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Clinical characteristics and risk factors for tuberculosis during the COVID-19 pandemic: a longitudinal analysis in a trans-border Ukrainian region

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Conflict of interest: none

OBJECTIVE. To assess the dynamics of the clinical peculiarities and risk factors for tuberculosis (TB) during the coronavirus disease (COVID-19) pandemic through a longitudinal analysis in a trans-border Ukrainian region.
MATERIALS AND METHODS. Objectives were: 1) assessment of the general peculiarities, social and epidemiological risk factors of patients diagnosed with TB clinically managed during three phases of the COVID-19 pandemic in Ukrainian trans-border region Chernivtsi; 2) evaluation of the progression in the use TB diagnostic tools and their impact on the treatment effectiveness; 3) establishing the main issues and challenges in management of TB patients during three periods of the COVID-19 pandemic in the trans-border region. A prospective, case-control study, which was conducted from 2018 to 2023, included 896 patients registered during the pre-COVID pandemic, 579 patients during initial COVID-19 pandemic and 773 patients during the late-pandemic periods.
RESULTS. While the demographic characteristics of the patients did not differ during the pre-, initial and late-pandemic periods in a trans-border Ukrainian region, their clinical aspects, case-detection, management and treatment outcome were contrasting. The dynamics was negative during the initial COVID-19 pandemic in terms of severity of the clinical, radiological and laboratory aspects, which resulted in a higher rate of patients with negative outcomes.
CONCLUSIONS. Establishing the risk factors and issues with the greatest impact of the clinical case-management is crucial for targeted prevention and early intervention strategies for maintain the TB control at the regional trans-border level.

KEY WORDS: tuberculosis, risk factors, treatment, outcome.

Клінічні характеристики та фактори ризику туберкульозу під час пандемії COVID-19: лонгітюдний аналіз у транскордонному регіоні України

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МЕТА. Оцінити динаміку клінічних особливостей і факторів ризику туберкульозу (ТБ) під час пандемії коронавірусної хвороби (COVID-19) шляхом проведення лонгітюдного аналізу в транскордонному регіоні України.
МАТЕРІАЛИ ТА МЕТОДИ. Цілі: 1) оцінювання загальних особливостей, соціальних та епідеміологічних факторів ризику пацієнтів із клінічно пролікованим ТБ протягом трьох фаз пандемії COVID-19 у транскордонному регіоні України на прикладі Чернівецької області; 2) аналіз використання засобів діагностики ТБ та їх впливу на ефективність лікування; 3) визначення основних проблем і викликів у веденні хворих на ТБ протягом трьох періодів пандемії COVID-19 у транскордонному регіоні. Проспективне дослідження типу «випадок – контроль», що проводилося з 2018 по 2023 рік, включало 896 пацієнтів, які перебували на обліку в період до пандемії COVID-19, 579 пацієнтів у ранній період пандемії та 773 пацієнти – в пізній період.

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РЕЗУЛЬТАТИ. Хоча демографічні характеристики пацієнтів не відрізнялися протягом періодів до пандемії, на початку та наприкінці в транскордонному регіоні України, клінічні аспекти, виявлення випадків, ведення й результати лікування були контрастними. Динаміка була негативною в ранній період пандемії COVID-19 за тяжкістю клініко-рентгенологічних і лабораторних аспектів, що призвело до більшого відсотка хворих з негативним прогнозом.
ВИСНОВКИ. Встановлення факторів ризику та проблем, які мають найбільший вплив на ведення клінічного випадку, має вирішальне значення для пацієнтоорієнтованої профілактики, стратегій раннього втручання й контролю ТБ на регіональному транскордонному рівні.

КЛЮЧОВІ СЛОВА: туберкульоз, фактори ризику, лікування, результат.

Introduction

Tuberculosis (TB) is an infectious and contagious disease caused by the *Mycobacterium tuberculosis* (MTB) complex. Annually 55,000 new cases are reported in the European Union / European Economic Area. Most of the European Union countries are low incidence, however increased rates were registered in South Eastern European Region, in which the public health concern are the drug-resistant (MDR-TB) strains of MTB. It constitutes a priority of the Ukrainian public health system, were the prevention and infection control are national strategic objectives [3, 4].

Academic publications described several common peculiarities of SARS-CoV-2 and MTB infections: airway transmission through droplets, target organs-lungs and advanced respiratory syndrome. The coronavirus disease (COVID-19) pandemic has significantly impacted TB notification and infection control efforts in Ukrainian and Moldovan trans-border regions in several ways: reduced the intensity of the screening of high risk group for TB, disrupted activity of specialized TB services, restricted the patients' mobility, decreased the accessibility to healthcare services, and reduced the treatment adherence [13]. The COVID-19 pandemic restricted citizens mobility into several phases: initial strong restrictions (January-March 2020 – early 2021, early-pandemic period), during which the government implemented severe mobility restrictions and closed the borders for international tourism. Middle phase (2021 – early 2022, mid-pandemic period) was characterised by the gradual easing and fluctuating restrictions [11]. Last-pandemic period was characterised by targeted restrictions (2022-2023), which involved the gradual lifting of the mobility restrictions (late 2023 onwards). During the initial phase the COVID-19 vaccination campaign started and was increased adoption of digital solutions for safe travel and international mobility, which finally reduce the spread of infections. In summary, the COVID-19 pandemic evolved from severe, widespread mobility restrictions in early 2020 to more targeted, less severe measures by 2022-2023, with an overall trend towards lifting restrictions [13].

The most recently research papers emphasised that there are several risk factors for MTB infection and TB progression, which were affected by the COVID-19 pandemic: a) environmental factors: close contact with TB patients, particularly in-household clusters, overcrowding in high burden and congregate settings (nursing homes, homeless shelters and prisons); b) demographic factors: people older 65 had a higher risk for TB during COVID-19 pandemic, women due clinical and medical peculiarities (pregnancy / post-partum period, obesity/malnutrition, diabetes mellitus, low hemoglobin levels) were more often affected; c) medical factors: HIV/AIDS infection, chronic respiratory diseases, and associated with tobacco smoking, alcohol consumption, injecting and non-injecting drug use were more often detected. COVID-19 impact was perceived on the most economical defavorised populations due to worsening of the living conditions, food insecurity and reducing mobility [3]. When COVID-19 vaccination rates increased and better management strategies were developed, the decreased the burden on public health healthcare system allowed restarting the detection campaigns [13].

Scientific research established that during the evolution of COVID-19 pandemic the diagnostic tools changed rapidly and significantly in Ukraine [1, 2]. During the early pandemic phase were performed different molecular tests (reverse transcriptase polymerase chain reaction, RT-PCR) which finally were adopted as the gold standard for early detection of SARS-CoV-2 viral infection [6, 7]. Caused by the shortages of the reagents and testing materials during the pandemic early phase, the antigen rapid detection tests (Ag-RDTs) were implemented, offering faster results and easier use. While RT-PCR tests remained the gold standard, rapid antigen tests (Ag-RDTs), self-testing became the main method for diagnosing SARS-CoV-2 infection during the mid-pandemic period and antibody tests were introduced for surveillance purposes [1, 2, 7]. Genomic sequencing assays were used for research purposes to detect new SARS-CoV-2 virus strains at the regional level [6, 7].

The diagnosis of active TB in Ukraine follows the World Health Organization (WHO) and international recommendations, which incorporated the latest evidence-based practices and technologies [12]. Nucleic acid amplification tests (GeneXpert MTB/Rif) are now the primary recommended method for detection of TB. Moderate complexity automated NAATs (GeneXpert MTB/Rif) are currently used for detecting resistance to rifampicin, and fluoroquinolones. Chest X radiography is the basic tool in TB screening and diagnosis [5, 12]. Some specialized healthcare settings used the computer-aided detection (CAD) software for interpreting chest radiographs and diagnosing radiologically pulmonary TB. At the primary healthcare settings, the diagnostic algorithm, which include the symptom screening, sputum smear microscopy and chest radiography remained the basic tool for diagnosis of pulmonary TB [9]. In children and people living with HIV the *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs) for diagnosing

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TB infection is usually used [5]. Summarizing data provided by the specialized literature was pointed out that the COVID-19 influenced the screening campaigns for detection of TB then decreased the number of registered cases, as well required a wider use of molecular genetic assays for diagnosis of both infections. As well, there were no found data on the shifting of the risk factors for TB, evolution of the diagnostic tools for MTB infection, treatment effectiveness in Ukrainian trans-border regions, which constituted the basis of the presented study.

The objectives of the study were: 1) assessment of the general peculiarities, social and epidemiological risk factors of patients diagnosed with TB clinically managed during three phases of the COVID-19 pandemic in Ukrainian trans-border region Chernivtsi; 2) evaluation of the progression in the use TB diagnostic tools and their impact on the treatment effectiveness; 3) establishing the main issues and challenges in management of TB patients during three periods of the COVID-19 pandemic in the trans-border region.

Materials and methods

There was realized a longitudinal, case-control research, conducted between 01.01.2018-31.12.2023 in Ukrainian trans-border region Chernivtsi, in which were included 2248 TB patients, from which 896 cases (1st group) were registered and clinically managed during the pre-COVID-19 period (01.01.2018-31.12.2019), 579 patients (2nd group) during the initial phase of COVID-19 pandemic (01.01.2020-31.12.2021) and 773 patients (3rd group) during the late-pandemic period (01.01.2022-31.12.2023).

The research reported ethics committee approval (no. 14 from 21.11.2017) and the patients consent were obtained. Including criteria in the research were: age more than 18 years old; diagnosis of pulmonary TB and signed informed consent. The main enrolment criteria in the study was the diagnosis of pulmonary TB according to radiological, microbiological or histological criteria, the investigations and treatment were accomplished during the stated period of time in the Ukrainian trans-border region Chernivtsi.

The study investigation schedule included information about demographic characteristics, clinical symptomatology, radiological and microbiological aspects, therapeutic regimens, and the results of the treatment outcome. All patients with TB were investigated and treated according to the national clinical protocol. Statistical analysis was carried out using quantitative and qualitative research tests of the SPSS Statistics 23.0 software in which the paired sample t-test and Anova tests were performed. The differences were considered statistical significant with the probability of more than 95 % and $p < 0.05$.

Results

According to the distribution by gender criteria was established the male/female rate 2.9/1 in the 1st group, 3/1 in the 2nd group and 4/1 in the 3rd group. Even the rate of men affected by TB increased during the period of 2018-2023, the statistical threshold was not achieved.

Repartition of patients in age groups, according to the WHO recommendations identified that the largest subgroups were between 35-54 years old during the entire assessed period, which constituted 247 (51 %) in the 1st group, 290 (49 %) in the 2nd group and 438 (57 %) in the 3rd group. It was followed the youngest groups, between 18-34 years, which predominated statistically significant in the 1st group 123 (24 %) patients, compared with the 3rd group 102 (13 %) and insignificantly in the 2nd group with 104 (18 %) cases. The statistical threshold was achieved while comparing the subgroups of patients between 25 and 34 years old which predominated in the pre-pandemic period – 92 (18 %) compared with the late-pandemic period with 67 (9 %) cases. Regrouping the patients in two age groups: younger and older 45 years was established that younger patients statistically predominated in the pre-pandemic period – 260 (30 %) and older in late-pandemic period with 452 (58 %) cases (table 1).

National policy which is based on WHO recommendations requires the examination of the symptomatic patients through microbiological and molecular genetic tests

Table 1. Distribution by demographic data

Indices		N=2248		
		1st group (N=896)	2nd group (N=579)	3rd group (N=773)
Gender	Men	369 (74)	433 (75)	623 (80)
	Women	127 (26)	146 (25)	150 (20)
Age groups	18-24 years	31 (6)	25 (4)	35 (4)
	25-34 years	92 (18)$^{!}$	79 (14)	67 (9)
	35-44 years	137 (28)	154 (26)	222 (29)
	45-54 years	113 (23)	136 (23)	216 (28)
	55-64 years	67 (13)	123 (21)	122 (16)
	65 and more	56 (11)	62 (11)	114 (15)
Age categories	18-44 years	342 (69)$^{!!}$	258 (45)	324 (42)
	45+ years	154 (31)$^{!!}$	321 (55)	449 (58)

Notes: 1st group – pre-pandemic period 2018-2019, 2nd group – initial phase of the pandemic period 2020-2021, 3rd group – late-pandemic period 2022-2023; $^{!}$ $p < 0.05$; $^{!!}$ $p < 0.01$.

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and the radiological investigation or tuberculin skin test of people from the high risk groups. Studying the case-detection was found that two thirds of patients from entire evaluated period were detected by the general practitioners during the investigation of the symptomatic cases. Active screening of the high risk groups detected a higher proportion of the patients during the pre-pandemic compared with the late-pandemic period and the medical specialists detected more often TB in late-pandemic period compared with the pre-pandemic. Were detected due to direct referring to the specialised phthisiological clinical services a low proportion of patients during the entire evaluated period, however the rate was slightly higher in the late-pandemic period compared with earlier periods. It was not achieved the statistical threshold while comparing the rate of patients detected by general practitioners, medical specialists and addressed autonomously to the TB dispensaries during the evaluated period.

The use of microbiological diagnostic tools: sputum smear, cultures and molecular genetic assays for the etiological diagnosis of TB is a standard requirement according to the national policy and was applied to all patients. The rate of patients diagnosed through the microbiological methods was statistically higher in the late pandemic period compared with early periods and diagnosed through the clinical radiological methods were statistically more often the patients in the pre-pandemic and initial phase of the COVID-19 pandemic periods. As one of the consequence, the late detected forms which included distructive, diseminated, generalised and complicated TB prevailed during the pandemic period compared with pre-pandemic and late-pandemic periods. Histologically diagnosed using the organs biopsies were a low proportion of patients. While comparing the rate of the case-types according to the latest WHO recommended definitions was identified a statistical higher rate of cases which restarted the treatment after the failure and loss to follow-up in pre-pandemic compared with later periods. Pulmonary location of TB was diagnosed in most of the patients during the evaluated period. Patients with associated extrapulmonary TB focuses were slightly more often during the pandemic compared with other periods. The same proportion of patients with multiple sites TB was detected during the assessed time. The rate of lung parenchymal destruction and fibro-cavernous forms statistically increased during each period compared with the previous periods, as during late-pandemic years was three times higher compared with the pre-pandemic period (table 2).

Important to emphasize that during the initial COVID-19 pandemic both infections were diagnosed in 131 (23 %) patients. Almost all cases (101; 77 %) contracted the SARS-CoV-2 infection in hospital conditions. In late-pandemic period only 56 (7 %) patients contracted SARS-CoV-2 infection, all in ambulatory conditions. The diagnosis of SARS-CoV-2 infection was initially established using the antigen tests for detection of specific viral proteins in respiratory samples (sputum, nasal secretions) for rapid screening in high-risk settings, such as hospitals and healthcare ambulatory settings. Then the diagnosis was confirmed through the molecular tests (RT-PCR). Antibody tests were used in a minor number of patients to detect antibodies produced by the immune system in response to SARS-CoV-2 infection and to establish the COVID-19 vaccination.

Table 2. Distribution according to the healthcare providers in detection, diagnostic and clinical features

Indices	N=2248		
	1st group (N=896)	2nd group (N=579)	3rd group (N=773)
Primary healthcare staff in the frame of the investigation of the symptomatic cases	651 (73)	413 (71)	532 (69)
Primary healthcare staff in the frame of the active screening	158 (18)	76 (13)	100 (13)
Specialists during the hospital staying	55 (6)	62 (11)	81 (10)
Directly addressed to the TB-specialized services (dispensaries)	32 (4)	28 (5)	60 (8)
Laboratory diagnosed	310 (35)!!!	310 (53)***	582 (75)
Clinical-radiologically diagnosed	555 (62)!!!	253 (44)***	174 (22)###
Histologically diagnosed	31 (4)	16 (3)	17 (2)
Late detected TB	341 (38)!!!	367 (63)***	401 (52)
New cases	366 (74)	400 (69)	553 (71)
Relapse	61 (23)	105 (18)	164 (21)
Treatment failure / lost to follow-up	69 (24)!!!	74 (13)	56 (7)
Pulmonary TB	435 (88)	532 (92)	680 (88)
Associated extrapulmonary TB	47 (9)	29 (5)	73 (9)
Generalized TB (multiple sites TB)	13 (3)	18 (3)	20 (3)
Parenchymal lung destructions/caverna	151 (30)***, !!!	439 (76)	521 (67)

Notes: 1st group – pre-pandemic period 2018-2019, 2nd group – initial phase of the pandemic period 2020-2021, 3rd group – late-pandemic period 2022-2023; *** p <0.001 comparing 1st and 2nd groups; !!! p <0.001 comparing 1st and 3rd groups; ### p <0.001 comparing 2nd and 3rd groups.

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Table 3. Distribution according to the microbiological assays results, and treatment outcomes

Indices		N=2248		
		1st group (N=896)	2nd group (N=579)	3rd group (N=773)
Laboratory assays results	Microscopic positive for AFB	192 (21)***, !!!	292 (50)###	556 (72)
	Conventional cultures positive for MTB	210 (35)***, !!!	322 (55)##	528 (68)
	GeneXpert MTB positive	310 (35)***, !!!	321 (55)###	625 (81)
	GeneXpert MTB positive / Rif sensible	210 (23)***	243 (42)###	102 (13)
	GeneXpert MTB positive / Rif resistant	100 (11)	56 (10)	71 (9)
	Confirmed / conventional sensible TB	376 (42)***, !!!	429 (74)	672 (87)
	Monoresistant TB[1]	29 (6)	42 (7)	11 (1)
	Polyresistant TB[1]	9 (1)	12 (2)	18 (2)
	Rifampicin resistant / MDR-TB[2]	84 (9)	96 (16)	72 (9)
	AFB positive at the end of the 2nd month	52 (7)	42 (7)	52 (7)
	AFB positive at the end of the 3rd month	23 (4)	16 (3)	21 (3)
Treatment outcomes	Treatment success	588 (66)***	282 (48)	549 (71)
	Lost to follow-up	49 (5)	28 (9)	22 (3)
	Treatment failure – transferred to MDR-TB treatment	158 (17)***	191 (33)	110 (14)
	Died	101 (11)	78 (13)	92 (11)
Treatment delivery	DOT at dispensary	773 (86)!!	390 (67)	552 (71)
	DOT in ambulatory	118 (13)***	181 (31)###	111 (14)
	Video observed treatment	5 (1)	8 (1)	7 (1)
	Hospitalized during the intensive phase of the treatment	345 (69)***, !!!	444 (89)###	331 (43)

Notes: 1st group – pre-pandemic period 2018-2019, 2nd group – initial phase of the pandemic period 2020-2021, 3rd group – late-pandemic period 2022-2023; monoresistant TB[1] and polyresistant TB[1] at the DST; rifampicin resistant / MDR-TB[2] detected through the molecular genetic either drug susceptibility tests; DOT – directly observed treatment; * p <0.05, ** p <0.01, *** p <0.001 comparing 1st and 2nd groups; ! p <0.05, !! p <0.01, !!! p <0.001 comparing 1st and 3rd groups; # p <0.05, ## p <0.01, ### p <0.001 comparing 2nd and 3rd groups.

The microbiological tests – sputum smear microscopy, conventional cultures and molecular-genetic assays were positive at detection in a statistical higher rate during the pandemic and late-pandemic compared with pre-pandemic periods.

The rates of the monoresistant TB and polyresistant TB which were detected only through the drug susceptibility tests (DST) on conventional media did not differ significantly through the assessed periods. Rifampicin resistance detected through molecular genetic tests either multidrug-resistant TB confirmed through the DST diminished over the entire evaluated period, and resulted in a lower proportion during the late compared with pre and initial pandemic periods.

The therapeutic regimens were applied according to the case-types and the results of the drug-susceptibility resistance (molecular genetic either conventional cultures). Overall rate of the treatment success was statistically lower during the initial pandemic compared with pre- and late-pandemic periods, which was accompanied by a slightly higher rate of patients which were lost-to follow-up and those who evolved in treatment failure. So, during the anti-TB treatment the drug-resistance was acquired in a higher proportion during the initial pandemic, compared with pre- and late-pandemic periods. Assessing the location of the clinical case-management was established that the rate of patients which were treated under direct supervision by the specialized dispensary was higher during the initial pandemic compared with pre-pandemic and late-pandemic periods. The in-patient staying reduced drastically during the assessed periods, being two timed lower in the late-compared with initial pandemic periods.

While the demographic characteristics of the patients did not differ between the groups of the patients diagnosed in a trans-border Ukrainian region, their case-management, etiological examination results and treatment outcome were contrasting. Similar aspects were identified in other international researches [8].

The dynamics of the clinical peculiarities and risk factors for tuberculosis during the initial phase of the COVID-19 pandemic demonstrated that the epidemiological situation worsened as a consequence of the barriers in accessing the specialized in TB healthcare settings revealed by the severity of clinical radiological peculiarities, higher rate of the positive microbiological results and high rate of patients who were lost to follow-up, evolved with treatment failure and acquired TB, as well the increased death rate. Such results were published in other scientific papers [10].

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Conclusions

1. The demographic characteristics of the patients did not differ during the pre-, initial and late-pandemic periods in a trans-border Ukrainian region, but the clinical aspects, risk factors, case-detection tools, clinical case-management and treatment outcome were contrasting.
2. The dynamics was negative during the initial COVID-19 pandemic in terms of severity of the clinical, radiological and laboratory aspects, which resulted in a higher rate of patients with negative outcomes.
3. Establishing the risk factors and issues with the greatest impact on the dynamics of the clinical case-management is crucial for targeted prevention and early intervention strategies for maintain the TB control at the regional trans-border level.

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