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Prevalence and risk factors of Adverse Drug Reactions among Newly Diagnosed Tuberculosis Patients at Kalutara district, Sri Lanka.

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Abstract:

Tuberculosis (TB) is a major public health problem in Sri Lanka. Anti-TB treatment may have considerable adverse drug reactions (ADRs) due to the long-term use of several drugs. This research aimed to explore the prevalence and risk factors of ADRs associated with Anti-TB treatment in the Kalutara district, Sri Lanka.

A descriptive cross-sectional study was conducted in District Chest Clinic Kalutara. Interviewer administered questionnaire used to collect data. Most common 14 ADRs and 11 risk factors (socio-demographic characteristics and co-morbidities) were selected for assessment. Multivariable Logistic regression analysis was performed. Significance level was considered as 0.05.

One hundred seventy-eight patients were selected for the study. Prevalence of ADRs was 51.68%. Most common ADRs were nausea/vomiting (24.16 %), Dyspepsia/ gastritis (12.36%), and Liver injury (8.43%). Age was significantly associated with liver injury (p=0.0304), gender was significantly associated with arthralgia (p=0.0440) and peripheral neuropathy (0.0063), alcohol intake was significantly associated with headache (p=0.0294) and liver injury (p=0.0306), DM was significantly associated with peripheral neuropathy (p=0.0277), Chronic Live Cell Disease was significantly associated with liver injury (p=0.0010) and anorexia (p=0.0017).

ADRs are common during TB treatment. Therefore, it is necessary to educate about ADRs to treatment providers and patients. Further, patients with risk factors should be closely monitored for ADRs.

Keywords: Tuberculosis, Risk factors, Adverse Drug Reactions

1. Introduction

"Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis and occasionally by Mycobacterium bovis and Mycobacterium africanum. TB commonly affects the lungs, but it can affect any other organ in the body" (1).

TB is a common communicable disease. Approximately 10 million people are annually affected by TB (2). Sri Lanka is not a high TB burden country. Annually around 8000 to 10000 people are affected by TB in Sri Lanka. In 2019, 8396 TB patients and 266 TB deaths were reported in Sri Lanka (3).

The National Program for Tuberculosis Control and Chest Diseases (NPTCCD) is a central-level organization responsible for TB control activities in the country. There are 26 District Chest Clinics (DCC) in Sri Lanka. When a patient is diagnosed with TB, the patient should register in DCC. Then the patient refers to the Directly Observed Treatment for Short course (DOTS) center to provide drugs and observe drug intake (1).

There are two treatment categories for TB. Category one is given to all newly diagnosed TB patients. Category one regime consists of two phases: the intensive phase and the continuation phase. Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol daily use in intensive phase for two months. Isoniazid, Rifampicin, daily for four months use in the continuation phase. Category two treatment regime is given to all re-treatment cases, such as relapses, treatment after failure, and treatment after loss to follow-up cases (1). This study mainly focused on the drugs used for the category one treatment regime.

There are many Adverse Drug Reactions (ADR) caused by anti-TB medication (Isoniazid - Systemic or cutaneous hypersensitivity reactions, peripheral neuropathy, hepatitis, Rifampicin - gastro-intestinal disturbances {nausea, anorexia, vomiting, abdominal pain}, hepatitis, skin rashes, acute renal failure, thrombocytopenia/ purpura, hemolytic anemia, pyrazinamide - gastro intestinal symptoms {nausea, anorexia}, hypersensitivity skin reactions, hepatitis, hyperuricemia, Arthralgia, Ethambutol - Optic neuritis {can result in impairment of visual acuity and color vision}) (4), (1).

The main challenges of TB control are low detection rate and cure rate/ treatment success rate. It is necessary to comply with TB treatment to increase the cure/treatment success rate. According to the research findings, ADRs were high in TB treatment due to the simultaneous use of several drugs for a longer duration and other individual factors (extremes of age, pregnancy, breastfeeding, some hereditary diseases, and some acquired diseases like liver diseases). Further, ADRs are the main reason for hospital admission during TB treatment (5), (6).

Understanding the prevalence of ADRs and risk factors would be useful for healthcare workers in many aspects. It will help to identify the ADRs early, prevent hospital admission, reduce out-of-pocket expenditure, reduce noncompliance, increase the cure rate and reduce the disease and drug-related complications.

Several types of research were done in several countries to determine ADR prevalence and risk factors. But in Sri Lanka, there is not much research conducted on ADRs. Therefore it is worth researching the above topic. Kalutara district was selected due to the high feasibility of researchers.

The main purpose of this study was to assess the prevalence and risk factors associated with ADRs among tuberculosis patients Kalutara district, Sri Lanka.

2.0 Methodology

A descriptive cross-sectional study was conducted in DCC Kalutara. Newly diagnosed TB patients registered in DCC Kalutara for 6 months (March to August 2021) were considered as the study population. Patients with a category 2 treatment regime (due to differences in drug combinations) and ages less than18 years were excluded from the study. Total of 218 patients was registered from 1st of March to 31st of August 2021. Among them, 192 patients were eligible for the study after exclusions (under-age and category 2 patients). According to Lawanga and Lemeshow (1991) formula, sample size was 384. As total population (192) was less than sample size, total population was selected for the study. Interviewer administered questionnaire was used to collect data. Age, tobacco smoking (tobacco smoke by cigarettes, cigarillos, cigars, pipes or water pipes more than 4 times per week) , alcohol intake (Subjects consuming alcohol either regular or occasionally in the month preceding the data collection), Body Mass Index (BMI), and co morbidities (diagnosed at the time of start anti TB treatment) (such as Diabetes Mellitus {DM}, Chronic Kidney Disease {CKD}, cardiac disease, Chronic Liver Cell Disease {CLCD}, hypertension, Chronic Obstructive Pulmonary Disease {COPD}/asthma) taken as risk factors for ADRs and most ADRs such as nausea/vomiting, dyspepsia/gastritis, arthralgia, skin rash/itchy, headache, blurred vision (confirmed by ophthalmologist fallowing patient complain), dizziness/vertigo, burning sensation of foot/body (peripheral neuropathy), diarrhea, liver injury (will detect by increase Alanine Aminotransferase {ALT} and Aspartate Aminotransferase {AST} more than threefold of normal {can obtain from TB file} and asking relevant symptoms from patient during interview), Hearing impairment (confirmed by audiometry fallowing complain by patient), Psychosis (Diagnosed by consultant psychiatrist), swelling or pain at injection site, loss of appetite (anorexia), sleep disturbance were selected as ADRs. The questionnaire consisted of three components, Part A – Socio-demographic characteristics, Part B - Risk factors for ADRs, and Part C – ADRs. Primary data were obtained from the District Tuberculosis register and TB treatment card for verify the information collected by interviews. The questionnaire was developed in English, translated to Sinhala and Tamil, and back-translated to English to minimize language bias. Data collectors were trained to have uniformity of questionnaires. Data collectors were fluent in all three languages.

Data were collected from the patients who have completed two months of TB treatment. (Some ADRs can manifest just after starting treatment, and some ADRs may take considerable time. Therefore, data were collected after the completion of the first 2 months but before the end of treatment). Collected data has been entered into an EpiData, and subsequently exported to analyzing software (SPSS version 25). Categorical data were summarized by using frequency and proportions. Continuous data were summarized by mean and standard deviation. Multivariable Logistic regression analysis was performed. Significance level was considered 0.05.

3.0 Results

Data were collected from 178 patients. Non-respondent rate was 7.3%. Majority of TB patients were middle age (48.3%) (Table 1). Out of 178 patient 64.6% (n=115) were males and 35.4% (n=63) were females (Table 1). Majority were non-drinkers (59.6%), non-smokers (73.6%) and underweight (14.61+46.07=60.7%). Among the TB patients, 24.7% had DM, 11.8% had CKD, 9.0% had cardiac diseases, 9.6% had CLCD, 15.2% had hypertension and 18.0% had COPD/asthma (Table 1). 51.7% (n=92) patient complained of at least one ADR. Most common ADRs were nausea/vomiting (24.2%), dyspepsia/gastritis (12.4%), skin rash/itchy (10.7%), liver injury (8.4%), anorexia (6.2%), arthralgia (5.1%) and peripheral neuropathy (5.1%). Other ADRs, such as headache (3.4%), dizziness (1.7%), sleep disturbances (1.7%), diarrhea (1.1%), visual disturbances (0.6%) and hearing impairment (0.6%) were rare. No patient had psychosis as an ADR (table 2).

According to the results, there were significant associations between age with liver injury (p=0.0304), gender with arthralgia (p=0.0440) and peripheral neuropathy (0.0063), alcohol intake with headache (p=0.0294), and liver injury (p=0.0306), DM with peripheral neuropathy (p=0.0277), CLCD with liver injury (p=0.0010) and anorexia (p=0.0017) (Table 3).

Smoking, BMI level, and some co-morbidities (CKD, cardiac diseases, hypertension. COPD/Asthma) were not significantly associated with any ADRs.

4.0 Discussion

All newly diagnosed TB patients must take anti-TB drugs minimum of 6 months. Therefore, it is common to have ADRs among TB patients. Most common ADRs (Nausea/vomiting, dyspepsia/gastritis, arthralgia, skin rash/itchy, headache, blurred vision, dizziness, peripheral neuropathy, diarrhea, liver injury, hearing impairment, psychosis, anorexia and sleep disturbances) for category one treatment regime were selected for the study (1), (7). Age, gender, alcohol intake, smoking, BMI, and some co-morbidities were considered risk factors in the study.

The majority of TB patients were within the economically active age group (35.39%+48.31%=83.7%) (Table1). In the current study, the majority was males (64.6%), and the male-to-female ratio was 2:1, which resembles WHO and other published data (8). This could be because men are more exposed to the wider world, thus more likely to get infected by TB. 10.3% of the general population were DM patients, with the highest prevalence in the Western province (18.6%) (9). In the current study DM prevalence among TB patients in the Kalutara district was 24.71%, means DM prevalence was higher among TB patients.

The prevalence of ADRs in first line anti-TB drugs was 51.68%. More than half of patients have shown some ADR during treatment. Studies in other countries reported that ADRs were around 30% to 50%, which was compatible with the result of our research (10), (7). First-line anti-TB drugs reported lesser ADRs than second-line anti-TB drugs (11).

The most common ADR was nausea and vomiting (24.16%). More than 10% of the study population reported having dyspepsia/gastritis (12.36%), skin rash/itchy (10.67%), and the rest of the ADRs were reported by less than 10% of the study population. Different studies reported different ADRs were commonest to their study population. For example, a study done in Iran reported liver injury as a commonest ADR for their study population (12). A study done in India reported cutaneous drug reaction as the commonest ADR for their population (7).

The reasons for heterogeneity in the prevalence of adverse events across the various studies are unclear. Still, it might be related to several factors such as definition of adverse events, study design, demography, gene variation, pharmacokinetic and nutritional status.

In this study, age, gender, alcohol intake, smoking, BMI, and selected co-morbidities (DM, CKD. Cardiac disease, CLCD, Hypertension, COPD/Asthma) were taken as risk factors for ADRs. According to the study, the patient's age was significantly associated with liver injury (p=0.0304) (Table 3). The probability of liver injury will increase with the age of the patients. Other researchers also demonstrated a similar association (13). Some researchers suggest rifampicin is the main reason for ADR in elderly while some suggest pyrazinamide is the main reason for ADR in elderly (14).

Gender (female) was significantly association with arthralgia (p=0. 0.0440) and peripheral neuropathy (P=0.0063) (Table 3). Most of the Food and Drug Administration approved drugs examined, elevated blood concentrations and longer elimination times were manifested by women, and these pharmacokinetics were strongly linked to sex differences in ADRs (15).

Alcohol intake was associated with headache (p=0.0294) and liver injury (p=0.0306) (Table 3). Alcohol intake itself causes liver injury. Therefore, patients who take alcohol are more susceptible to get liver injury with anti-TB medications. According to the literature, alcohol intake increases ADR and has associated with poor treatment outcomes (17).

Among the selected co-morbidities, DM and CLCD showed a significant association with ADRs, DM significantly associated with peripheral neuropathy (p=0.0277), and CLCD significantly associated with liver injury (p=0.0010) and loss of appetite (anorexia) (p=0.0017) (Table 3). DM causes peripheral neuropathy (18), and CLCD also causes liver injury and loss of appetite (19). This may be the reason for the significant association between ADRs with DM and CLCD.

This study failed to show any association between tobacco smoking, BMI, and other co-morbidities (CKD, cardiac diseases, hypertension and COPD/asthma) with any selected ADRs, thought, in literature, there were many research that revealed an association between above risk factors and ADRs E.g.; BMI and ADRs (13), CKD and ADRs (20).

4.1 Conclusions

According to the results, TB was more prevalent among economically active age group, males and DM patients. Patients who received 1st line anti-TB drugs have presented with many ADRs. ADRs of anti-TB treatment are common. Gastrointestinal events (nausea, vomiting, dyspepsia, and gastritis) were the most common ADRs.

Elderly patients, Female gender, alcohol intake, and people with DM, and CLCD were more prone to get ADRs. Older people were more inclined to get liver injury; female gender was significantly associated with arthralgia and peripheral neuropathy. Alcohol intake was more commonly associated with headaches and liver injury. There was a significant association between DM and peripheral neuropathy, CLCD with liver injury, and loss of appetite. All these evidence concludes that it is essential to understand on ADR to manage TB patients.

4.2 Recommendations

As ADRs are common during TB treatment, it is recommended to educate TB treatment providers and patients about ADRs. Alcohol intake should be stopped or minimized during the treatment as alcohol intake will increase the prevalence of ADRs. DM patients should be closely monitored for diabetic control and ADRs. All elderly patients (age > 65) should assess the liver function test before and during (two weekly or monthly) the anti-TB

treatment. It is recommended to start pyridoxine prophylactic for Patients who are predisposed to get peripheral neuropathy, especially alcoholic and DM patients.

Table 1- Socio-demographic characteristics and distribution of risk factors

Characteristics	Frequency	Percentage
Age (Years)		
Young adult (18y to 39y)	63	35.39
Middle age (40y to 65y)	86	48.31
Senior citizen (> 65y)	29	16.30
Highest Educational achievement		
No schooling	2	1.12
GCE A/L[1] or below	139	78.09
Diploma/Graduate/ Postgraduate	37	20.79
Average monthly income (Sri Lanka Rupee – SLR)		
No income	53	29.77
0-50000	55	30.90
50000 – 100000	47	26.40
More than 100000	23	12.93
Risk Factors		
Gender		
Male	115	64.60
Female	63	35.40
Alcohol consumption		
Yes	72	40.44
No	106	59.56
Smoking		
Yes	47	26.40
No	131	73.60
BMI (kg/m^2)		
Severe thinness (BMI < 15.9)	26	14.61
Moderate to mild thinness (BMI 16 to 18.5)	82	46.07
Normal weight (BMI 18.5 to 24.9)	59	33.15
Pre obesity and obesity (BMI >25)	11	6.17
Co-morbidities		
Diabetes		
Yes	44	24.71
No	134	75.29
Chronic kidney disease		
Yes	21	11.80

No	157	88.20
Cardiac disease		
Yes	16	8.99
No	162	91.01
Chronic liver cell disease		
Yes	17	9.55
No	161	90.45
Hypertension		
Yes	27	15.17
No	151	84.83
COPD/Asthma		
Yes	32	17.98
No	146	82.02
Total	**178**	**100.00**

1 - GCE A/L - General Certificate of Education Advanced Level

Table 2 - Prevalence of adverse drug reactions due to TB treatment

Adverse drug reaction	Frequency	Percentage
Nausea/ vomiting	43	24.16
Dyspepsia/ gastritis	22	12.36
Skin rash/ itchy	19	10.67
Liver injury {elevated alanine (ALT) or aspartate transaminase (AST) of 3 times upper limit of normal range with symptoms abdominal pain, nausea, vomiting, unexplained fatigue or jaundice}	15	8.43
Anorexia	11	6.18
Peripheral neuropathy (numbness, tingling, burning, stabbing or shooting pain in the feet or hands.)	09	5.06
Pain in joints (arthralgia)	09	5.06
Others	07	3.93
Headache	06	3.37
Sleep disturbance	03	1.68
Dizziness	03	1.68
Diarrhea	02	1.12
Blurred vision/Visual disturbances	01	0.56
Hearing impairment	01	0.56
Psychosis	00	0.00

Table 3 - Summary of risk factors associated with adverse drug reaction

Risk Factor	Adverse drug reaction	P value
Age	Liver injury	0.0304
Gender	Arthralgia	0.0440
	Peripheral neuropathy	0.0063
Alcohol intake	Headache	0.0294
	Liver Injury	0.0306
Diabetes	Peripheral Neuropathy	0.0277
Chronic Liver Cell Disease	Liver injury	0.0010
	Anorexia	0.0017

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