for IgG against viral antigens (Fig. 2). Thus, positive results of the test for antibodies against the coronavirus antigens were reported in 79% of patients without active TB, while among patients diagnosed with pulmonary TB positive test results were reported only in 47.4%. No IgG antibodies to the SARS-CoV-2 antigens were detected in 12 patients diagnosed with pulmonary TB (44.7%) 6 months after having COVID-19 (Fig. 2).

The titers of IgG to SARS-CoV-2 antigens were different in the groups of patients without diagnosed TB and patients with diagnosed active pulmonary TB. 3 months after COVID-19, the maximum antibody titers to coronavirus antigens were detected in both the group of patients with and without a history of TB (Fig. 3). The IgG titers decreased 6 months after coronavirus infection, and the significantly greater decrease in IgG antibody titers was observed in the group of patients with active TB (Fig. 3).

Thus, titers of SARS-CoV-2 virus-specific IgG and duration of immune memory have been shown to be affected by the TB status.

Assessment of immunological memory to the SARS-CoV-2 antigens

Immunologic memory to the SARS-CoV-2 antigens was assessed using the TigraTest® SARS-CoV-2 kit. The kit is designed to determine the number of $CD4^+/CD8^+$ T cells responding to stimulation with SARS-CoV-2 specific antigens and to enumerate individual activated T cells. Test results were interpreted according to the manufacturer's recommendations. It was shown that, as in the case with antibodies to the coronavirus antigens, the presence of active TB affected the duration of the immunologic T-cell memory to SARS-CoV-2. Thus, in the groups of individuals without TB, there was no change in the percentage of patients with positive test results within 6 months after COVID-19 (Fig. 4), while in patients with active pulmonary TB, the percentage of patients with positive test results decreased by 6 months after viral infection. We also observed significant differences in the number of patients with positive TigraTest® SARS-CoV-2 results in the groups of patients with active TB and no history of TB 6 months after COVID-19 (60.5% and 84.2%, respectively) (Fig. 4).

One of the antigens in the TigerTest® SARS-CoV-2 test system is the S protein of the SARS-CoV-2 virus. This allowed us to study the duration of T-cell immune memory directly against this protein. With this approach, both in the group of patients with active TB and in the group of patients without a history of TB, the number of patients with a negative test result was higher than with the standard assessment of the presence of memory T cells to multiple antigens of the SARS-CoV-2 virus (Fig. 4–5). In the group of patients with lung TB, memory T cells

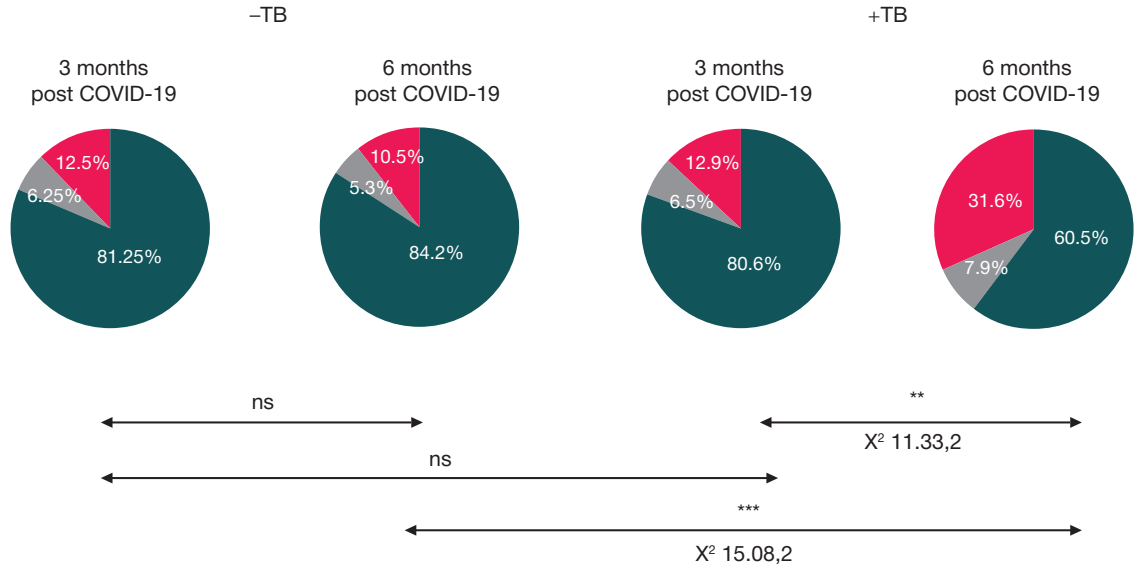

Fig. 4. Differences in the number of positive, negative, or questionable $CD4^+/CD8^+$ T-cell memory test results for SARS-CoV-2-virus antigens in COVID-19 survivors with and without pulmonary TB diagnosed 3 and 6 months before enrollment in the study. Green sector of the diagram — patients testing positive for memory T cells to SARS-CoV-2 antigens; gray sector of the diagram — patients with questionable results of the test for memory T cells to SARS-CoV-2 antigens; red sector of the diagram — patients testing negative for memory T cells to SARS-CoV-2 antigens. (–TB) — patients, who experienced COVID-19, with no history of TB; (+TB) — patients diagnosed with TB, who experienced COVID-19; ns — non-significant differences; ** — $p < 0.01$; *** — $p < 0.001$

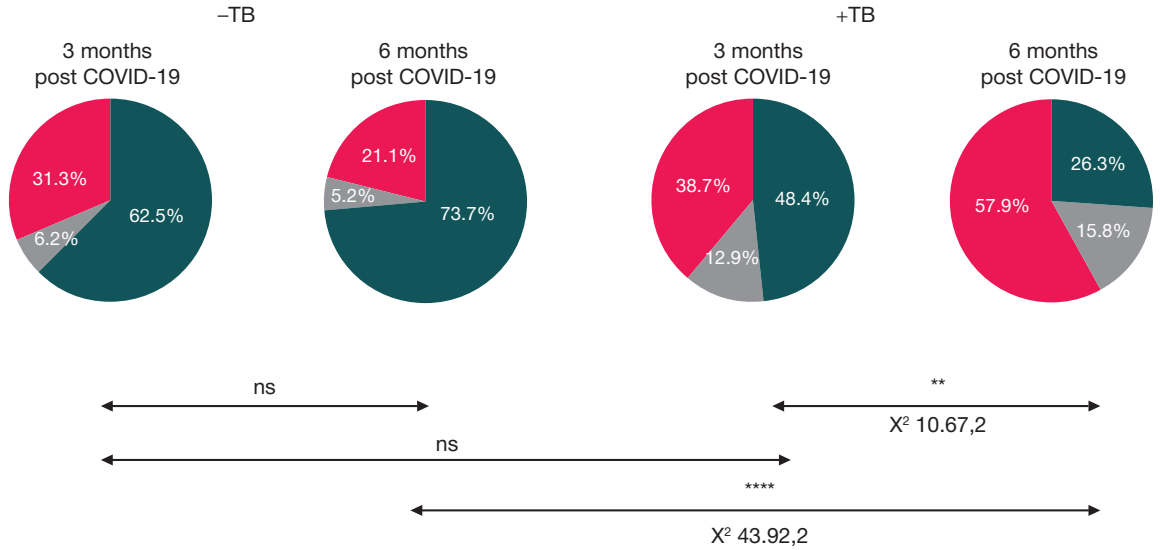

Fig. 5. Differences in the number of positive, negative, or questionable CD4⁺/CD8⁺ T-cell memory test results for S-protein antigens of SARS-CoV-2-virus in COVID-19 survivors 3 and 6 months before inclusion in the study diagnosed with pulmonary TB (+TB) and without pulmonary TB (–TB). Green sector of the diagram — patients testing positive for memory T cells against the SARS-CoV-2 S-protein antigens; gray sector of the diagram — patients with questionable results of the test for memory T cells against the SARS-CoV-2 S-protein antigens; red sector of the diagram — patients testing negative for memory T cells against the SARS-CoV-2 S-protein antigens. ns — non-significant differences; ** — $p < 0.01$; **** — $p < 0.0001$

to the SARS-CoV-2 S protein could not be detected in 57.9% of cases 6 months after the virus infection, while in the group of patients without lung TB, only 21% of such patients could be detected (Fig. 5).

DISCUSSION

The relationship between the COVID-19 virus and TB has been extensively studied to date, with a focus on co-infection and the impact of SARS-CoV-2 infection on latent TB. In this study we assessed the impact of TB on the duration of immunologic memory to viral antigens. Our results suggest a possible decreased effector response and increased regulatory mechanisms of immune response to SARS-CoV-2 antigens under the influence of bacterial infection.

Circulating IgG titers to SARS-CoV-2 were well maintained for 3–4 months in two large studies (>1000 individuals) [19, 23]. Virus-specific memory B cells, antibodies, and memory T cells were detected in mild COVID-19 cases approximately 90 days after infection [24].

One of the studies focused on assessing interaction with latent TB (LTBI) involved examination of seropositive, asymptomatic individuals infected with SARS-CoV-2 in India and comparison of immune responses in the IGRA-positive (LTBI) and IGRA-negative individuals [25]. The authors showed that IGRA-positive individuals had higher levels of humoral, cytokine, and acute phase responses compared to IGRA-negative individuals and thus concluded that LTBI could have a significant effect on the systemic inflammation, as well as on the cytokine response and the increase in the neutralizing antibody potency in individuals infected with SARS-CoV-2.

Based on the analysis of the IFNγ production by T cells in the cohort of participants with co-infection, active TB can have a negative effect on the patient's ability to generate the SARS-CoV-2-specific immune response [26]. The lowest secretion of IFNγ in response to stimulation with the SARS-CoV-2 peptide compared to patients with COVID-19 and patients with LTBI/COVID-19 was detected in the whole blood of patients with TB/COVID-19. The authors demonstrated that patients with COVID-19 having latent or active TB were still able to respond to the Mtb-specific antigens. However, only 20% of patients with active TB and COVID-19 responded positively versus 64% of patients with COVID-19 and LTBI, suggesting that active TB suppresses the host's COVID-19-specific immune response [26] and confirming results obtained in a previous study [24] for COVID-19 and TB/HIV [27].

119 individuals were studied and the blood plasma immune profile of 14 TB/COVID-19 co-infected patients, COVID-19 co-infected patients, TB co-infected patients and 20 healthy controls was compared by 27-component multiplex analysis. [28]. The authors observed that circulating TNF levels were most strongly correlated with TB/COVID-19 co-infection in comparison to COVID-19. They also showed that patients with co-infection had a reduced SARS-CoV-2-specific response based on the number of pro-inflammatory cytokines and/or chemokines, anti-inflammatory cytokines and growth factors. Furthermore, they concluded that co-infection negatively affected the Mtb-specific response (to a lesser extent).

CONCLUSIONS

While the duration of antiviral immunity monitoring in TB patients with a history of COVID-19 has been limited to 3-4 months in the vast majority of studies [29], we have demonstrated a decrease in virus-specific humoral and cellular immune responses in patients with TB co-infection 6 months after COVID-19. Our data suggest that the duration of protective antiviral immunity is shortened by concomitant TB infection. The long-term consequences of SARS-CoV-2 and Mtb co-infection will be the subject of further studies.

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