PULMONARY TUBERCULOSIS IN THE CONTEXT OF COVID-19. DEMOGRAPHIC CHARACTERISTICS AND RISK FACTORS IN MOLDOVA AND UKRAINE

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ABSTRACT
The study aimed to analyze the main demographic characteristics and risk factors associated with tuberculosis (TB) before, during, and after the COVID-19 pandemic in the Republic of Moldova (RM) and Ukraine (UA) to identify the key determinants of their trends. A prospective case-control study was conducted between 2018 and 2023, including two cohorts: Moldovan (MD) comprised 1617 and Ukrainian (UA) 896 patients divided into three groups: 1st group corresponding to the pre-COVID-19 period (2018–2019), 2nd group (n=451) corresponding to the COVID-19 period (2020-2021), and 3rd group- post pandemic period (2022–2023). The main determinants influencing TB trends were the combination of social conditions (unemployment, low educational level, deprived housing, institutionalization), associated to malnutrition, harmful behaviors (smoking, alcohol, drug use), and increasing rate of comorbidities such as HIV, diabetes, chronic lung disease, and mental disorders, with each country having a distinct risk profile marked by the pandemic-related conditions. **Conclusions:** TB trends in MD and UA were determined by the complexity of socioeconomic risk factors, malnutrition, harmful behaviors, and rising comorbidities, with each country developing a distinct risk profile influenced by COVID-19-related conditions.
Keywords: Tuberculosis, COVID-19, Risk factors, Republic of Moldova, Ukraine.

1. INTRODUCTION
Socio-demographic determinants and epidemiological risk factors play a crucial role in the development of TB, a classic example of a socially determined disease (SDD), in which onset, progression, and outcomes are influenced primarily by social, economic, and environmental conditions rather than biological factors. The SDDs often disproportionately affect vulnerable and marginalized populations. Their occurrence is strongly influenced by poverty, overcrowded living conditions, limited access to healthcare, and malnutrition, which are deeply associated with social inequality [1]. Comorbid conditions, such as HIV infection, diabetes, chronic lung or kidney disease, undernutrition, and substance use, increase the TB risk by reducing immunity and accelerating progression from infection to active disease, as well as worsening treatment adherence and outcomes [2]. In this context, the implementation of health policies developed for the specific needs of individuals affected by TB, as stated in the WHO End TB Strategy, the Patients' Charter for TB Care, and the TB/HIV collaborative policy, demonstrated that targeted actions are essential to improve TB epidemiology globally and locally [2, 3]. Therefore, analyzing the demographic characteristics and risk factors of TB within different periods and regions is essential to identify the main determinants influencing their trends and elaborate target interventions for improving TB control in vulnerable populations. The study aimed to conduct a comparative assessment of the main demographic characteristics and risk factors associated with TB before, during, and after the COVID-19 pandemic in the Republic of Moldova (MD) and Ukraine (UA) to identify the key

determinants influencing their trends. Hypothesis: The demographic characteristics and risk factors associated with TB changed significantly during the COVID-19 pandemic, with specific demographic, socioeconomic, and health-related determinants.

2. MATERIAL AND METHODS

A prospective case-control study was conducted between 2018 and 2023, including two cohorts. The MD cohort comprised 1617 patients divided into three groups: 1st group (n=664) representing the pre-COVID-19 period (2018–2019), 2nd group (n=451) corresponding to the COVID-19 pandemic (2020–2021), and the 3rd group (n=502) representing the post-pandemic period (2022–2023). Similarly, the UA cohort was divided into three groups: 896 patients in the 1st group, 579 in the 2nd group, and 773 in the 3rd group.

3. RESULTS

The main demographic characteristics, including gender, age, and place of residence, were analyzed. The distribution of MD cohort by gender showed predomination of men in both cohorts (χ^2=101; p=0 in MA; χ^2=8; p=0.01 in UA) with an increasing trend of men over time from 474 (72%) vs 190 women (28%) in the 1st G, 330 (75%) men vs 121 (25%) women in the 2nd G and 376 (80%) men vs 126 (20%) women in the 3rd G. UA cohort showed similar trend: men 527 (69%) vs women 369 (41%) in the 1st G; 433 (75%) men vs 146 (25%) women in the 2nd G, 623 (80%) men vs 150 (20%) women in 3rd G. The increasing male predominance indicated the rise of TB cases, who are more affected by multiple risk factors. The male/female rate was higher in UA cohort - 2.9/1 in the 1st G, 3/1 in the 2nd G, and 4/1 in the 3rd G, compared with MD cohort: 2.5/1 in the 1st G, 2.7/1 in the 2nd G, and 2.9/1 in the 3rd G. The distribution of MD cohort in age subgroups showed that 35–44 years old (y. o.) cases represented the largest proportion and increased over time, accounting for 137 (21%) in the 1st G, 138 (31%) in the 2nd G, then decreased to 138 (27%) in the 3rd G. A similar trend was observed in the 45-54 y. o. subgroup - 156 (23%) in the 1st G, 136 (30%) in the 2nd G, and 135 (28%) in the 3rd G. The 55-64 y. o. Subgroup remained stable: 129 (19%) in the 1st G, 85 (19%) in the 2nd G, and 89 (17%) in the 3rd G. Lower proportions, with a decreasing trend, were observed in the 25–34 y group. o. subgroup, with 121 (18%), 70 (14%), and 77 (15%) across the three groups, also 18-24 y. o. subgroup with 36 (6%), 20 (4%), and 16 (4%) cases, respectively. The proportion of the older subgroup (+65) decreased from 85 (13%) cases in the 1st G to 2 (0.4%) in the 2nd G, then increased to 47 (9%) in the 3 rd G. The distribution of the UA cohort established that the largest subgroups were 35-44 years. o. and 45-54 y. o. which remained stable over time. The 35-44 y. o. Subgroup comprised 241 (27%) in the 1st G, 154 (26%) in the 2nd G, 222 (29%) in the 3rd G, and 45-54 y. o. - 215 (24%) in the 1st G, 136 (23%) in the 2nd G, and 216 (28%) in the 3rd G. Followed 55-64 y. o. Subgroup comprising 162 (18%) in the 1st G, 123 (21%) in the 2nd G, and 122 (16%) in the 3rd G. Lower proportions with an increasing trend were 55-64 y. o. subgroup- 162 (18%) in the 1st G, 123 (21%) in the 2nd G, 122 (16%) in the 3rd G, and 25-34 years. o. 148 (16%) in the 1st G, 79 (14%) in the 2nd G, and 67 (9%) in the 3rd G. In a very low proportion, with an increasing trend, were older adults aged 65 y. o. subgroup - 76 (8%) in the 1st G, 62 (11%) in the 2nd G, 114 (15%) in the 3rd, and a decreasing trend between 18-24 years. o. subgroup-54 (6%) in the 1st G, 25 (4%) in the 2nd G, and 35 (4%) in the 3rd G. The proportions of age subgroups did not differ significantly between the groups and across cohorts. After regrouping into two age categories (18-44 y. o. and ≥45 y. o.), in the MD cohort, the rate of young patients (18-44 y. o. subgroup) did not differ significantly over - 294 (44%) in the 1st G, 228 (45%) in the 2nd G, and 231 (42%) in the 3rd G, also older subgroup (≥45 y. o.) - 370 (56%), 223 (55%), and 271 (58%), respectively. In the UA cohort, 18-44 y. o. Subgroup decreased from 443 (49%) in the 1st group, 258 (45%) in the 2nd group, and 324

(42%) in the 3rd group, whereas older increased 453 (51%), 321 (55%), and 449 (58%) in the respective groups. The mean age did not differ significantly between groups: 46.2±14.7 y.o. in the 1st G and 47.5±12.4 y.o. o. in the 2nd G, and 45.5±13.5 in the 3rd G in MD cohort and 43.5±12.7 y. o. in the 1st G, 46.1±11.5 y. o. in the 2nd G, and 48.4±9.5 y. o. in the 3rd G. Although the majority of TB cases in both cohorts were included in the 35–44 and 45-54 age subgroups, the proportion of older individuals increased over time, while younger subgroups decreased, indicating a shift of TB burden toward older adults.

Urban residence was more common than rural in both cohorts (χ^2=46; p=0 in MD and χ^2=57; p=0 in UA), but its distribution showed different trends. In MD cohort, the rate of urban cases significantly increased over time from 442 (67%) in the 1st G to 378 (83%) in the 2nd G (χ^2=41, p=0) then decreased to 392 (78%) in the 3rd G, whereas the rate of rural residents declined from 222 (33%) in the 1st G to 73 (17%) in the 2nd G, then increased to 109 (24%) in the 3rd G (χ^2=5, p=0.02). In the UA cohort, the proportion of urban residents decreased from 692 (77%) in the 1st G to 421 (73%) in the 2nd G, then increased to 625 (81%) in the 3rd G. The rural residents increased from 204 (23%) in 1st G to 158 (27%) in 2nd G then decreased to 148 (21%) in 3rd G. Homelessness was more frequently established in the MD cohort, with an increasing tendency from 52 (8%) cases in the 1st G to 42 (9%) in 2nd G and 48 (10%) in 3rd G. In contrast, in the UA cohort, it remained at lower levels - 31(3%) in 1st G, 22 (4%) in 2nd G, and 27 (3%) in 3rd G. This pattern demonstrated that homelessness represents a key driver of TB burden, reflecting the intersection of housing instability, social marginalization, and limited access to healthcare.

The socio-economic characteristics assessed included marital status, economic condition, and education level. The distribution of patients by marital status in the MD cohort showed that married or partnered individuals increased from 326 (49%) in the 1st G to 281 (62%) in the 2nd G, then declined to 278 (55%) in the 3rd G. In the UA cohort, married or partnered individuals increased from 521(58%) in the 1st G to 381(66%) in the 2nd G, and decreased to 409 (53%) in the 3rd G, suggesting that partnerships, often associated with prolonged household exposure, contributed to intensified household transmission. In contrast, unpartnered individuals (single, widowed, or divorced) decreased from 375 (42%) in the 1st G to 381 (34%) in the 2nd G (198; 34%), then increased to 364 (47%), suggesting the widening rate of socially isolated TB patients over time. Unemployment was the prevailing economic status in both cohorts. Still, the pattern differed across groups: in MD, it significantly decreased from 465 (70%) in the 1st G to 206 (46%) in the 2nd G (χ^2=66, p=0.2), then rose to 337 (67%) in the 3rd G (χ^2=46, p=0.2). In comparison, professional employment increased from 199 (30%) in the 1st G to 245 (54%) in the 2nd G, then decreased to 165 (33%), respectively. This trend suggested that employment and related working conditions, often involving overcrowded workplaces and prolonged close contact, contributed to the transmission of TB within congregate settings. In the UA cohort, unemployment significantly predominated in all groups: 618 (69%) in the 1st G, 400 (69%) in the 2nd G, and 493 (64%) in the 3rd G, compared with professional employment, which remained lower at 278 (31%), 179 (31%), and 280 (36%), respectively, underscoring persistent economic vulnerability among TB patients (χ^2=6.3, p=0.04). Lower educational level (primary and incomplete secondary) consistently predominated in majority of cases in both cohorts, in MD cohort was common and stable: 459 (69%) in the 1st G, 296 (65%) in the 2nd G, and 325 (65%) in the 3rd G, whereas higher education (secondary and university) moderately increased from 205 (31%) to 157 (35%) and 176 (35%), respectively. In the UA cohort, low education decreased from 502 (56%) patients in the 1st G to 268 (46%) in the 2nd G, then increased to 446 (58%) in the 3rd G, compared with higher education (secondary and high) which increased from 394 (44%) to 311 (54%), then decreased to 327 (42%), respectively. The predominance of a lower educational pattern demonstrated that limited education

increased the vulnerability to TB, through socio-economic disadvantage, inadequate health literacy, and reduced access to healthcare.

The assessed risk factors included household characteristics, the presence of a TB source within the household, and behavioral risks such as smoking, substance use, and alcohol consumption, as well as migration characteristics. The assessment of household types revealed that deprived households characterized by the absence of centralized heating, water supply and sanitation increased from 186 (28%) in the 1st G to 162 (36%) in the 2nd G, then declined to 98 (19%) in the 3rd G. Also, in the UA cohort deprivation increased from 128 (14%) cases in the 1st G to 147 (25%) in the 2nd G, and then decreased to 152 (20%) in the 3rd G, indicating moderate but persistent level of inadequate living conditions contributing to TB transmission. The proportion of TB cases from institutional households, such as shelters, residences for older persons, and facilities for people with mental disorders) was higher in the MD cohort compared with the UA cohort. In the MD cohort the rate increased from 81(12%) in 1st G to 92 (20%) in 2nd G then decreased to 78 (15%) in 3rd G, while in UA cohort remained stable low: 18 (2%) patients in the 1st G, 12 (2%) in the 2nd G, and 11 (1%) in the 3rd group, indicating a much smaller proportion of UA patients were exposed to congregate living condition, that facilitate TB transmission, while in MD cohort even increased over time. Patients with prolonged household contact with an active TB, remained at the same level in both cohorts, with an increased tendency in MD cohort from 67 (10%) in the 1st G, 42 (9%) in the 2nd G, to 69 (14%) in the 3rd G, whereas in UA cohort remained stable 82 (9%) in 1st G, 58 (10%) in 2nd G and 81 (10%) in the 3rd G, indicating the persistence of household TB transmission and a continued presence of TB sources in the community. Analysis of migration-related characteristics in the MD cohort revealed that, refugees or migrants represented in a minor proportion, 9 (1%) cases in the 1st G, 5 (1%) in the 2nd G, and 11 (2%) in the 3rd G, while patients returning from abroad within the last year were more frequent and increased over time from 52 (8%) cases in the 1st G to 68 (15%) in the 2nd G, and 62 (12%) in the 3rd G, suggesting that returning migrants constitute a specific subgroup in MD cohort. In the UA cohort, temporarily displaced individuals accounted for 9 (1%) cases in the 1st G, 5 (1%) in the 2nd G, and 11 (2%) in the 3rd G, reflecting the impact of the recent geopolitical context. Behavioral risk factors, particularly active tobacco smoking, showed divergent patterns between cohorts, as it increased in MD cohort from 582 (64%) in 1st G to 403 (70%) in 2nd G and 581 (75%) in 3rd G, whereas in the UA cohort decreased from 551 (83%) in 1st G to 382 (85%) in 2nd G and 348 (69%) in the 3rd G. The high rate of smokers highlighted that it is an important risk factor due to associated comorbid background such as chronic lung disease, cardiovascular conditions, and bronchoplmonary malignancy. Alcohol abuse slightly decreased in both cohorts: in MD from 87 (13%) cases in the 1st G to 49 (11%) in the 2nd G, and 52 (10%) in the 3rd G, and in UA from 101 (12%) cases in the 1st G to 52 (9%) in the 2nd G, and 76 (10%) in the 3rd G. In the MD cohort, the substances or drug use decreased from 19 (3%) cases in the 1st group, 8 (2%) in the 2nd group, and 9 (2%) in the 3rd group, whereas in UA sample was less frequent, accounting for 9 (1%) cases in the 1st G, 8 (1%) in the 2nd G, and 7 (1%) in the 3rd G. Despite low downward trends, alcohol and drug use remained important behavioral risk factors for TB, as they contribute to immune dysfunction, poorer treatment adherence, and higher exposure in high-risk settings.

Biological characteristics analyzed included nutritional status (body mass index, BMI), the presence of comorbidities, and their potential associations. The distribution of underweight patients in the MD cohort showed an increased rate across all groups -119 (13%) cases in the 1st G, 101 (22%) in the 2nd G, and 104 (21%) in the 3rd G, while in UA cohort decreased, from 181 (20%) cases in the 1st G, to 78 (13%) in the 2nd G, and 83 (14%) in the 3rd G. HIV coinfection increased in MD cohort from 52 (6%) cases in 1st G to 49 (11%) in 2nd G, and decreased to 39 (8%) in 3rd G, while in UA cohort significantly increased from 82 (9%) in 1st

G to 121 (21%) in 2nd G (X=x, p=0.05) and decreased to 84 (13%) in 3rd G. Prior TB infection in MD cohort slightly increased from 69 (8%) of 1st G to 78 (17%) in 2nd G, then decreased to 49(10%) in 3rd G, while in UA cohort remained stable across groups - 72(8%) in 1st G1, 44(8%) in 2nd G, and 52 (8%) in 3rd G. Chronic lung diseases (including post-TB lung disease) were diagnosed in 82 (12%) in 1st G, 42 (9%) in 2nd G, and 58 (11%) in 3rd , while in UA cohort remained stable - 72(8%) in 1st G1, 44(8%) in 2nd G, and 52 (8%) in 3rd G. Glucose metabolism disorders, including diabetes, were identified in 61 (9%) cases of 1st G, 48 (11%) in 2nd G, and 31 (6%) cases in 3rd G in MD cohort, while in UA cohort was established a significant increase, rising from 49(5%) in 1st G to 86 (15%) in 2nd G and 97 (17%) in 3rd G (χ^2=6.2, p=0.04). The proportion of gastrointestinal diseases, including viral or toxic hepatitis decreased in MD cohort, from 115 (13%) in 1st G to 78 (17%) in 2nd G, and 52 (10%) in 3rd G, while in UA cohort increased from 128 (14%) patients of 1st G, to 94(16%) in 2nd G, and 103(18%) in 3rd Gr. Chronic renal disease were diagnosed increasingly from 32 (3%) of 1st G to 45 (10%) in 2nd G, and decreased to 12 (2%) in 3rd G of MD cohort, whereas in UA cohort remained in stable low proportion 18 (2%) in 1st G, 12 (2%) in 2nd G, and 21(4%) in 3rd G. Mental health disorders increased in MD cohort from 79 (9%) to 58 (13%), and 39 (8%) of the MD cohort, while in UA cohort in 95(11%) of 1stG, 68(12%) of 2nd G, and 72(12%) of 3rd G.

4. DISCUSSION

Tuberculosis predominantly affected working-age adults, individuals living in urban areas, the unemployed, and those with lower levels of education, findings reported in multiple large cohort studies [2-6]. Comorbidities and poor nutritional status followed divergent trajectories within cohorts but demonstrated a high impact on vulnerability. Particularly, HIV-coinfection increased, highlighting rising TB/HIV in Eastern Europe; also, prior TB infection and chronic lung diseases suggested the persistence of latent TB infection within the population. In contrast, glucose metabolism disorders increased in UA, but declined in MD. At the same time, gastrointestinal disease, chronic renal disease, and mental health disorders showed variable but persistent rates, demonstrating that TB disproportionately affects patients with multiple comorbidities, which worsen prognosis and amplify transmission risk. A potential limitation of the study is that the analysis was restricted to selected regions during specific periods, so results may not reflect national cohorts or fully establish the effect of the pandemic in the context of broader socioeconomic and healthcare system changes.

5. CONCLUSIONS

The analysis of demographic characteristics and risk factors for TB before, during, and after the COVID-19 pandemic in the MD and UA identified several key determinants: TB predominantly affected working-age adults (35–54 years), with an increasing rate of older individuals; urban residence, unemployment, and lower education were associated with higher TB burden. In the MD cohort, homelessness, institutionalization, and malnutrition prevailed, especially during the pandemic period; in contrast, in the UA cohort, diabetes and HIV coinfection prevailed. Prolonged household TB contact and previous TB infection remained stable in both cohorts, indicating persistent transmission.

DECLARATIONS

Conflict of Interest Statement: The authors declare that they have no conflict of interest.
Author Contributions: E. L. designed the study; E. L. and L. T. analyzed data; E. L. drafted the manuscript; Both authors have reviewed and approved the final version of the manuscript.
Ethics Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the State Pharmacy and Medicine University ethics committees on

13.11.2017. All participants provided informed consent, and data were anonymized to ensure confidentiality.

Originality Statement: The authors confirm that this manuscript is original, has not been published previously, and is not under consideration elsewhere.

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