CLINICAL AND LABORATORY CHARACTERISTICS OF PULMONARY TUBERCULOSIS IN THE CONTEXT OF THE COVID-19 PANDEMIC IN THE REPUBLIC OF MOLDOVA AND UKRAINE

Evelina LESNIC[1]*, Lilia TODORIKO[2], Ihor SEMIANIV[2]

7. Internal Medicine Department, Nicolae Testemițanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
8. Phthisiology Department, Bukovinian State Medical University, Chernivtsi, Ukraine

*Corresponding author: evelinalesnic@yahoo.com

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ABSTRACT

The study aimed to analyze the main clinical and laboratory characteristics of tuberculosis and their impact on case management and outcomes before, during, and after the COVID-19 pandemic in the Republic of Moldova (RM) and Ukraine (UA). 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). Primary healthcare providers played a central role in TB case detection and clinical assessment of the majority of TB cases in both countries, which were clinically symptomatic with TB-related presentations, whereas active screening made a limited contribution. The COVID-19 period impacted the case-management, determining a marked increase in laboratory-diagnosed TB, a higher rate of late-detected cases, and lower outcomes, particularly in drug-resistant TB. The results highlighted the importance of strengthening primary care-based case detection, expanding active screening, and sustaining progress in TB control while adapting to region-specific needs.

Keywords: Tuberculosis, COVID-19, Microbiology, Case management, Republic of Moldova, Ukraine.

1. INTRODUCTION

The COVID-19 pandemic had a profound impact on global tuberculosis (TB) control efforts, significantly disrupting the progress [1]. According to the World Health Organization (WHO) Global Tuberculosis Report, while some improvements have been made, TB case numbers continue to exceed pre-pandemic levels. In 2023, an estimated 10.8 million people developed TB, slightly more than in 2022, 7.5 million, with an incidence rate rising to 134 per 100,000 population [2]. At a rate of 87%, these cases occurred in 30 high-TB burden (HTB) countries, including the Republic of Moldova (MD) and Ukraine (UA). At the same time, India, Indonesia, China, the Philippines, and Pakistan accounted for half of global cases [3]. Although TB-related deaths declined to 1.25 million in 2023, from 1.32 million in 2022, the COVID-19 pandemic reversed the progress, and TB is now the leading global cause of death from a single infectious agent [2]. The COVID-19 pandemic severely disrupted TB diagnostic and treatment services, leading to delayed detection, increased transmission, and undiagnosed 2.7 million cases [4]. It is important to mention that RM continues to advance in the fight against TB, although it did not meet the 2025 global targets set by the WHO's End TB Strategy [2]. In 2023, RM, with a population of 3.1 million, reported 2300 new TB cases and 204 TB-related deaths (6.7/100000 people), reflecting a 33% reduction in TB mortality and a 26% reduction in TB incidence compared to 2015, still below the milestones of 75% and 50% reductions, respectively. According to national reports, the TB incidence rate in 2023 reached

76/100.000 population (range 64–88), reflecting a 2% increase from 2022 (74.5/100.000) and an 8.4% increase from 2021 (67.1/100.000). The incidence of TB relapses showed a fluctuating trend, with 14.8/100.000 population (range 11-19) in 2022 (457 cases), slightly increased from 14.7/100.000 population in 2021 (454 cases) and 13.9/100.000 population in 2020 (566 cases), then decreased compared with 18.8/100.000 population in 2019 (670 cases). The rate of destructive forms among new pulmonary cases increased from 37% in 2020 to 41% in 2023. Only 44% of estimated multidrug- or rifampicin-resistant TB (MDR/RR-TB) cases were treated in 2022, achieving a success rate of 68%, while in drug-susceptible TB, the rate remained high at 88% [5]. In this context, analyzing how risk factors affect the clinical course and paraclinical features across different periods of the COVID-19 pandemic and across various regions is essential to identify the main determinants of outcomes and to develop targeted interventions aimed at strengthening TB control in vulnerable populations [7]. The study aimed to conduct a comparative assessment of the main clinical and laboratory characteristics and their impact on case management and disease outcome before, during, and after the COVID-19 pandemic in the Republic of Moldova (MD) and Ukraine (UA).

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 distribution of patients from MD cohort according to the pathway of accessing the healthcare system showed that the majority were detected by primary healthcare providers during the evaluation of TB-related symptomatic cases, which complained persistent cough with expectorations, associated with loss of weight and night sweets, with fluctuating trend from 451 (68%) in 1st G, to 282 (62%) in the 2nd G and increasing to 375 (74%) in the 3rd G. Similarly, in the UA cohort, the majority were detected by primary healthcare providers during the evaluation of TB-related symptomatic cases, in a similar proportion across all groups: 651 (73%) in the 1st G, 413 (71%) in the 2nd G, and 532 (69%) in the 3rd group, indicating the central role of the primary-care providers in the detection and clinical evaluation of TB cases. Detection through active screening by primary healthcare staff in the MD cohort showed an increasing trend over time, rising from 35 (5%) in the 1st G to 37 (8%) in the 2nd G, and 47 (9%) in the 3rd G. In the UA cohort, this pathway accounted for a higher initial proportion. Still, it demonstrated a decreasing trend, from 158 (18%) in the 1st G to 76 (13%) in the 2nd G and 100 (13%) in the 3rd G, indicating a gradual strengthening of active screening in MD and a relative decline in UA over the study period, with statistically higher rates in the UA cohort. Direct referrals to TB-specialized services (dispensaries), representing patients who went straight to TB-specialized facilities without contacting primary-care providers, in MD cohort had an important fluctuant rate from 127 (19%) in the 1st G decreasing to 36 (8%) in the 2nd G, and to 38 (7%) in the 3rd G, with a statically higher rate in the 1st G compared with other SGs ($\chi 2 = 31$; $p=0$). Medical specialists diagnosed TB during hospital stay in a higher proportion of patients in the MD cohort, with a significantly increased rate from 51 (8%) in the 1st G to 96 (21%) in the 2nd G, followed by a decrease to 42 (9%) in the 3rd G ($\chi 2 = 52$; $p=0$). In contrast, in the UA cohort, this pathway accounted for a lower proportion but demonstrated a gradual increase, from 55 (6%) in the 1st G to 62 (11%) in the 2nd G and 81 (10%) in the 3rd G, showing a significantly higher proportion in

the MD 2nd G. Direct referrals to TB-specialized services (dispensaries) decreased from 127 (19%) in the 1st G, to 36 (8%) in the 2nd G and 38 (7%) in MD cohort, while in UA cohort showed a gradual increasing trend from 32 (4%) in the 1st G to 28 (5%) in the 2nd G, and 60 (8%) in the 3rd G, with a significantly higher rate in the Moldovan 1st G compared with Ukrainian 1st G (127 (19%) vs. 32 (4%), ($\chi 2$ =80; p=0).

Patient distribution by TB localization showed that pulmonary TB was the most common diagnosis in both cohorts. Associated extrapulmonary TB, involving mediastinal lymph nodes, pleura, joints, or bones, occurred at low rates in the MD cohort with an increasing trend from 57 (8%) in the 1st G to 48 (11%) in the 2nd G, then reducing to 37 (7%) in the 3rd G. In comparison, in UA cohort it decreased from 47 (9%) in the 1st G to 29 (5%) in the 2nd G, and increased to 73 (9%) in the 3rd G. Generalized TB, including multisite or disseminated disease, was diagnosed in a slightly higher rates in MD cohort 21 (3%) in the 1st G, to 34 (7%) in the 2nd G then to 29 (6%) in the 3rd G compared with UA cohort: 13 (3%) in the 1st G, 18 (3%) in the 2nd G, and 20 (3%) in the 3rd G.

The distribution of TB cases by treatment history showed that new cases, patients who had never previously been treated for TB, constituted the largest category in both cohorts with increasing trend from 491 (74%) in the 1st G to 341 (76%) in the 2nd G and 422 (84%) in the 3rd G in MD cohort and decreasing trend in the UA cohort from 366 (74%) in the 1st G to 400 (69%) in the 2nd G, and 553 (71%) in the 3rd G. Relapse cases, patients who were successfully treated before and later developed TB again, were in a smaller in proportion and showed fluctuating trends in both cohorts: in UA from 61 (23%) in the 1st G to 105 (18%) in the 2nd G and 164 (21%) in the 3rd G and in lower rates in MD from 101 (15%) in the 1st G to 87 (19%) in the 2nd and 34 (7%) in the 3rd G, being significantly lower in 3rd Ukrainian group 34 (7%) compared with the 3rd Moldovan group 164 (21%); ($\chi 2$ =130; p=0) Patients re-enrolled in treatment after treatment failure or after being lost to follow-up were relatively few and exhibited a marked decline over time in both cohorts: 69 (24%) in the 1st G, 74 (13%) in the 2nd G, and 56 (7%) in the 3rd G in UA cohort while in MD increased from 101 (15%) in the 1st G to 87 (19%) in the 2nd G and 34 (7%) in the 3rd G. Reduced proportions of re-enrolled cases in the 3rd SGs indicated improved treatment continuity and better retention in specialized healthcare in the post–COVID-19 period.

The tools used for TB diagnosis showed a distinct distribution and trend across the groups, with laboratory-diagnosed TB, based on Ziehl-Neelsen smear, conventional culture, and molecular-genetic tests being predominant with a sharply increasing trend in both cohorts: in MD from 252 (38%) in the 1st G to 201 (44%) in the 2nd G and 276 (55%) in the 3rd G. In comparison, in the UA cohort, it increased more evidently from 310 (35%) patients in the 1st G to 310 (53%) in the 2nd G and 582 (75%) in the 3rd G, which was statistically higher compared with the 3rd Moldovan group ($\chi 2$ =11; p=0). Results reflected the expanding proportion of cases microbiologically confirmed in the post–COVID-19 period in line with WHO recommendations. The microbiological diagnostic results for acid-fast bacilli (AFB) and *Mycobacterium tuberculosis* (MTB) showed that microscopic AFB positivity increased in UA cohort from 192 (21%) in the 1st G to 292 (50%) in the 2nd G and further to 556 (72%) in the 3rd G while in MD cohort was a lower rates: 127 (19%) in the 1st G to 186 (41%) in the 2nd G and 201 (40%) in the 3rd G. Significant higher rate of positive AFB results were established in the 3rd Ukrainian compared with Moldovan group (556 (72%) vs 201 (40%); ($\chi 2$ =34; p=0) which was the consequence of the specific case-management in the post–COVID-19 period. Conventional culture positivity for MTB followed a similar upward trend, rising from 210 (35%) in the 1st G to 322 (55%) in the 2nd G and 528 (68%) in the 3rd G in UA cohort, while in MD cohort was in lower rates: 176 (26%) in the 1st G to 222 (49%) in the 2nd G and 231 (46%) in the 3rd G. GeneXpert MTB positivity also increased progressively, from 310 (35%) in the 1st G to 321 (55%) in the 2nd G and 625 (81%) in the

3rd G in the UA cohort compared with 218 (33%) in the 1st G to 241 (53%) in the 2nd G and 267 (53%) in the 3rd G in MD cohort, being lower compared with UA 3rd G ($\chi 2$ =128; p=0). So, laboratory-confirmed TB cases were significantly higher in the post–COVID-19 period in both countries, driven by WHO-recommended case management and the complex COVID-19-related constraints. GeneXpert results indicating rifampicin-sensitive TB rose from 142 (21%) in the 1st G to 189 (142%) in the 2nd G and 178 (35%) in the 3nd G in MD cohort, while in UA cohort rose from 210 (23%) in the 1st G to 243 (42%) in the 2nd G, but decreased to 102 (13%) in the 3rd G. In contrast, rifampicin-resistant cases remained relatively low and stable, with 100 (11%) in the 1st G, 56 (10%) in the 2nd G, and 71 (9%) in the 3rd G in UA cohort, compared with increasing trend in MD cohort: 76 (11%) in the 1st G, 52 (11%) in the 2nd G and 89 (18%) in the 3rd G. Confirmed sensible TB predominated, rising from 376 cases (42%) in the 1st G to 429 cases (74%) in the 2nd G and peaking at 672 cases (87%) in the 3rd G in UA cohort, while in MD cohort had a decreasing trend: 553 (82%) in the 1st G to 376 (83%) in the 2nd G and 349 (70%) in the 3rd G. Monoresistant TB was diagnosed in 29 (6%) cases in the 1st G, increasing slightly to 42 (7%) in 2nd G, then decreasing to 11 (1%) cases in the 3rd G in UA cohort while in MD was in a lower rates: 19 (3%) in 1st G, to 14 (3%) in the 2nd G and 38 (7%) in the 3rd G. Polyresistant TB remained low, with 9 (1%) cases in the 1st G, 12 cases (2%) in the 2nd G, and 18 cases (2%) in the 3rd G in UA cohort, while in MD was in 14 (2%) in 1st G, 9 (2%) in 2nd G and 24 (5%) in the 3rd G .Multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) was diagnosed in an increasing trend din MD cohort and was microbiologically confirmed in 76 (11%) cases in the 1st G and 52 (11%) cases in the 2nd group increasing to 89 (18%) in the 3rd G, while in UA cohort had a fluctuating trend from 84 (9%) cases in the 1st G, then rose to 96 (16%) cases in the 2nd G, and then decreased to 72 (9%) cases in the 3rd G, highlighting shifting patterns in drug resistance over the periods. The results showed divergent trends across both countries, with an increasing trend of MDR-TB in the Moldovan cohort, similarly identified in a wide national study [8]. The distribution of AFB positivity during the anti-TB treatment follow-up showed similar proportions across the three groups over time. At the end of the 2nd month of the anti-TB treatment, AFB positivity was moderately higher in UA cohort, being recorded in 52 (7%) cases in the 1st G, 42 (7%) in the 2nd G, and 52 (7%) in the 3rd G while in MD cohort was established in 23 (3%) in the 1st G, 12 (3%) in the 2nd G and 19 (4%) in the 3rd G. By the end of the 3rd month of the treatment, the proportions of the AFB-positive results decreased to 23 (4%) cases in the 1st G, 16 (3%) in the 2nd G, and 21 (3%) in the 3rd G in UA cohort and remained stable low in the MD cohort. The results demonstrated a stable trend in treatment effectiveness across both cohorts, as evaluated by microbiological status. The rate of cases diagnosed based on TB-related symptoms and chest imaging without microbiological confirmation decreased over time: 555 (62%) in the 1st G to 253 (44%) in the 2nd G, and 174 (22%) in the 3rd G in UA cohort while in MD the decrease was not so evident: 400 (60%) in the 1st H to 241 (53%) in the 2nd G and 216 (43%) in the 3rd G. The decreasing trend in the clinical radiological diagnosis in both countries reflected a shift toward more laboratory-based diagnosis, as recommended by the WHO, and in the context of the COVID-19 pandemic. In contrast, histologically diagnosed TB through tissue biopsy during bronchoscopic fibroscopy accounted for a small proportion in both cohorts, with slightly higher rates in MD: 12 (2%) in the 1st G, to 9 (2%) in the 2nd G and 10 (2%) in the 3rd G, as well in UA cohort: 31 (4%) in the 1st G, 16 (3%) in the 2nd G, and 17 (2%) in the 3rd G, indicating that histology played a minor role in TB diagnosis in both countries, compared with laboratory and clinical-radiological methods. Radiological evaluation showed a significantly higher proportion of patients meeting all severity criteria-extensive lung involvement (more than three segments), parenchymal destruction, and disseminated lesions - in the MD 2nd SGs (289 [64%]) vs. the UA cohort (52%). In the 1st SGs, the proportions

were similar between cohorts: 201 (30%) in MD and 272 (30%) in UA. In the MD 3rd SG, the proportion was slightly higher than in UA: 356 (47%) vs 253 (51%). The treatment outcomes showed variation across both cohorts and according to the drug-resistance profile. In the MD cohort, the overall success rate was 517 (78%), with 420 (76%) for DS-TB and 54 (69%) for MDR-TB in the 1st G, 315 (70%) patients, comprising 269 (71%) with DS-TB and 32 (69%) with MDR-TB in the 2nd G cohort, 318 (76%), including 279 (80%) for DS-TB and 67 (74%) for MDR-TB in the 3rd G. The proportion of patients lost to follow-up rose slightly from 43 (6%) in the 1st G to 37 (8%) in the 2nd G and 38 (7%) in the 3rd G. the rate of patients who failed treatment and were switched to another regimen remained stable - 36 (5%) in the 1st G, 25 (6%) in the 2nd G and 32 (6%) in the 3rd G. There were 58 deaths (8%) in the 1st G, 51 (11%) in the 2nd G, and 37 (7%) in the 3rd G. Additionally, no outcome data were available for 58 (8%) patients in the 1st G, 51 (11%) in the 2nd G, and 37 (7%) in the 3rd G. In the UA cohort, treatment success increased over time, from 627 (70%) in the 1st G to 393 (68%) in the 2nd G, and reached 580 (76%) in the 3rd G. The proportion of patients lost to follow-up showed a fluctuating pattern, from 69 (5%) in the 1st G to 52 (9%) in the 2nd G, and then to 56 (7%) in the 3rd G. The treatment failure increased from 58 (6%) in the 1st G to 47 (8%) in the 2nd G, and declined to 39 (5%) in the 3rd G. Mortality remained relatively stable across groups, reported in 101 (11%), 78 (13%), and 92 (11%) of cases, respectively. No outcome data were available for 53 (6%) patients in the 1st G, 20 (4%) in the 2nd G, and 6 (1%) in the 3rd G. Lower treatment success rates in both countries during the COVID-19 period reflected resource shortages, while the subsequent improvement indicated enhanced effectiveness of TB care and rehabilitation, driven by gradual alignment with WHO standards in healthcare and TB treatment.

4. DISCUSSION

The majority of TB cases in both countries were identified by primary healthcare providers during the evaluation of symptomatic, TB-related presentations, underscoring their central role in case detection and clinical assessment, confirming the consistently high reliance on primary care in both countries, as stated in multiple studies [4-7]. Active screening conducted by primary healthcare staff showed divergent trends between the two cohorts, as in the MD cohort, the share remained low; in the UA cohort, the proportion initially higher, it declined, indicating a relative reduction in active-screening–driven detection, which is relevant for the actual epidemiological context [7]. Laboratory-diagnosed TB, based on Ziehl–Neelsen smear, conventional culture, and molecular genetic tests, showed a sharply increasing trend in both cohorts, in line with WHO recommendations [2]. The treatment outcomes varied across both cohorts and by drug resistance profile, with higher success rates observed in the post-COVID-19 period, reflecting improved effectiveness driven by the progressive alignment with WHO standards in healthcare and TB treatment. An important limitation of the study was its restricted geographical scope and time period, which limits the generalizability of the findings, particularly for the MDR-TB cohort at the national level, so the results may not fully reflect the broader epidemiological and programmatic context across the entire country.

5. CONCLUSIONS

Primary healthcare providers play a central role in detecting and clinically assessing the majority of TB cases in both countries, including those with clinical symptoms. Active screening by primary healthcare staff showed divergent trajectories: in the MD cohort, the contribution remained limited, while in the UA cohort, it was initially higher but declined over time. The marked increase in laboratory-diagnosed TB, based on Ziehl–Neelsen smear, conventional culture, and molecular genetic tests, reflected the progressive adoption of WHO-recommended diagnostic algorithms and improved laboratory capacity in both countries.

Furthermore, treatment outcomes varied by cohort and drug-resistance profile, with higher success rates in the post-COVID-19 period. The COVID-19 pandemic impacted the case-management, determining a marked increase in laboratory-diagnosed TB, a higher rate of severe cases, and lower outcomes, particularly in drug-resistant TB. The results highlighted the importance of strengthening primary care–based case detection, expanding active screening, and maintaining robust laboratory diagnostics to sustain progress in TB control, while acknowledging the need for context-specific adaptations at the national level.

DECLARATIONS

Conflict of Interest Statement: The authors declare that they have no conflict of interest.
Author Contributions: E. L. designed the study; E. L., L. T., and I. S. analyzed data; E. L. drafted the manuscript; all 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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