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Characterizing Adverse Effects and Risk Factors in Multidrug Tuberculosis Regimens: Implications for Personalized Treatment Protocols

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Abstract

Tuberculosis treatment requires complex multidrug regimens that present significant challenges, including drug-induced hepatotoxicity, pharmacokinetic interactions, and complications in HIV co-infection. Rifampin's potent enzyme induction and adverse effect profiles, particularly in drug-resistant cases, necessitate a comprehensive understanding of drug-drug interactions. This study addresses important knowledge gaps in tuberculosis treatment by identifying predictors of individual patient responses, characterizing interactions with high-dose rifampicin, and developing evidence-based strategies to optimize treatment protocols while minimizing adverse effects. Data were systematically collected from 459 participants across multiple healthcare facilities, analysing demographics, treatment regimens, and adverse effects through standardized forms and hospital management systems. The analysis revealed that age significantly influences treatment complications, with insomnia (62%), vomiting (61%) and neuropathy (60%) being the most prevalent. Dose levels were significantly associated with rifampicin, cycloserine and ethambutol use, while geographical location did not show significant associations. The findings underscore the need for personalized treatment protocols that consider age-related differences and optimal dosing strategies to improve adherence and outcomes in tuberculosis management.

Keywords: Tuberculosis Treatment, Drug-Drug Interactions, Adverse Drug Reactions, Rifampicin, Pharmacokinetics Interactions, Multidrug-Resistant Tuberculosis, HIV-Tuberculosis Co-infection

Introduction

Tuberculosis continues to be a global public health problem challenges, requiring complex multidrug regimens for effective Treatment. The World Health Organization recommends using a standardized first-line treatment regimen that includes revamping, isoniazid, ethambutol, and pyrazinamide. While this combination has proven effective against drug-susceptible tuberculosis, its implementation is fraught with significant challenges that compromise patient outcomes [1]. The treatment landscape is further complicated when tuberculosis coexists with other conditions, particularly HIV infection, where the interaction between anti-tuberculosis drugs and antiretroviral therapy poses a clinical conundrum. Despite decades of research and clinical experience, improving tuberculosis treatment protocols, especially in the context of drug-resistant disease and co-infections, remains an urgent priority requiring innovative solutions and a comprehensive understanding of the underlying pharmacokinetic issues [2].The therapeutic management of tuberculosis is significantly challenged by the adverse effect profile of first-line drugs. Drug-induced hepatotoxicity is of particular concern, as patients are frequently exposed to multiple hepatotoxic agents simultaneously within a standard regimen [3]. When severe adverse reactions necessitate the discontinuation of an essential drug, patients can no longer receive optimal therapy, significantly increasing the risk of treatment failure and the emergence of drug-resistant tuberculosis [4]. Beyond direct toxicity, pharmacokinetic interactions pose equally formidable obstacles to therapeutic success. Rifampin acts as A strong activator of cytochrome P450 enzymes, which accelerates the breakdown of other drugs taken with it and render them therapeutically ineffective [5, 6].

These interactions assume critical importance when involving drugs with narrow therapeutic indices, where even small fluctuations in plasma concentrations can trigger serious adverse events. However, the translation of pharmacodynamics interactions into clinical outcomes is variable, with individual patient responses ranging from severe reactions to complete intolerance of drug combinations [7]. The burden the risk of adverse drug reactions increases significantly during the management of drug-resistant tuberculosis.

Although any anti-tuberculosis drug can induce adverse effects, second-line regimens for drug-resistant tuberculosis show a higher frequency of serious reactions. Most adverse events are mild to moderate and are managed with vigilant monitoring and supportive interventions, although a subset prove severe or life-threatening, requiring withdrawal of the causative agent and complex treatment regimen adjustments [8]. Global drug-resistant tuberculosis patterns highlight scale this challenge, with approximately half a million newly identified cases of rifampicin-resistant tuberculosis diagnosed annually, 78% of which exhibit multidrug resistance to both isoniazid and rifampicin [9, 10]. Quality concerns have arisen regarding fixed-dose combinations, with stability studies revealing significant physical and chemical degradation under accelerated experimental conditions, primarily resulting in isonicotiny hydrazine [11, 12]. The intersection of tuberculosis and HIV therapy poses particularly complex pharmacological challenges. Rifamycins, although a cornerstone of tuberculosis therapy, are involved in significant interactions with antiretroviral drugs such as protease inhibitors and non-nucleoside reverse-transcriptase inhibitors. These interactions significantly reduce

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antiretroviral plasma concentrations, compromise antiviral efficacy, and promote HIV drug resistance through the gradual accumulation of resistance mutations [13]. The potent CYP450 induction by rifamycins accelerates antiretroviral metabolism, resulting in sub therapeutic doses that may compromise HIV control [14]. Recent studies with high-dose rifampicin (35 mg/kg) have shown preserved plasma exposure of other first-line TB drugs, but the broad interaction profile is incompletely characterized, with reductions in tolutegravir and efavirenz concentrations compared with standard doses [15]. Standard WHO chemotherapy for drug-susceptible TB follows a two-phase approach: an intensive a two-month intensive phase using four drugs, followed by a four-month continuation phase with isoniazid and rifampicin. [16]. Treatment efficacy is further complicated by the lack of adequate drug penetration into tissue lesions containing Mycobacterium tuberculosis, where rifampicin concentrations are significantly lower than plasma levels, a state of drug-tolerance induced by the stress of the pathogen within the complex lesion microenvironment [17].

Despite extensive documentation of drug interactions and side effects during tuberculosis treatment, significant knowledge gaps persist. The complete interaction profile of high-dose rifampicin with various drug classes remains uncharacterized, limiting evidence-based dosing strategies. The variability in individual patient responses to drug combinations lacks predictive biomarkers, which precludes personalized treatment approaches. Furthermore, particularly in the HIV-infected population, the optimization of treatment regimens that balance efficacy against drug-resistant tuberculosis while minimizing interactions and toxicity has not been adequately addressed.This research aims to comprehensively assess drug-drug interactions in tuberculosis treatment regimens. Particular attention is paid to identifying factors that predict individual patient responses to combination therapy, characterizing the interaction profile of high-dose rifampicin with commonly co-administered drugs, and developing evidence-based strategies to optimize treatment protocols that minimize adverse effects while maintaining therapeutic efficacy against both tuberculosis resistant to standard drugs and forms resistant to multiple major drugs.

Methodology

Hospital and physician data are systematically collected from multiple healthcare facilities in different regions and time periods. Primary data sources include hospital administrative records, patient registration systems, and clinical service documents that track patient visits, treatment procedures, and health outcomes. Information is collected through standardized forms that record patient demographics, consultation details, diagnostic codes, and treatment protocols. Healthcare professionals enter data electronically into hospital management information systems or maintain manual records that are later digitized. Data collection occurs at various points of contact, including outpatient departments, emergency services, and inpatient wards. Regular audits ensure the accuracy and completeness of records. Rifampin is a broad-spectrum antimicrobial agent that was first introduced for clinical use in 1968 after being discovered in 1965. As a member of the antimicrobial drug class, it is a cornerstone in tuberculosis treatment, which works by preventing bacterial DNA-dependent RNA polymerase. Beyond tuberculosis, the drug is also used to manage various types of mycobacterial infections and infections caused by gram-positive bacteria.Cycloserine it is an antibiotic mainly used to control tuberculosis, in which it is always used in combination with other anti-tuberculosis drugs. In addition to its role in managing tuberculosis, this drug is also it is commonly recommended to manage many types of bacterial infections. These include urinary tract infections, bacterial skin infections, and conjunctivitis, as determined by a healthcare professional.

The significance of this work lies in its ability to quantitatively rank the performance of major TB drugs—such as rifampicin, isoniazid, levofloxacin, moxifloxacin, and ethambutol—using normalized GRA coefficients and Gray Relational Grades (GRG), thereby enabling transparent comparisons of therapeutic strength, reliability, and clinical compatibility. The study demonstrates, for example, how ethambutol emerged as the top-performing drug with the highest GRG score, while others displayed critical trade-offs across efficacy, precision, and applicability. Beyond its immediate clinical relevance, Dr. Kandula's research establishes a scalable analytical framework that can be extended to emerging pathogens, multidrug-resistant infections, and broader public-health decision-making. Its depth, rigor, and methodological originality position the authors as thought leaders advancing global health analytics—providing tools that meaningfully accelerate diagnostic precision, optimize treatment strategies, and support the WHO's mission to reduce the global TB burden through data-driven, personalized medical interventions.

Rifapentine it is an antibiotic used to treat tuberculosis, a bacterial disease that mainly targets the lungs. It works by preventing or eliminating the growth of bacteria, and it is important to note that it is not effective against viral infections. This medication is administered orally as a tablet, which should be taken with a full glass of water and with food. Furthermore, rifapentine is never used alone; it is always part of a combination therapy, which works in conjunction with other anti-tuberculosis medications such as isoniazid, pyrazinamide, or ethambutol, to treat both active and latent forms of the disease.Isoniazid, often abbreviated as INH, is a first-line anti-tuberculosis agent that has been the cornerstone of tuberculosis treatment regimens for decades.

The drug is designed to kill the bacteria that cause tuberculosis, a serious infection that primarily targets the lungs. It is used to treat active tuberculosis disease and as a preventive measure in individuals at high risk of infection.Ethambutol is a bacteriostatic antimicrobial agent that works by inhibits bacterial cell wall formation. It is primarily it is given along with other medicines to treat and control tuberculosis. Its suitability other infections is determined by a healthcare professional, as its effectiveness depends on the specific causative germ; it is not suitable for all infections. Furthermore, its effectiveness may be compromised in cases where bacterial strains have developed resistance to the drug.Kanamycin, an aminoglycoside antibiotic derived from the bacterium Streptomyces kanamyceticus, is a bactericidal agent used to treat a variety of infections. It is commercially available in several oral, intravenous, and intramuscular forms, with kanamycin sulphate being the most commonly used preparation.Pyrazinamide is an antibacterial a drug approved by the U.S. Food and Drug Administration for the treatment of active tuberculosis. It is a key component of combination therapy used to combat this disease, which can also manifest as an opportunistic infection in people with HIV.

Vomiting, commonly referred to as feeling sick or retching, is an involuntary reflex in which the contents of the stomach are forcibly expelled through the mouth. This physiological response serves as a defines mechanism for the body, helping to expel ingested toxins or other harmful substances from the upper digestive system.Anemia is a blood disorder characterized by an insufficient number or impaired function of red blood cells. Some forms are inherited and lead to lifelong health challenges, while others are acquired. The impact of anemia varies widely; some types present with mild, treatable symptoms, while severe cases can be life-threatening. Furthermore, the presence of anemia can sometimes indicate a serious underlying condition, such as cancer.Anorexia is a severe eating disorder marked by unusually low body weight for a person's age and height, usually resulting in extreme weight loss behaviours. Sufferers often experience an intense and irrational fear of gaining weight,

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even though they are underweight. This leads them to engage in severe calorie restriction, excessive exercise, and other harmful practices in an attempt to lose weight.Arthralgia, the medical term for joint stiffness, can be caused by a variety of reasons. These range from acute problems like sprains, injuries, or overuse to chronic conditions like various types of arthritis and tendonitis. It can also be a symptom associated with several infectious diseases, including rheumatic fever and chickenpox.A skin rash is characterized by red, swollen, and often raised areas of skin.

These rashes can be dry and have a variety of symptoms, from severe itching to painful. Possible triggers for a skin rash are numerous and include allergic reactions, bacterial or viral infections, and chronic skin conditions such as eczema.Peripheral neuropathy encompasses a variety of disorders that can lead to the following injury to the peripheral nervous system, which consists of nerves located outside the brain and spinal cord. Because many underlying conditions can cause it, the resulting symptoms can vary greatly. The specific areas of the body affected depend on the cause and nature of the nerve damage.Headaches are the most common form of pain in the head or face, and can be throbbing, constant, sharp, or dull. The experience can vary considerably in terms of type, intensity, location, and frequency. As the most common type of pain, it is a leading cause of missed work or school and medical attention. While most headaches are not dangerous, some types may indicate a more serious underlying condition.

Results and Discussion

According to the information shown in Table 1, the study population 459 participants was predominantly young, with the largest group (37.7%) being 30–40 year olds, followed by 20–30 year olds (35.3%). A slight majority of participants were male (53.8%) [19]. Geographically, most respondents lived in urban areas, with 39.7% living in cities and 31.6% in towns, compared to 28.8% who came from rural areas. In terms of size, the distribution was relatively even, although medium size was the most common (39.9%), followed by low (28.7%) and high (31.4%) sizes. This profile indicates a sample consisting of young to middle-aged adults from primarily urban settings.

Table 1. Socio-demographic profile of study participants (N = 459)

Characteristics	Frequency	Percentage (%)
Age		
Under 20	29	6.3
20-30 years old	162	35.3
30-40 years old	173	37.7
Over 40 years old	13	2.8
Gender		
Male	247	53.8
Female	212	46.2
Demography		
Village	132	28.8
Town	145	31.6
city	182	39.7

Table 2 presents descriptive statistics for binary variables (coded as 0 or 1) among 459 participants, revealing the prevalence of various anti-TB drugs and their associated side effects. The mean scores indicate the proportion of the sample who experienced each item. For example, the most commonly reported side effects were insomnia (62%), vomiting (61%), and ethambutol/kanamycin use (61% each). In contrast, headache (40%) and pyrazinamide use (41%) were the least common. The standard deviations, all close to 0.5, confirm the expected variability for binary data, indicating that for each variable, the sample was divided between those who reported it and those who did not.

Table 2. Descriptive Statistic

	N	Range	Minimum	Maximum	Sum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic
Rifampicin	459	1	0	1	271	.59	.023	.492
Cycloserine	459	1	0	1	243	.53	.023	.500
Rifapentine	459	1	0	1	254	.55	.023	.498
Isoniazid	459	1	0	1	225	.49	.023	.500
Ethambutol	459	1	0	1	279	.61	.023	.489

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Kanamycin	459	1	0	1	279	.61	.023	.489
Pyrazinamide	459	1	0	1	187	.41	.023	.492
Vomiting	459	1	0	1	280	.61	.023	.488
Irritable	459	1	0	1	228	.50	.023	.501
Anorexia	459	1	0	1	266	.58	.023	.494
Fatigue	459	1	0	1	212	.46	.023	.499
Insomnia	459	1	0	1	284	.62	.023	.486
Neuropathy	459	1	0	1	276	.60	.023	.490
Headache	459	1	0	1	183	.40	.023	.490

Table 3. Chi-square analysis showing significant interactions of age and gender

	Age			Gender		
	χ2 value	p-value	Inference	χ2 value	p-value	Inference
Rifampicin	20.781	0.04	significant	0.17	0.68	Non-significant
Cycloserine	7.778	0.353	Non-significant	1.169	0.28	Non-significant
Rifapentine	12.639	0.081	Non-significant	2.453	0.117	Non-significant
Isoniazid	13.561	0.6	Non-significant	4.305	0.038	significant
Ethambutol	14.182	0.048	significant	4.339	0.037	significant
Kanamycin	11.072	0.135	Non-significant	0.001	0.979	Non-significant
Pyrazinamide	12.43	0.087	Non-significant	0.014	0.905	Non-significant
Vomiting	16.024	0.025	significant	2.773	0.096	Non-significant
Irritable	6.475	0.485	Non-significant	1.395	0.238	Non-significant
Anorexia	16.036	0.025	significant	0.951	0.329	Non-significant
Fatigue	19.606	0.006	significant	0.3	0.863	Non-significant
Insomnia	15.531	0.03	significant	0.866	0.352	Non-significant
Neuropathy	10.802	0.147	Non-significant	0.224	0.636	Non-significant
Headache	9.917	0.193	Non-significant	0.85	0.771	Non-significant

Table 3 reveals distinct patterns in how age and gender are associated with drug use and side effects. A significant relationship with age was found for several variables, including rifampicin, ethambutol, vomiting, anorexia, fatigue, and insomnia, indicating that the prevalence of these treatments and side effects differs between different age groups. In contrast, gender showed only two significant associations: its distribution was significantly different for isoniazid and ethambutol users. For all other variables, no statistically significant association was found with age or gender.

Table 4. Chi-square analysis showing significant interactions of Demography andDosage

	Demography			Dosage		
	X2 value	P-value	Inference	X2 value	P-value	Inference
Rifampicin	4.806	0.09	Non-significant	16.328	0.012	Significant
Cycloserine	1.434	0.488	Non-significant	19.805	0.003	Significant
Rifapentine	2.223	0.329	Non-significant	6.945	0.326	Non-significant
Isoniazid	0.466	0.792	Non-significant	17.171	0.009	Non-significant
Ethambutol	0.811	0.667	Non-significant	12.265	0.056	Significant
Kanamycin	0.262	0.877	Non-significant	4.2	0.65	Non-significant
Pyrazinamide	3.799	0.15	Non-significant	28.025	<0.01	Non-significant
Vomiting	1.797	0.407	Non-significant	20.65	0.002	Significant
Irritable	0.161	0.923	Non-significant	15.931	0.014	Significant
Anorexia	1.692	0.429	Non-significant	7.243	0.299	Non-significant
Fatigue	2.583	0.275	Non-significant	6.464	0.373	Non-significant
Insomnia	3.736	0.154	Non-significant	5.705	0.457	Non-significant

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Neuropathy	4.084	0.13	Non-significant	6.626	0.357	Non-significant
Headache	7.205	0.27	Non-significant	20.465	0.002	Non-significant

Table 4 indicates that geographic population (village, town, and city) did not show a significant association with the use of any TB drug or the incidence of any of the listed side effects. In contrast, dose level (low, medium, high) showed significant relationships with several variables. In particular, the distribution of patients using rifampicin, cycloserine, and ethambutol, as well as those experiencing side effects such as vomiting and irritability, depended on the dose level administered. For all other drugs and side effects, no significant association with dose was found.

Table 5. One-sample t-test results for drug-related adverse effects

	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Kanamycin	26.644	458	.000	.608	.56	.65
Pyrazinamide	17.745	458	.000	.407	.36	.45
Vomiting	26.766	458	.000	.610	.57	.65
Irritable	21.262	458	.000	.497	.45	.54
Anorexia	25.124	458	.000	.580	.53	.62
Fatigue	19.827	458	.000	.462	.42	.51
Insomnia	27.263	458	.000	.619	.57	.66
Neuropathy	26.282	458	.000	.601	.56	.65
Rifampicin	25.694	458	.000	.590	.55	.64
Cycloserine	22.699	458	.000	.529	.48	.58
Rifapentine	23.822	458	.000	.553	.51	.60
Isoniazid	20.985	458	.000	.490	.44	.54
Ethambutol	26.644	458	.000	.608	.56	.65

Table 5 presents the results of the one-sample t-test, demonstrating that all drug-related adverse effects and the prevalence of drug use were statistically significant, as indicated by p-values of .000. The mean differences, which represent the average proportion of the sample experiencing each effect, were all positive and significant. For example, insomnia had the highest mean difference (.619), while pyrazinamide had the lowest (.407). The 95% confidence intervals for all items did not contain zero, confirming that the reported levels of these adverse effects and drug use were consistently and significantly different from the test value of zero across the entire study population.

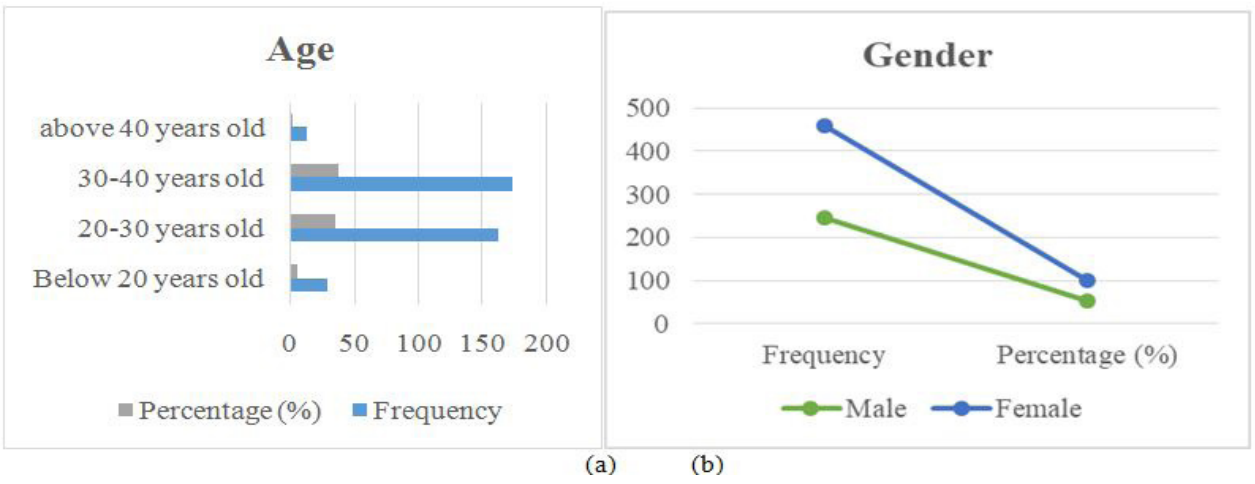

Figure 1: (a) Age-wise distribution of respondents based on frequency and percentage; (b) Gender-wise distribution showing male and female frequency and percentage.

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Figure 1 illustrates the key demographic characteristics of the respondents, including (a) presenting the age-wise distribution using both frequency and percentage, highlighting the main age groups, while (b) depicting the gender-wise distribution, comparing male and female respondents based on their frequencies and percentage contributions [20].

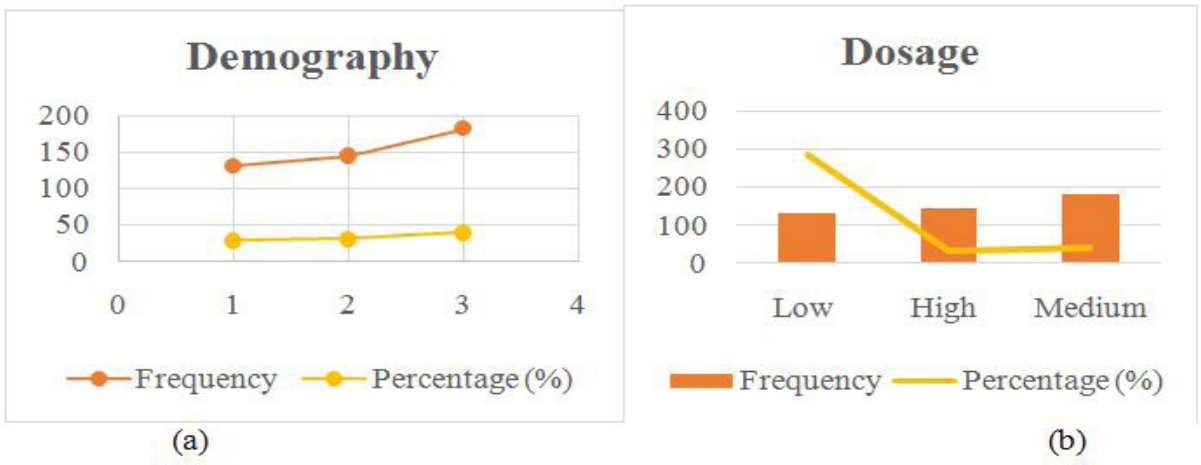

Figure 2: (a) Population distribution of respondents based on frequency and percentage; (b) Dose-level distribution showing frequency and associated percentage values.

Figure 2 presents essential characteristics of the responder, in which (a) illustrates the population distribution using both frequency and percentage to show variations across groups, while (b) depicts the dose-level distribution, comparing low, high, and medium doses in terms of frequency and their corresponding percentage values for clarity.

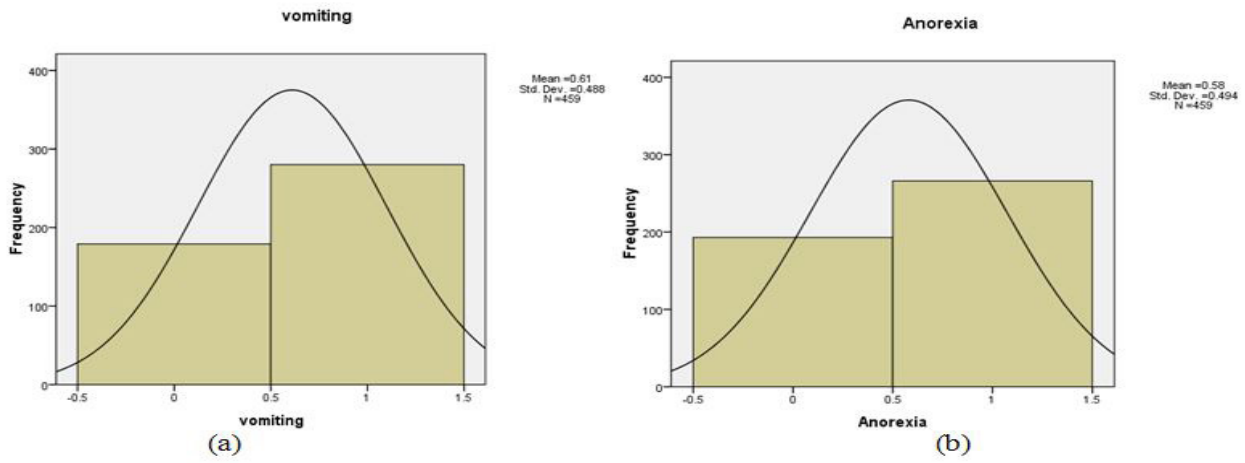

Figure 3: (a) Frequency distribution graph of vomiting; (b) Frequency distribution graph of anorexia

Figure 3 presents the prevalence of two clinical symptoms, including (a) the frequency distribution of vomiting, which illustrates how frequently the symptom occurs among respondents, and (b) the relative frequency distribution of anorexia, which allows for comparison of symptom prevalence and overall variation within the study population

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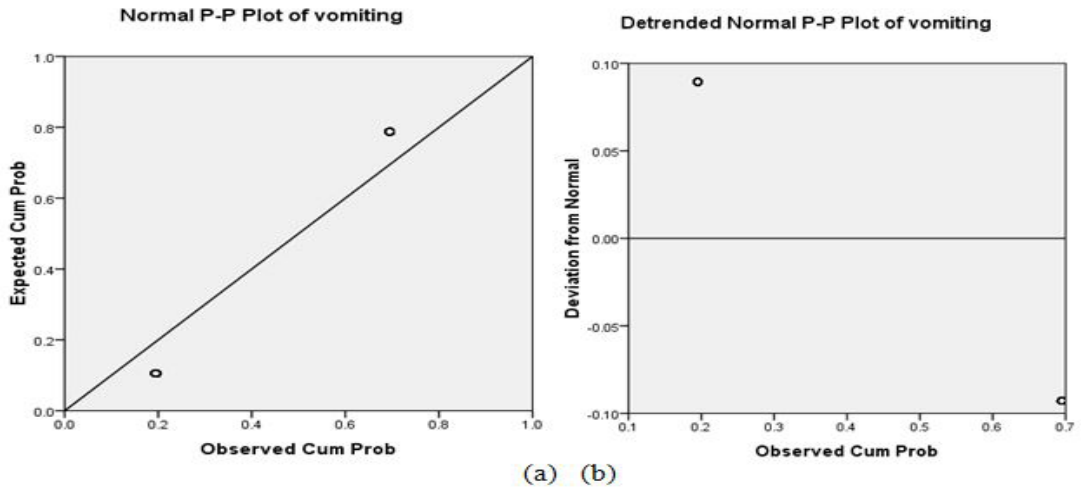

Figure 4: (a) Normal P–P plot for vomiting; (b) Inclined normal P–P plot for vomiting.

Figure 4 (a) the normal P–P diagram contrasts the observed overall probabilities with those expected. for vomiting, showing a significant deviation from the diagonal line. (b) The skewed normal P–P plot highlights these deviations more clearly, indicating that the data do not closely follow a normal distribution and show variation from expected patterns.

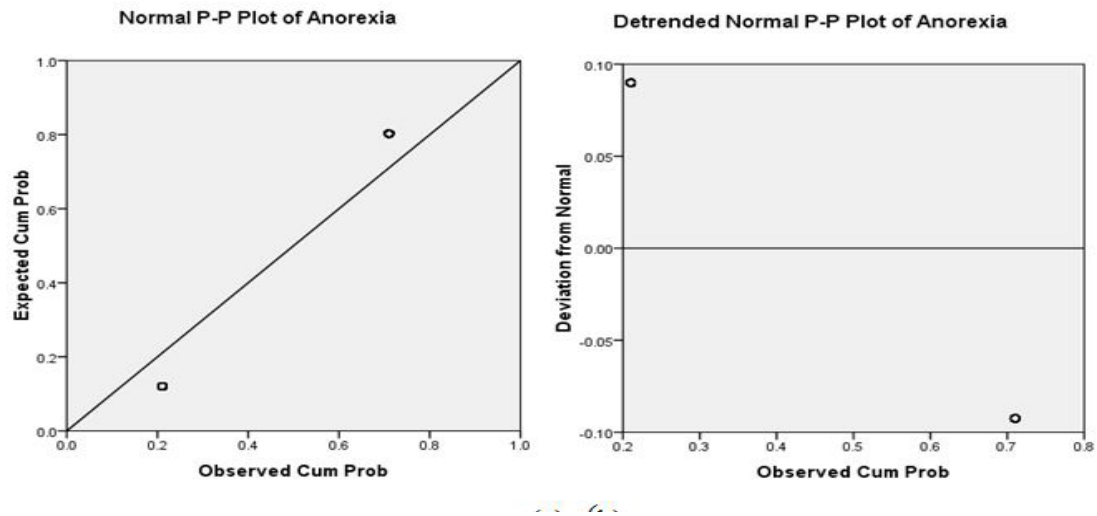

Figure 5: (a) Normal P–P plot for anorexia; (b) Inclined normal P–P plot for anorexia.

Figure 5 (a) shows the comparison between the observed and expected cumulative probabilities, shows significant departures from the diagonal reference line. (b) The skewed normal P–P plot further highlights these deviations, indicating that the appetite data do not closely follow a normal distribution and show variation from expected patterns.

Conclusion

Based on a comprehensive analysis of TB treatment outcomes among 459 participants, this study also examined anti-tuberculosis drugs, adverse drug reactions. The findings demonstrate that age significantly influences the incidence of treatment-related complications, with significant associations observed for rifampicin, ethambutol, vomiting, anorexia, fatigue, and insomnia. Gender showed a more limited impact, affecting only isoniazid and ethambutol distributions. Importantly, dose levels emerged as an important determinant, with rifampicin, cycloserine, and ethambutol use and significantly associated with vomiting and irritable symptoms. The high prevalence of adverse effects, particularly insomnia (62%), vomiting (61%), and neuropathy (60%), underscores the considerable burden that patients experience during TB treatment. Geographic location did not show significant associations, indicating that

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adverse effects transcend population boundaries.

These results emphasize the importance of personalized treatment protocols that account for age-related physiological differences and optimize dosing strategies to minimize toxicity while maintaining treatment efficacy. The findings of this study are highly relevant to the treatment of drug-resistant tuberculosis and HIV-TB co-infections, as treatment complexity is magnified. Future research should focus on developing predictive biomarkers for individual patient responses, establishing evidence-based high-dose rifampicin protocols, and developing integrated treatment guidelines that balance efficacy against multidrug-resistant TB with reduced adverse effects. Implementing such personalized approaches could significantly improve treatment adherence, reduce complications, and ultimately improve outcomes in TB management, addressing an important global health priority that affects vulnerable populations worldwide.

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