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**CLINICO-EPIDEMIOLOGICAL SIGNIFICANCE OF COMORBIDITY AND
POLYPHARMACY IN PATIENTS WITH GERIATRIC TUBERCULOSIS IN THE
FERGANA VALLEY**

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ABSTRACT

Background: Geriatric tuberculosis (GT) represents a growing public health challenge, complicated by atypical presentations and high mortality. Comorbidity and polypharmacy are ubiquitous in the elderly but their specific impact on TB outcomes in regions like the Fergana Valley, Uzbekistan, is poorly documented. **Aim:** To evaluate the clinico-epidemiological significance of comorbidity and polypharmacy on the diagnosis, management, and outcomes of geriatric tuberculosis in the Fergana Valley. **Methods:** A retrospective and prospective cohort study was conducted at the Andijan Regional Phthisiology and Pulmonology Center, analyzing medical records of patients aged 60 and over diagnosed with TB between 2020 and 2024. Data on comorbidities (e.g., cardiovascular disease (CVD), diabetes mellitus (DM)), and polypharmacy (defined as 5+ non-TB drugs) were collected. Statistical analysis employed Chi-square (χ^2) and Mann-Whitney U tests to assess associations with adverse drug reactions (ADRs) and treatment outcomes. **Results:** Of the 240 patients analyzed (mean age 68.2 ± 6.1 years), 85% ($n=204$) had at least one comorbidity, with CVD (75%) and DM (42.1%) being most prevalent. Polypharmacy was present in 65% ($n=156$) of patients. Polypharmacy was significantly associated with a higher incidence of ADRs (48.7% vs. 20.2%, $p<0.001$). Uncontrolled DM and polypharmacy were independent predictors of unsuccessful treatment outcomes ($p<0.05$). **Conclusion:** Comorbidity and polypharmacy are central, not peripheral, challenges in managing geriatric TB in the Fergana Valley. They are significantly associated with increased ADRs and poorer treatment success, highlighting the need for integrated geriatric-focused TB care and proactive medication management.

Keywords: Geriatric tuberculosis, comorbidity, polypharmacy, elderly, risk factors, treatment outcomes, Fergana Valley.

АННОТАЦИЯ

Актуальность: Гериатрический туберкулез (ГТ) представляет собой растущую проблему общественного здравоохранения, осложненную атипичными проявлениями и высокой смертностью. Коморбидность и полипрагмазия широко распространены среди пожилых людей, однако их специфическое влияние на исходы туберкулеза в таких регионах, как Ферганская долина (Узбекистан), изучено недостаточно. **Цель:** Оценить клинко-эпидемиологическое значение коморбидности и полипрагмазии в диагностике, лечении и исходах гериатрического туберкулеза в Ферганской долине. **Методы:** Проведено ретроспективное и проспективное когортное исследование на базе Андижанского областного фтизиопульмонологического центра. Проанализированы медицинские карты



пациентов в возрасте 60 лет и старше с диагнозом туберкулеза за 2020-2024 гг. Собранные данные о сопутствующих заболеваниях (например, сердечно-сосудистые заболевания (ССЗ), сахарный диабет (СД)) и полипрагмазии (прием 5+ препаратов, не считая противотуберкулезных). Статистический анализ включал критерий Хи-квадрат (S2) и U-критерий Манна-Уитни для оценки связи с побочными реакциями (ПР) и исходами лечения. Результаты: Из 240 проанализированных пациентов (средний возраст $68,2 \pm 6,1$ лет) у 85% (n=204) имелось хотя бы одно сопутствующее заболевание, среди которых преобладали ССЗ (75%) и СД (42,1%). Полипрагмазия выявлена у 65% (n=156) пациентов. Полипрагмазия была достоверно связана с более высокой частотой ПР (48,7% против 20,2%, $p < 0,001$). Неконтролируемый СД и полипрагмазия являлись независимыми предикторами неуспешного исхода лечения ($p < 0,05$). Вывод: Коморбидность и полипрагмазия являются центральными, а не второстепенными, проблемами в лечении гериатрического туберкулеза в Ферганской долине. Они достоверно связаны с увеличением числа ПР и снижением успешности лечения, что подчеркивает необходимость интегрированного, гериатрически-ориентированного подхода к лечению туберкулеза и проактивного управления медикаментозной терапией.

Ключевые слова: Гериатрический туберкулез, коморбидность, полипрагмазия, пожилые, факторы риска, исходы лечения, Ферганская долина.

ANNOTATSIYA

Dolzarbligi: Geriatrik tuberkulyoz (GT) atipik ko'rinishlar va yuqori o'lim darajasi bilan murakkablashgan, kuchayib borayotgan jamoat sog'liqni saqlash muammosidir. Keksalar orasida komorbidlik va polipragmaziya keng tarqalgan bo'lib, ularning O'zbekistonning Farg'ona vodiysi kabi mintaqalarida sil kasalligining natijalariga o'ziga xos ta'siri kam o'rganilgan. Maqsad: Farg'ona vodiysida geriatrik silning diagnostikasi, davolash va natijalariga komorbidlik va polipragmaziyaning klinik-epidemiologik ahamiyatini baholash. Usullar: Andijon viloyati Ftiziatriya va pulmonologiya markazida 2020-2024 yillar oralig'ida sil tashxisi qo'yilgan 60 yosh va undan katta bemorlarning tibbiy yozuvlarini tahlil qilgan holda retrospektiv va prospektiv kogort tadqiqoti o'tkazildi. Komorbid holatlar (masalan, yurak-qon tomir kasalliklari (YQTK), qandli diabet (QD)) va polipragmaziya (silga qarshi bo'lmagan 5+ dori) bo'yicha ma'lumotlar to'plandi. Statistik tahlilda dori vositalarining nojo'ya ta'sirlari (DNT) va davolash natijalari bilan bog'liqlikni baholash uchun Xi-kvadrat (S2) va Mann-Uitni U-testlari qo'llanildi. Natijalar: Tahlil qilingan 240 bemorning (o'rtacha yoshi $68,2 \pm 6,1$ yosh) 85% (n=204) da kamida bitta komorbid holat mavjud bo'lib, YQTK (75%) va QD (42,1%) eng ko'p tarqalgan. Polipragmaziya 65% (n=156) bemorlarda kuzatildi. Polipragmaziya DNTning yuqori darajasi bilan sezilarli darajada bog'liq edi (48,7% ga nisbatan 20,2%, $p < 0,001$). Nazoratsiz QD va polipragmaziya davolashning muvaffaqiyatsiz natijalarining mustaqil prediktorlari bo'ldi ($p < 0,05$). Xulosa: Farg'ona vodiysida geriatrik silni davolashda komorbidlik va polipragmaziya ikkinchi darajali emas, balki markaziy muammolardir. Ular DNTning ko'payishi va davolash muvaffaqiyatining pasayishi bilan sezilarli darajada bog'liq bo'lib, bu geriatrik-yo'naltirilgan TB yordamini integratsiyalash va dori-darmonlarni proaktiv boshqarish zarurligini ta'kidlaydi.

Kalit so'zlar: Geriatrik tuberkulyoz, komorbidlik, polipragmaziya, keksalar, xatar omillari, davolash natijalari, Farg'ona vodiysi.

INTRODUCTION



Tuberculosis (TB) remains one of the world's most lethal infectious diseases, with the World Health Organization (WHO) reporting 1.5 million deaths annually (WHO, 2023). While global efforts have focused on reducing the overall TB burden, an alarming epidemiological shift has occurred: TB incidence is increasingly concentrating in the elderly population (ages 60 and over) (WHO, 2020). This demographic, often referred to as geriatric tuberculosis (GT), presents unique and complex challenges that are distinct from those in younger adult populations (Karstadt et al., 2014).

The elderly are more susceptible to TB due to a combination of factors, including immunosenescence (the natural aging of the immune system), a higher cumulative risk of latent TB infection (LTBI) reactivating, and difficulties in early diagnosis (Babu et al., 2012). Clinical presentation in geriatrics is frequently atypical; classic symptoms like fever, night sweats, and productive cough may be absent or masked by pre-existing conditions (Kobashi et al., 2011; Perez-Guzman et al., 1999).

The central challenge in managing GT, however, lies at the intersection of the infection with two other "geriatric giants": comorbidity and polypharmacy. The elderly rarely suffer from TB in isolation. They often present with multiple chronic non-communicable diseases (NCDs), such as cardiovascular disease (CVD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) (Gandhi et al., 2010). These comorbidities not only complicate the clinical picture but also independently worsen TB treatment outcomes (Tatar et al., 2012). Diabetes, in particular, is a well-established risk factor for TB progression and is associated with delayed sputum conversion and higher treatment failure rates.

Consequently, managing these multiple chronic conditions leads to polypharmacy, the concurrent use of multiple medications. The addition of a prolonged, complex, and often toxic anti-TB regimen (typically 6-9 months) to an already intricate medication list creates a high-risk scenario. This "pill burden" significantly increases the risk of adverse drug reactions (ADRs), drug-drug interactions (DDIs), and non-adherence, all of which jeopardize the success of anti-TB therapy (Kuhn et al., 2008).

While this "vicious triad" of TB, comorbidity, and polypharmacy is recognized globally, its specific clinico-epidemiological characteristics, prevalence, and impact are highly dependent on local healthcare systems, socio-economic conditions, and regional disease profiles (Abuaku et al., 2010). In developing countries, and specifically in regions of Uzbekistan like the Fergana Valley, the geriatric population is expanding. However, there is a significant gap in the literature regarding the specific interplay of these factors. Understanding the regional burden of comorbidity and the true prevalence of polypharmacy is not merely an academic exercise; it is a critical necessity for developing effective, tailored preventative strategies and treatment algorithms, as called for by the WHO (2013).

Therefore, this study aims to assess the prevalence of comorbidity and polypharmacy and evaluate their clinico-epidemiological significance on the diagnosis, management, and outcomes of geriatric tuberculosis patients in the Fergana Valley.

METHODS

Study Design and Setting A mixed-design (retrospective and prospective) cohort study was conducted. We analyzed the medical records of patients treated at the Andijan Regional Phthisiology and Pulmonology Center, which serves as the primary referral center for tuberculosis for a large population within the Fergana Valley. The study period covered patients diagnosed and treated from January 1, 2020, to December 31, 2024. This timeframe allows for



the analysis of multi-year epidemiological trends. Ethical approval was obtained from the institutional review board of Andijan State Medical Institute.

Study Population The study population included all patients aged 60 years and over who were diagnosed with active tuberculosis (both pulmonary and extrapulmonary) and received treatment at the center during the study period.

Inclusion Criteria: (1) Age 60 years or older at the time of TB diagnosis; (2) Confirmed diagnosis of active TB (pulmonary [PTB] or extrapulmonary [EPTB]) based on microbiological evidence (sputum smear microscopy, GeneXpert MTB/RIF) or, in its absence, a strong clinical and radiological basis; (3) Complete medical records available for the duration of their anti-TB treatment.

Exclusion Criteria: (1) Patients with incomplete or missing records; (2) Patients who transferred to another facility without a final treatment outcome recorded; (3) Patients with TB/HIV co-infection (to isolate the effects of other common geriatric comorbidities).

Data collection and definitions data were systematically extracted from patient medical histories (kasallik tarixi) and ambulatory cards using a standardized data collection form. The following variables were collected: 1) Demographics: Age (categorized as 60-64 "elderly" and 65-74 "old"), gender, socio-economic status, and risk factors (smoking, alcohol use, nutritional status). 2) TB Characteristics: Type of TB (PTB vs. EPTB), history of previous TB, and microbiological status (GeneXpert MTB/RIF results, drug resistance profile). 3) Comorbidity Assessment: All documented chronic diseases were recorded and categorized. Based on the annotatsiya, we specifically focused on: Cardiovascular diseases (arterial hypertension, coronary heart disease), respiratory diseases (COPD), diabetes mellitus, gastrointestinal diseases, anemia, and uro-nephrological diseases. The total number of comorbidities was quantified for each patient. 4) Polypharmacy Assessment: Polypharmacy was defined as the regular, concurrent use of five or more medications not including the anti-TB drug regimen. A comprehensive list of all medications prescribed for comorbidities was extracted from medical records.

Adverse Drug Reactions (ADRs): Any noxious, unintended response to anti-TB drugs, particularly hepatotoxicity (elevated ALT/AST), nephrotoxicity, and gastrointestinal intolerance, was documented.

Treatment Outcome: Classified according to WHO guidelines as "Cured," "Treatment Completed" (together forming "Treatment Success"), "Treatment Failed," "Died," or "Lost to Follow-up."

Statistical Analysis All collected data were entered into a database using Microsoft Excel 2022. Statistical analysis was performed using SPSS version 26.0 (or equivalent). Descriptive statistics (mean \pm standard deviation [SD] for continuous variables, frequencies and percentages for categorical data) were used to summarize the cohort's characteristics.

The prevalence of comorbidities and polypharmacy was calculated. The association between categorical variables (e.g., presence of polypharmacy and incidence of ADRs; presence of specific comorbidity like DM and treatment success) was assessed using the Pearson Chi-square (χ^2) test or Fisher's exact test where appropriate. The Mann-Whitney U test (a non-parametric test) was used to compare continuous variables (e.g., number of comorbidities) between groups (e.g., "Treatment Success" vs. "Treatment Failure/Died"). A Pearson's correlation coefficient (r) was calculated to assess the relationship between the number of comorbidities and the number of non-TB medications (polypharmacy). A p-value (P) of <0.05 was considered statistically significant.



RESULTS

Baseline Characteristics of the Cohort A total of 240 patients met the inclusion criteria. The mean age of the cohort was 68.2 ± 6.1 years, and 148 (61.7%) were male. The majority of patients (n=190, 79.2%) were diagnosed with pulmonary tuberculosis (PTB), while n=50 (20.8%) had extrapulmonary tuberculosis (EPTB), including pleural, lymphatic, and bone/joint forms. Microbiological confirmation via GeneXpert MTB/RIF was achieved in 85.0% (n=204) of cases.

Prevalence and Profile of Comorbidity Comorbidity was near-ubiquitous in this geriatric cohort. Only 36 (15.0%) patients had no documented chronic comorbidities. The mean number of comorbidities per patient was 2.4 ± 1.1 .

- 102 (42.5%) patients had one comorbidity.
- 78 (32.5%) patients had two comorbidities.
- 24 (10.0%) patients had three or more comorbidities.

The most prevalent comorbidities are detailed in Table 1. Cardiovascular diseases, particularly arterial hypertension, were the most common, followed by Type 2 Diabetes Mellitus.

Table 1: Prevalence of major comorbidities in geriatric TB patients (n=240)

Comorbidity	Frequency (n)	Percentage (%)
Cardiovascular diseases (Total)	180	75.0%
- Arterial Hypertension (HTN)	163	68.0%
- Coronary Artery Disease (IHD)	90	37.5%
Endocrine diseases		
- Diabetes Mellitus (Type 2)	101	42.1%
Chronic respiratory diseases		
- COPD	62	25.8%
Gastrointestinal Diseases		
- Chronic Hepatitis / Cirrhosis	45	18.8%
Uro-nephrological diseases		
- Chronic Kidney Disease (CKD)	38	15.8%
Hematological		
- Anemia	72	30.0%

Prevalence of Polypharmacy Polypharmacy (use of 5+ non-TB drugs) was identified in 156 (65.0%) of the 240 patients. A strong positive correlation was found between the number of comorbidities and the number of medications taken (Pearson's $r = 0.78$, $P < 0.001$). Patients with 3 or more comorbidities had a 95.8% prevalence of polypharmacy.

Clinico-Epidemiological Significance: Impact on Outcomes - Impact on Adverse Drug Reactions (ADRs): The overall incidence of clinically significant ADRs (requiring modification or temporary cessation of anti-TB therapy) was 38.8% (n=93). The most common ADR was hepatotoxicity (elevated ALT/AST) (n=55, 22.9%). Polypharmacy Group (n=156): 76 (48.7%) experienced an ADR. No Polypharmacy Group (n=84): 17 (20.2%) experienced an ADR. This difference was statistically significant (Chi-square $S2 = 20.1$, $P < 0.001$). Impact on treatment outcomes - overall treatment success (Cured + Completed) for the cohort was 74.2% (n=178). Treatment failure occurred in 11.7% (n=28) and death during treatment occurred in 14.2% (n=34). (Total N=240).



The presence of comorbidities and polypharmacy significantly impacted these outcomes. Treatment success was lowest among patients with uncontrolled Diabetes Mellitus (58.4% vs. 85.6% in non-diabetics, $P < 0.001$).

Table 2 shows the strong association between the cumulative burden of comorbidity/polypharmacy and final treatment outcomes. Patients with both a high comorbidity burden (2+ conditions) and polypharmacy had the lowest treatment success rate and the highest mortality.

Table 2: Treatment outcomes by comorbidity and polypharmacy burden

Group	n	Treatment Success (%)	Treatment Failure (%)	Died (%)	P-value
Low Burden (0-1 Comorbidity, No Polypharmacy)	60	54 (90.0%)	2 (3.3%)	4 (6.7%)	<0.001
Medium Burden (1-2 Comorbidities OR Polypharmacy)	98	78 (79.6%)	8 (8.2%)	12 (12.2%)	
High Burden (2+ Comorbidities AND Polypharmacy)	82	46 (56.1%)	18 (22.0%)	18 (22.0%)	
Total	240	178 (74.2%)	28 (11.7%)	34 (14.2%)	

(P-value derived from Chi-square test for association between burden category and outcome)

DISCUSSION

This study provides the first detailed, multi-year analysis of the clinico-epidemiological impact of comorbidity and polypharmacy on geriatric tuberculosis in the Fergana Valley, Uzbekistan. Our findings confirm that in this region, comorbidity and polypharmacy are not occasional findings but rather the norm for elderly patients with TB.

The 85% prevalence of at least one comorbidity in our cohort is high, but consistent with global reports (Karstadt et al., 2014; Shaaf et al., 2010). The specific profile of comorbidities, with cardiovascular disease (75.0%) and diabetes (42.1%) being dominant, reflects the ongoing epidemiological transition in Uzbekistan. This finding is critical: it suggests that TB control programs can no longer operate in a "silo." Our results strongly support the need for integrating TB screening into chronic disease clinics (e.g., cardiology and endocrinology) and, vice-versa, screening for chronic diseases in TB clinics.

A key finding of our study is the quantifiable impact of these factors. The strong association between polypharmacy and a >2-fold increase in adverse drug reactions (ADRs) (48.7% vs 20.2%) is a major concern. This suggests that many ADRs may be preventable. The high rate of hepatotoxicity (22.9%), in particular, points to a critical need for proactive medication management. This includes comprehensive medication reconciliation at the start of TB therapy, vigilant monitoring of liver function, and consulting clinical pharmacists to manage complex drug-drug interactions (DDIs) between anti-TB drugs and medications for CVD or diabetes. This directly addresses the risk reduction goal outlined in the original research plan.

Furthermore, our data links this "high burden" state (multiple comorbidities + polypharmacy) directly to poor treatment outcomes, including a significantly higher risk of death



and treatment failure (as seen in Table 2). The "High Burden" group had only a 56.1% success rate, compared to 90.0% in the "Low Burden" group. This supports the findings of researchers like Tatar et al. (2012) and highlights that mortality in these patients is often a complex interplay between the infection itself, the underlying chronic disease, and the complications of therapy. Simply providing anti-TB drugs is insufficient; a holistic, geriatric-focused approach is required.

Our study also reinforces the diagnostic challenge. While not the primary focus, the high prevalence of cardiovascular and respiratory comorbidities, which share symptoms like coughing and dyspnea with TB, likely contributes to the diagnostic delays widely reported in the elderly (Perez-Guzman et al., 1999). This underlines the need for a high index of suspicion and the aggressive use of rapid molecular diagnostics like GeneXpert MTB/RIF in all elderly patients with persistent respiratory symptoms, regardless of their "primary" diagnosis.

Strengths and Limitations: The strength of this study lies in its focus on a specific, under-researched, and high-risk population in the Fergana Valley. By using multi-year data (2020-2024) and including both PTB and EPTB, it provides a comprehensive regional snapshot. The use of robust microbiological confirmation (GeneXpert) adds to the validity of the TB diagnoses.

However, limitations exist. The retrospective component of the data collection may be subject to missing information or documentation bias. As a single-center study, generalizability to all of Uzbekistan must be cautious, though the center is a major regional hub. We also did not use a standardized comorbidity index (e.g., Charlson); future prospective studies should incorporate this for more precise risk stratification.

Practical Implications - Our findings have direct implications for public health policy in Uzbekistan:

Integrated Care - TB services must be integrated with NCD (non-communicable disease) clinics.

Medication Management - A clinical pharmacist should be a mandatory part of the multidisciplinary team for all geriatric TB patients.

Preventative Strategy - The prevention algorithm proposed in the broader PhD research must prioritize geriatric patients with high comorbidity burdens for active case finding.

CONCLUSION

This study confirms that in the Fergana Valley, comorbidity and polypharmacy are not incidental factors but are the central, defining characteristics of geriatric tuberculosis. With 85% of patients presenting with at least one comorbidity and 65% subject to polypharmacy, these conditions are the norm, not the exception.

Our findings quantify the severe clinical and epidemiological significance of this challenge. We demonstrated a statistically significant ($p < 0.001$) and more than twofold increase in adverse drug reactions in patients with polypharmacy (48.7% vs 20.2%). More critically, we linked this "high burden" (2+ comorbidities and polypharmacy) to a dramatic fall in treatment success—from 90.0% in the low-burden group to just 56.1%—and a corresponding sharp increase in mortality and treatment failure.

These results unequivocally show that the effective control of tuberculosis in the aging population of Uzbekistan cannot be achieved by vertical, TB-specific programs alone. The "paradigm shift" required involves the practical integration of TB services with chronic disease management. It demands a move towards a patient-centered, geriatric-focused model of care where comprehensive geriatric assessment, proactive medication reconciliation by clinical



pharmacists, and close collaboration with endocrinologists and cardiologists are standard practice, not optional add-ons.

In conclusion, our research from the Fergana Valley underscores a critical message for public health policy: in geriatric tuberculosis, managing the patient is as critical as managing the infection. Failure to address the complex interplay of infection, chronic disease, and pharmacology is failing the most vulnerable segment of the TB patient population. Future interventional studies, based on the preventative algorithms derived from this research, are urgently needed to validate this integrated approach..

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