ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES SCHOOL OF MEDICINE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

PREVALENCE AND ASSOCIATED RISK FACTORS OF ANTI-TUBERCULOSIS DRUG INDUCED LIVER INJURY AMONG CHILDREN SEEN AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA.

A RESEARCH THESIS SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, PEDIATRICS AND CHILD HEALTH DEPARTMENT, IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN PEDIATRICS AND CHILD HEALTH.

By: Dr. MEHRET FIKRE (PEDIATRICS YEAR III RESIDENT)
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ADDIS ABABA, ETHIOPIA

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Advisor: ELHAM SANI (MD, Pediatrician, Pediatric Infectious Diseases Sub specialist)

Declaration

I hereby declare that this thesis titled "***Prevalence and associated risk factors of anti-tuberculosis drug induced liver injury among children seen in Tikur Anbessa Specialized Hospital***" has been carried out by me in partial fulfillment of the requirements for Specialty Certificate in Pediatrics and Child Health with the guidance and support of my advisor Dr. Elham Sani department of pediatrics and child health. The information derived from the literature has been duly acknowledged in the text and a list of reference provided. I also reveal that the work has not been submitted for any other degree or professional qualification.

Name of investigator: Mehret Fikre

Department: _____

Date: _____

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Approval of Advisor

Name: Dr. Elham Sani

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Date: _____

Signature: _____

Acknowledgement

I would like to express my deepest gratitude to Addis Ababa University College of Health Sciences, Department of Pediatrics and Child Health for granting the budget and giving me the chance to do this research. I also would like to express my sincere respect to my advisor Dr. Elham Sani for her invaluable comments and readiness to help me until the end of the study.

In addition, I would like to thank the staff members of Pediatric Infectious Disease Clinic and medical records room. Finally, praise be to GOD, for HIS guidance throughout the whole process and for giving me the strength to be able to complete this work.

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Acronyms

AAP	American Academy of Pediatrics
AFB	acid fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AOR	adjusted odds ratio
ART	anti-retroviral therapy
AST	aspartate aminotransferase
ATLI	anti-tuberculosis drug-induced liver injury
ATS	American Thoracic Society
BMI	body mass index
BTS	British Thoracic Society
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	corona virus disease 2019
DILI	drug induced liver injury
DR-TB	drug resistant tuberculosis
DS-TB	drug susceptible tuberculosis
E	ethambutol
EPTB	extra-pulmonary tuberculosis
FDA	Food and Drug Administration
FMOH	Federal Democratic Republic of Ethiopia- Ministry of Health
H	isoniazid
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMIS	health management information system
IU	international unit
L	liter
LFT	liver function test
LPA	line probe assay
MDR-TB	multi drug-resistant tuberculosis
mg/dL	milligrams per deciliter
MRN	medical record number
ODK	Open Data Kit
PI	principal investigator
PIDC	pediatric infectious disease clinic
PTB	pulmonary tuberculosis
R	rifampicin
SPSS	statistical package for social sciences
TASH	Tikur Anbessa Specialized Hospital
TB	tuberculosis
ULN	upper limit of normal
WHO	World Health Organization
Z	pyrazinamide

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Abstract

Background: Treatment of patients with tuberculosis (TB) requires careful monitoring for a variety of adverse drug effects. Anti-tuberculosis drug-induced liver injury (ATLI) is one of the most frequent and serious toxic effects during TB treatment. In children, it is less common than adults, but can develop at any age or any dosage of anti-TB drugs, with signs and symptoms frequently overlooked in many cases. As compared to adults were various factors are reported to be associated with higher risk to develop ATLI, in children, susceptibility related to ATLI have been studied insufficiently.

Objective: This study aimed to determine the prevalence and associated risk factors of ATLI among children taking anti-TB therapy in Tikur Anbessa Specialized Hospital (TASH), Pediatric Infectious Disease Clinic (PIDC) from January 1, 2021 - December 31, 2022.

Method: Hospital-based retrospective cross-sectional study was conducted in a total of 144 selected patients at PIDC from January 1, 2021 - December 31, 2022 G.C. Data was collected by using a standard checklist through Open Data Kit (ODK) form from the patients' cards and analyzed using SPSS version 27 software package. Mean, and standard deviation were used to describe continuous data, and frequency and percentage were used to describe categorical data. To identify factors associated with ATLI bivariate and multivariable binary logistic regression analyses were done. Statistical significance was considered at level of significance of 5%, and adjusted odds ratio (AOR) with 95% confidence interval (CI) was used to present the estimates of the strength of the association.

Result: Among the 144 cases, ATLI was detected in 8 patients, with a prevalence of 5.6 %. Age group 5-15 years [AOR= 0.061; 95% CI: 0.007 – 0.52] and severe acute malnutrition [AOR=13.2; 95% CI: 1.38 -126.3; p-value 0.025] were significantly associated with ATLI prevalence.

Conclusion: This study indicated that close monitoring of ATLI should be performed for children with severe acute malnutrition receiving anti-TB therapy.

Key words: anti-tuberculosis drug-induced liver injury, prevalence, risk factors, TASH, Ethiopia

1. INTRODUCTION

1.1. Background

Worldwide, Tuberculosis (TB) is a significant global health problem and is ranked 13th as a cause of mortality. It is the 2nd cause of death from communicable diseases after COVID-19, which is above HIV/AIDS.[1]

The WHO 2022 Global Tuberculosis Report revealed, an estimated 10.6 million people were diagnosed with tuberculosis in 2021, of which 1.2 million were children and young adolescents under 15 years of age representing about 11% of all TB cases globally, with almost half of them below five years of age.[1]

An estimated 1.6 million people died from TB in 2021, and of the 54% of the HIV-negative people who died, 14% were children (aged <15 years).[1]

Ethiopia ranks 7th among the 30 High TB burden countries, with an estimated incidence of 119/100,000 population and children aged 0-14 years accounted for nearly 10% of all TB case notifications in 2021.[1]

The management basis of drug sensitive TB is a combination of anti-tuberculosis drug regimens comprising first-line drugs isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) which are taken for 2 months in the intensive phase followed by a 4 to 10 months use of RH in the continuation phase.[2]

Although these drugs are effective, safe and well tolerated by children, they are also associated with many adverse drug reactions one of which is Anti-Tuberculosis drug-induced Liver Injury (ATLI).[4]

ATLI is an adverse toxic drug reaction from anti-TB drugs resulting in liver injury. The first-line anti-TB drugs which commonly cause hepatotoxicity include isoniazid, rifampicin and pyrazinamide.[5]

ATLI may result from the parent compounds' or a metabolites' direct toxicity, or from an immune mediated response affecting the liver's parenchymal cells, epithelial cells of the biliary system, and/or vascular system of the liver.[7] Released or accumulated metabolites during the metabolic process lead to idiosyncratic reactions, which are thought to be the most common causes of the majority forms of ATLI.[7]

In our setup, hepatotoxicity due to anti-TB drug is defined as elevation of serum liver enzymes, aspartate aminotransferase (AST) or alanine aminotransferase (ALT), by ≥3 times the upper limit of normal (ULN) in the presence of symptoms of hepatitis, or by ≥5 times ULN in the absence of symptoms &/or a total bilirubin of >2mg/dl.[2]

Presentations can be variable, from asymptomatic liver injury to clinically overt hepatitis.[6] Patients who are symptomatic may develop nausea, vomiting, loss of appetite, abdominal pain and jaundice, with physical findings of right upper quadrant tenderness and hepatomegally.

Different recommendations have been made for monitoring patients on anti-TB therapy,[6] with some like ATS, CDC and BTS favoring screening of all patients before initiation of treatment, then requiring frequent monitoring for those with risk factors.[18] In contrast, the recent AAP clinical report[20] and the current WHO guideline[3] do not advocate routine determination of serum liver enzyme levels, and encourages evaluating compliance and toxicity by regular clinical assessment, which in most recorded cases is often ignored in pediatric patients.[5]

ATLI has an important role in decreasing treatment effectiveness by increasing patient morbidity and mortality creating challenge to treatment.[5] It can reduce compliance to therapy, disrupt adherence and prolong treatment. This may result in interruption or discontinuation of therapy which may contribute to treatment failure that can possibly cause drug resistance.[5] If not recognized early, liver dysfunction due to anti-TB drug could also negatively impact treatment outcome resulting in acute liver failure and death.[7]

1.2. Statement of the Problem

Even though children experience ATLI less frequently than adults [3], the majority of children being treated for TB in the world belong to resource-limited, developing countries were TB is endemic, and were monitoring and reporting of adverse reactions to anti-TB drugs is poor.[8]

The prevalence among children specifically has been described in only a limited number of studies and data have wide variations, with rates ranging from 3%-4% in developed countries to 8%-39% in developing countries.[8] The probable reasons attributed for the higher incidence seen in developing countries were, rampant malnutrition, indiscriminate use of drugs, a high incidence of coexisting viral hepatitis resulting in misdiagnosis, and a genetic predisposition. In addition, variations in, drug regimens and dosage, a threshold used to define ATLI and monitoring practices, contribute to variable reports.[21] Data on the mortality rate of children due to ATLI are also scarce and frequency varies from 1–50%.[8,19]

Studies have investigated many clinical parameters in adults associated with higher risk to develop ATLI, such as older age, being female, ethnicity, alcohol intake, pretreatment hypoalbuminemia, HIV/AIDS, preexisting liver disease, slow acetylator phenotype of N-acetyltransferase 2, malnutrition, decreased glutathione-S transferase activity, hepatotoxic co-medications and genetics.[9] In contrast, susceptibility related to ATLI in children have been studied insufficiently and associated factors are controversial among different study findings, therefore there is a clear necessity to identify the incidence and associated risk factors of hepatotoxicity during anti-TB chemotherapy in children.[10]

1.3. Significance of the study

Currently there are very few studies done in Africa and no published data in our country on the prevalence and related factors associated with liver dysfunction in children taking anti-TB drugs.

The knowledge obtained from this study regarding the magnitude of childhood ATLI in our setup, and identifying possible risk factors for its occurrence will aid in early diagnosis and management, which in turn will help prevent negative treatment outcomes.

2. LITERATURE REVIEW

Prior studies have identified that the overall occurrence of ATLI to be lesser in children than in adults, but a paper which reviewed prior articles related to the prevalence of ATLI in children, confirms ATLI does occur in children and attention is always necessary to avoid the occurrence of acute liver failure.[11]

In an era before the use of pyrazinamide as a standard first-line anti-TB therapy, a retrospective analysis performed in 1983 in the United States to estimate rates of hepatotoxicity among children treated for TB reported 14/430 (3.3%) children receiving isoniazid and rifampin had a hepatotoxic reaction (AST >100 IU/L) with risk factors for developing hepatotoxicity being the presence of miliary tuberculosis or tuberculous meningitis.[12]

In contrast to the above study, two studies reported higher incidence of hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis.

A prospective study from Greece done in 1985 evaluated 44 children with age group 6 month to 12 year (mean 4.9 year) with severe, disseminated and meningitic TB treated with isoniazid and rifampin. ALT elevation >100 IU/l occurred in 36 patients (82%) of which 15 (42%) developed clinical hepatitis with jaundice. Liver failure with subsequent death occurred in one child (2.3%) with the study concluding incidence of hepatotoxicity is related with the severity of TB, while patients' age or sex showed no correlation.[13]

In another early study done in Gabon in 1989, 47 children with TB were treated with isoniazid and rifampin, of which 14 (29.2%) had ALT elevation > 100 IU/L. The main identified factors in increasing the risk of hepatic toxicity were a high dosage of isoniazid and malnutrition.[15]

After the introduction of pyrazinamide as one of the first-line anti-TB agents, in 2002 a retrospective study done in Japan investigated the risk factors for developing severe hepatotoxicity in 99 children aged 0-16 years treated for TB. The study demonstrated that 22 children (22.2%) had AST or ALT values elevated, but < 5X the ULN and 8 (8.1%) children developed severe hepatotoxicity defined as elevation of AST or ALT values of > 5X the ULN. All 8 children with severe hepatotoxicity were below age 5 years.

Although the uni-variate analysis revealed, majority of children with hepatotoxicity to were male, in the younger age group, with most of them having extrapulmonary type

of TB, and received pyrazinamide more often than those who had no hepatotoxicity, the multivariate logistic regression analysis showed only age (odds ratios of 143, 95% confidence interval, 4.2 to 4934.9), and pyrazinamide administration (odds ratios of 0.60, 95% confidence interval, 0.39 to 0.90) to have a significant contribution ($P < .05$) to the development of severe hepatotoxicity. Because none of their patients had Retro-viral or viral hepatitis infections, and since majority of them were well nourished, they were unable to determine if these risk factors were relevant.[10]

As compared to the above studies, a Chinese series of nearly 600 children reported a lower incidence of anti-TB drug induced hepatotoxicity. 11 of 599 (1.84%) cases developed hepatotoxicity, of which 75% of the inpatients were asymptomatic and majority of the cases were detected within the first four weeks of initiation of treatment. Hepatotoxicity was attributed to isoniazid, rifampin and pyrazinamide.[14]

A 2005 article from Peru, presented 5 pediatric cases treated throughout a period of 10 year. Two individuals showed only increase in serum liver enzymes with no symptoms, while 2 individuals had clinical hepatitis, and 1 individual had acute liver failure. They reported most patients were school-aged females, while associated risk factors were malnutrition and therapy reintroduction after the resolution of hepatic damage.[22]

According to an Indian study undertaken at a tertiary pediatric hospital from April 2007 to February 2008, 7 (15.2 %) out of 46 children developed drug induced hepatic dysfunction. Liver dysfunction was analyzed for related factors and was found to be associated with age younger than 3½ years, with no association with sex, weight, malnutrition and type or severity of tuberculosis.[9]

A 2010 Pakistanis case series which was conducted for 6 months, demonstrated that 11 (13.92%) among 79 children aged 1-14 years developed anti-TB drug induced hepatotoxicity. They observed that anti-TB drug-induced hepatotoxicity was more common in males (9, 81.8%) than females, which showed statistical significance ($p=0.060$). All of the cases were in the initial two months treatment and 8/11 of cases with hepatotoxicity had pulmonary TB. The most common drugs found to be responsible with decreasing frequency were isoniazid in 6 (54.5%) patients, followed by rifampicin (18.2%) and combined drug toxicity {(27.3%) $p <0.05$}.[8]

In a 2009 cohort study performed in Indonesia, incidence of anti-TB induced hepatotoxicity in children (age 0-18 years) during the first 2 weeks of therapy was assessed. 6 of 81 subjects had hepatotoxicity reaction (1 hepatitis, 2 mixed case, and 3

asymptomatic), with equal number of male and female patients. Most of the subjects with hepatotoxicity were 1 to 5 years old (67%) and 50% of the cases had good nutritional status. The study concluded incidence of anti-TB induced hepatotoxicity in children during the first 2 weeks of therapy was 7% with no difference in nutritional state as well as in sex distribution. The risk factor of using concomitant hepatotoxic drugs could not be determined as subjects receiving these drugs were small in number, therefore statistical analysis could not be performed.[4]

Another case-control Indonesian study published in 2017 reviewed medical records of hospitalized pediatric patients diagnosed and treated for TB from October 2010 to October 2015 in a referral hospital in West Java, Indonesia. Results showed, 50 (3.5%) out of 1424 pediatric TB patients (age 5 months to 13 years) developed anti-TB drug induced hepatotoxicity. Case-control analysis of the 50 cases and of the 100 TB controls without anti-TB drug induced hepatotoxicity showed that the correlation between gender, age, type of TB, nutritional status and comorbidities to occurrence of anti-TB drug induced hepatotoxicity was statistically insignificant. [16]

In contrast to the above two studies, another Indonesian observational analytic study with a cross-sectional approach conducted from January–December 2012 revealed, 28% (24/86) had anti-TB drug-induced hepatotoxicity(ATIH). ATIH predominantly occurred in girls (71%), aged 5–9 years old (42%) and in the intensive phase of therapy (58%).[23]

Similarly a 2018 article published from Indonesia with a prospective study done from September 2015 to April 2016 showed a higher incidence of ATLI in children. A total of 41 children aged 1 to 15 years who were diagnosed with TB and treated with first-line anti-TB drugs were followed prospectively. ATLI was detected in 11 (27%) patients, with duration of treatment from the start of therapy to the development of ATLI ranging from two to 6 weeks, with most of them (54%) occurring after 2 weeks. Factors which were not found to be associated with ATLI were gender, age, nutritional status, RVI status and baseline liver function abnormalities. Independently associated factors identified with multivariate analysis were hypoalbuminemia and hepatotoxic comedications (both $P < 0.1$).[5]

Contrary to above studies, an article published in Nigeria in 2017 concluded that hepatotoxicity from anti-TB therapy to be not common in children. The study was conducted among 62 cases (age range of 3 months to 17 years and mean age of 6.9 ±4.2 years) that were treated over a two year period reported that, four (6.5%)

children had elevation of ALT of 3 times the ULN at 2 months, but at the 5th month of treatment, repeated tests were within normal limits in all four patients.[6]

A local study conducted from May to November 2019 in selected general hospitals of Tigray, Ethiopia to assess drug induced hepatotoxicity and anemia among children with TB showed hepatotoxicity in those with TB to be 8.5% (8/94). The thesis concluded liver function tests were significantly increased among TB infected children as compared to control group with out TB, and also added that those with retro-viral co-infection showed higher occurrence of drug induced hepatotoxicity.[17]

2.1. Conceptual Framework

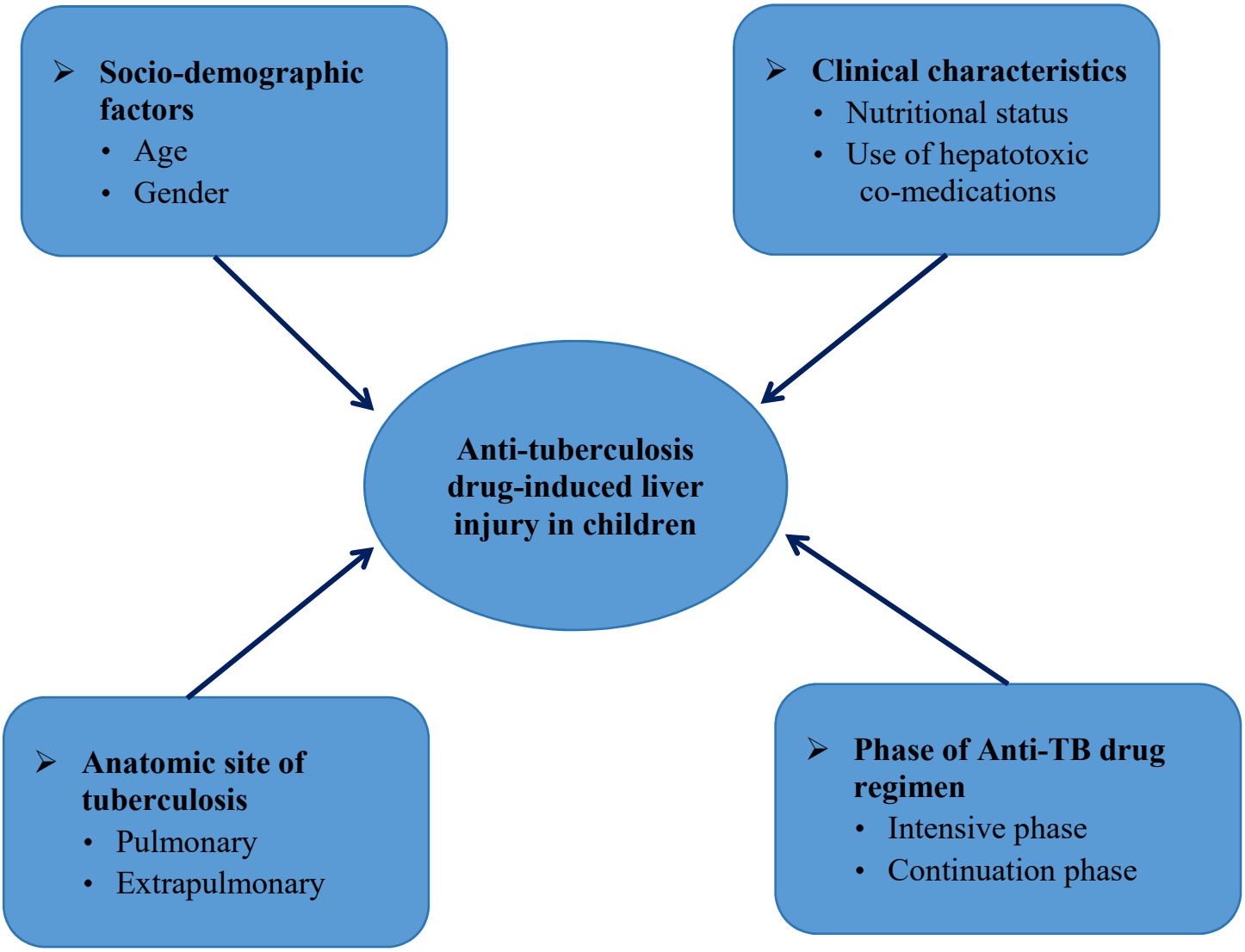

Figure 1. Conceptual framework of factors associated with Anti-tuberculosis drug-induced liver injury

3. OBJECTIVES

3.1. General objective

- To determine the prevalence and associated risk factors of ATLI among children taking anti- TB therapy in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

3.2. Specific objectives

- To determine the prevalence of ATLI among children taking anti-TB therapy.
- To identify risk factors associated with the development of ATLI among children.

4. METHODS AND MATERIALS

4.1. Study setting and period

The study was conducted in Tikur Anbessa Specialized Hospital at Pediatric Infectious Disease Clinic from January 1, 2021 - December 31, 2022, G.C. TASH, established in 1974, is the largest tertiary hospital in the country providing teaching for over 300 under graduate medical students and for over 350 post graduate residents annually. The hospital also offers diagnosis, treatment and followup for over 350,000 patients a year. The Department of Pediatrics and Child Health is one of the departments with ten sub-specialty clinics and the Pediatric Infectious Disease Clinic is among one of them providing daily outpatient visits and scheduled followups.

4.2. Study design

An institutional-based retrospective cross-sectional study was carried out.

4.3. Source population

All children with age 15 years and younger, newly diagnosed with TB and started anti-TB therapy at PIDC.

4.4. Study population

All children with age 15 years and younger, newly diagnosed with TB and started first-line anti-TB therapy at PIDC from January 1, 2021 - December 31, 2022, G.C

4.5. Inclusion and exclusion criteria

4.5.1. Inclusion criteria

Children with age 15 years and younger, newly diagnosed with active pulmonary TB or extra-pulmonary TB and received first-line anti-TB therapy.

4.5.2. Exclusion criteria

- Patients who had baseline ALT, AST and total bilirubin values in the range of the diagnostic values with or with out symptoms.
- Those patients with positive HCV, Hepatitis B virus or both at baseline.
- Those with Retro-viral Infection on ART.
- Re-treatment case of TB.
- Those with suspected MDR-TB.
- Patients who failed to complete treatment and those with poor adherence.

4.6. Sample size and sampling technique

4.6.1. Sample size determination

A prior Nigerian literature mentions ATLI in children to be somewhere around 3% and 10%.[6] Thus taking proportion of 10%, sample size was determined using single population proportion formula.

$$n = \frac{Z^2 P(1- P)}{d^2} = \frac{1.96^2 \times 0.10 (1- 0.10)}{0.05^2} = 138$$

where:

n= sample size

P=proportion of ATLI in children

d= desired degree of precision (5%)

Z= the value at 95% confidence level

Final sample size required is 152 after the addition of 10% of the calculated value for incomplete data.

4.6.2. Sampling technique

Medical record number (MRN) of all children with age 15 years and younger, newly diagnosed with TB and started on first-line anti-TB therapy was collected from the health management information system (HMIS) registration book of the pediatric infectious disease clinic within the study period. HMIS record of the clinic was used as a sampling frame and then, all patient were studied.

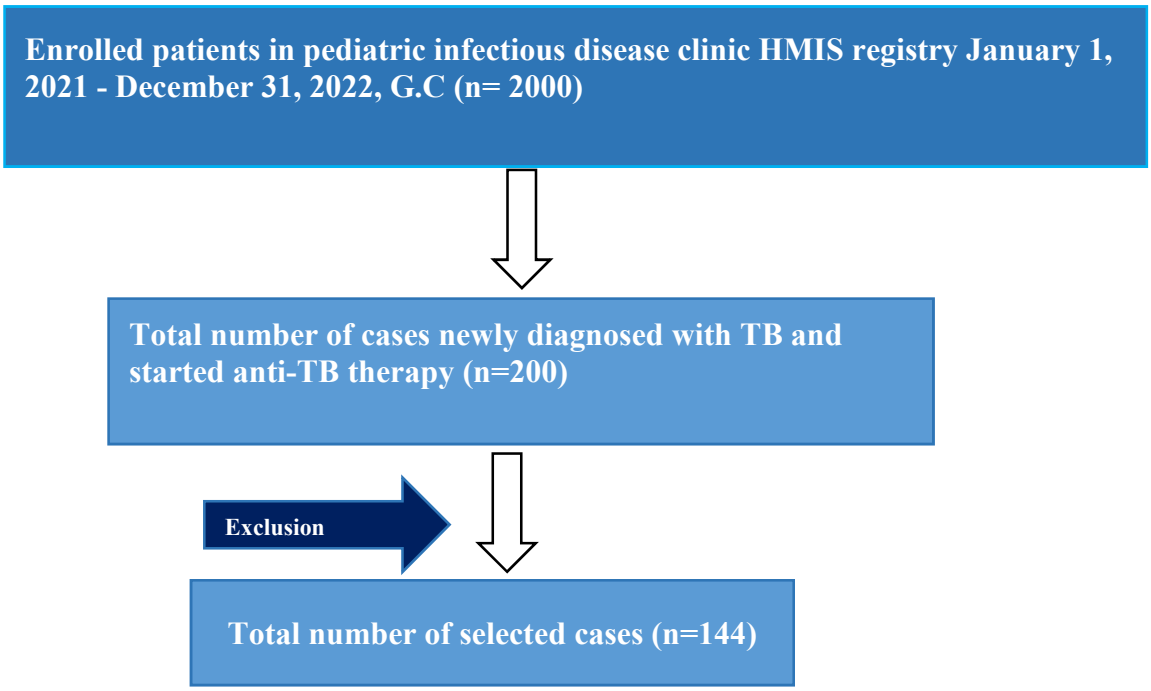

Figure 2. Schematic presentation of sampling procedure in TASH, PIDC, January 1, 2021 - December 31, 2022, G.C

4.7. Study variables

4.7.1. Independent variable

- Anti-tuberculosis drug induced liver injury

4.7.2. Dependant variables

- Socio-demographic data
- Nutritional status
- Phase of Anti-tuberculosis drug regimen
- Anatomic site of tuberculosis
- Hepatotoxic comedications

4.8. Operational definition

- **Anti-tuberculosis drug induced liver injury** - defined as elevation of serum liver enzymes, aspartate aminotransferase (AST) or alanine aminotransferase (ALT), by ≥3 times the upper limit of normal (ULN) in the presence of symptoms of hepatitis, or by ≥5 times ULN in the absence of symptoms &/or a total bilirubin of >2mg/dl.
- **Symptoms of hepatitis -** are characterized by nausea, vomiting, jaundice, icteric sclera, tea-colored urine, pale stool and diminished appetite.
- **Hepatotoxic comedications** - drugs listed under the Drug Induced Liver Injury Rank (DILIrank) data set, which is the largest reference drug list consisting of 1,036 FDA-approved drugs divided into classes according to their potential for causing DILI.

4.9. Data collection procedures

Data collection by reviewing charts was done by the principal investigator. A structured questionnaire was used which comprised two sections:

- *Section 1* - socio-demographic characteristics
- *Section 2* - clinical characteristics

ODK version 1.25.2 software and Kobo Toolbox server were used to collect the data and to store the collected data respectively.

4.10. Data quality assurance

Questionnaire consistency was checked with pretesting with 5% of the total sample size for ensuring the quality of the data. The questionnaire was modified based on problems highlighted during the pretest. Each question was properly coded, continuously supervised and checked for completeness and consistency both during the pretest and data collection period.

4.11. Data processing and analysis

After data collection by ODK application, data was exported to SPSS version 27 for analysis. Mean, and standard deviation were used to describe continuous data, and frequency and percentage were used to describe categorical data. To identify factors associated with ATLI, first, bivariate analysis was done. Then variables with a P-

value < 0.25 were selected and entered into a multivariable analysis. On subsequent multivariable analysis, variables with a p-value < 0.05 were labeled as statistically significant. An AOR with 95% CI was identified to measure the strength of the associations. Results are presented using text, tables and graphs, and finally interpreted into valuable information.

4.12. Ethical consideration

Ethical clearance was obtained from the Department of Research and Ethical Review Committee. The official ethical clearance and a signed letter of support were submitted to the card room. All the ethical principles were maintained at all levels of the study, with only using I care number of the study participants.

4.13. Dissemination of findings

The findings of this study will be submitted to Addis Ababa University, College of Health Sciences, School of Medicine, Department of Pediatrics and Child Health for the requirement of partial fulfillment of specialty certificate in pediatric and child health. Subsequently an attempt will be made to present the findings on different review meetings, seminars and workshops. Furthermore, the manuscript will be published on peer reviewed journals.

5. Results

5.1. Socio-demographic data

In the study period, a total number of 200 pediatric patients with age 15 years and younger, newly diagnosed with active pulmonary TB or extra-pulmonary TB were receiving anti-TB drugs at TASH, PIDC from January 1, 2021 to December 31, 2022. Of these, 144 cases were studied. Among the 144 cases, 86 (59.7%) were male and 58 (40.3%) were female, resulting in a male-to-female ratio of 1.4:1. The patients' mean age was 7.8 ±3.8 SD years, with a range of 4 months to 15 years. More than three-fourths, 113 (78.5%) of the patients were in the age group of 5 to 15 years.

The details of the socio-demographic characteristics of the study population are shown in table 1 and figure 3.

Sex	Frequency	Percentage
Male	**86**	**59.7**
Female	**58**	**40.3**

Table 1. Distribution of sex

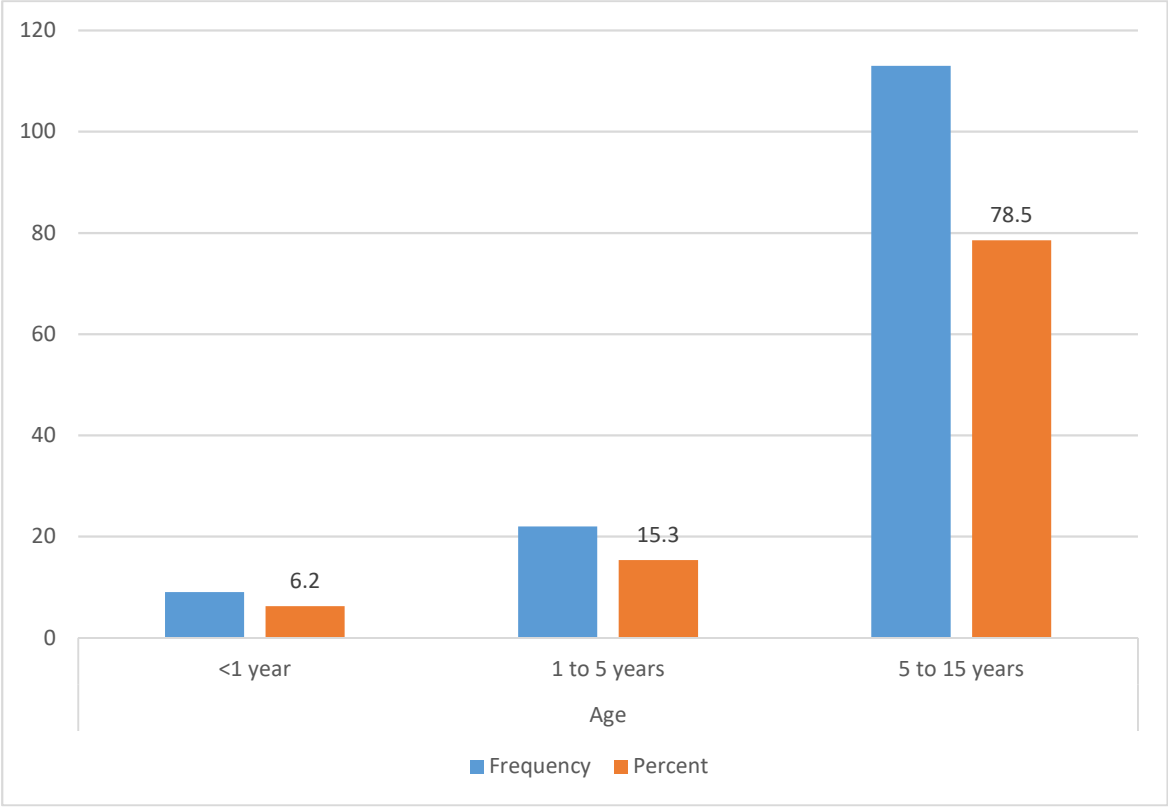

Figure 3. Age in years

5.2. Clinical characteristics

Seventy five (52.1%) of the patients were well-nourished, whereas 29.9% were moderately malnourished and 18.1% had severe acute malnutrition.

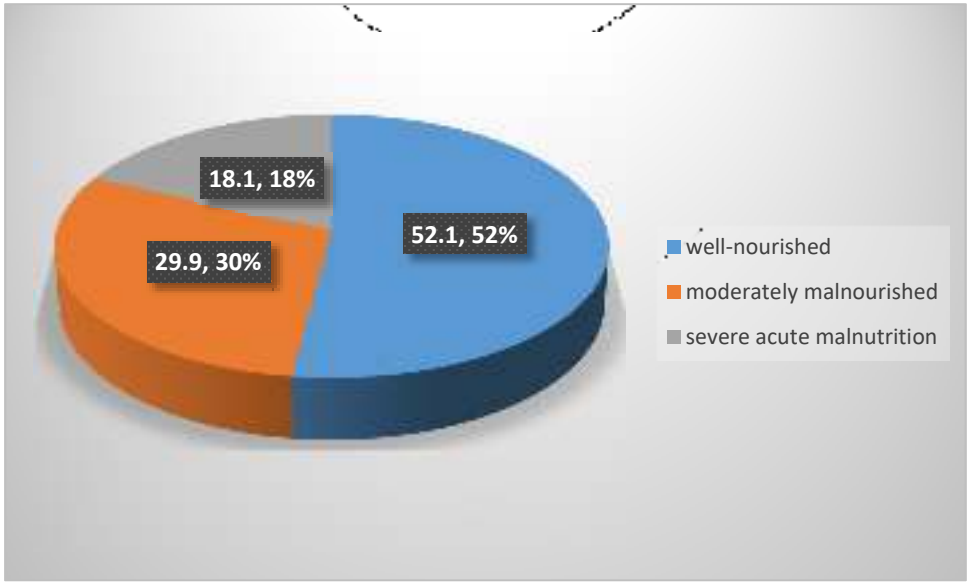

Figure 4. Nutritional status

Of the 144 patients, majority of them 119 (82.6%), had extrapulmonary TB, with the rest 17.4% having pulmonary TB. Of the 119 extrapulmonary TB cases, more than half (56.6%) of the cases were disseminated TB, while 22.7% were TB lymphadenitis and 6 % of cases had TB meningitis.

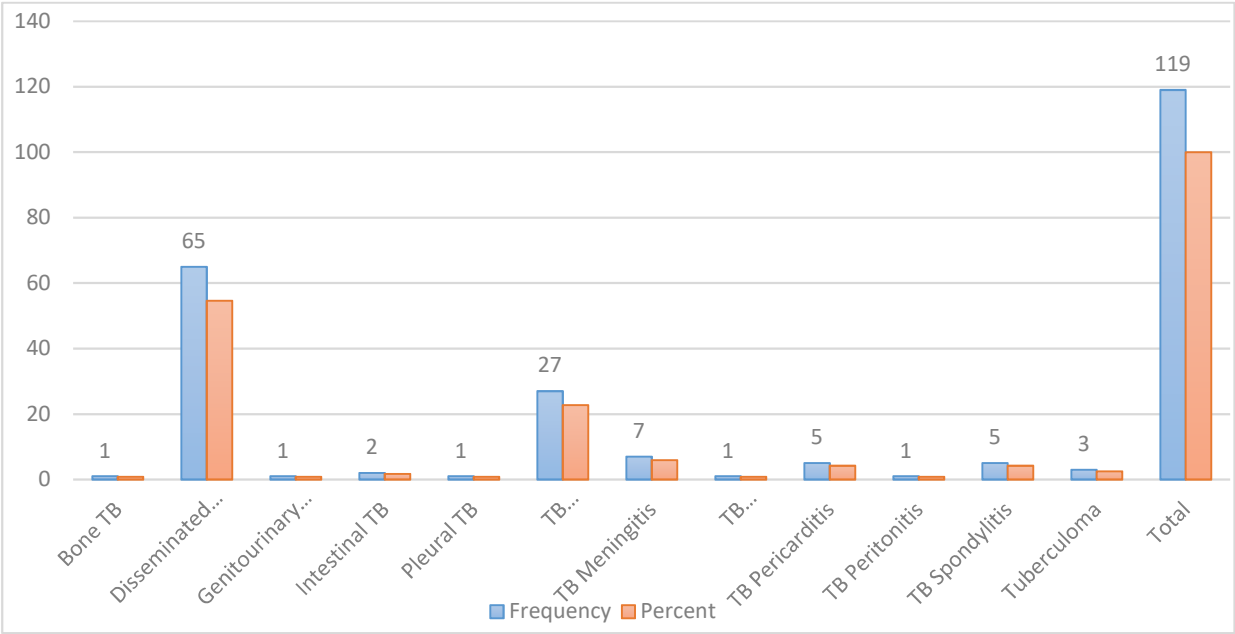

Figure 5. Distribution of types of extrapulmonary TB

Regarding method of diagnosis, majority of the cases were diagnosed with either radiologic methods, or with a clinical diagnosis supported by radiologic findings, each accounting 27.8% of the diagnostic methods used.

Of the 32 (22.2%) cases diagnosed with rapid molecular tests, 29 were diagnosed with Xpert® MTB/ RIF assay, while LF-LAM was used for the remaining 3 cases.

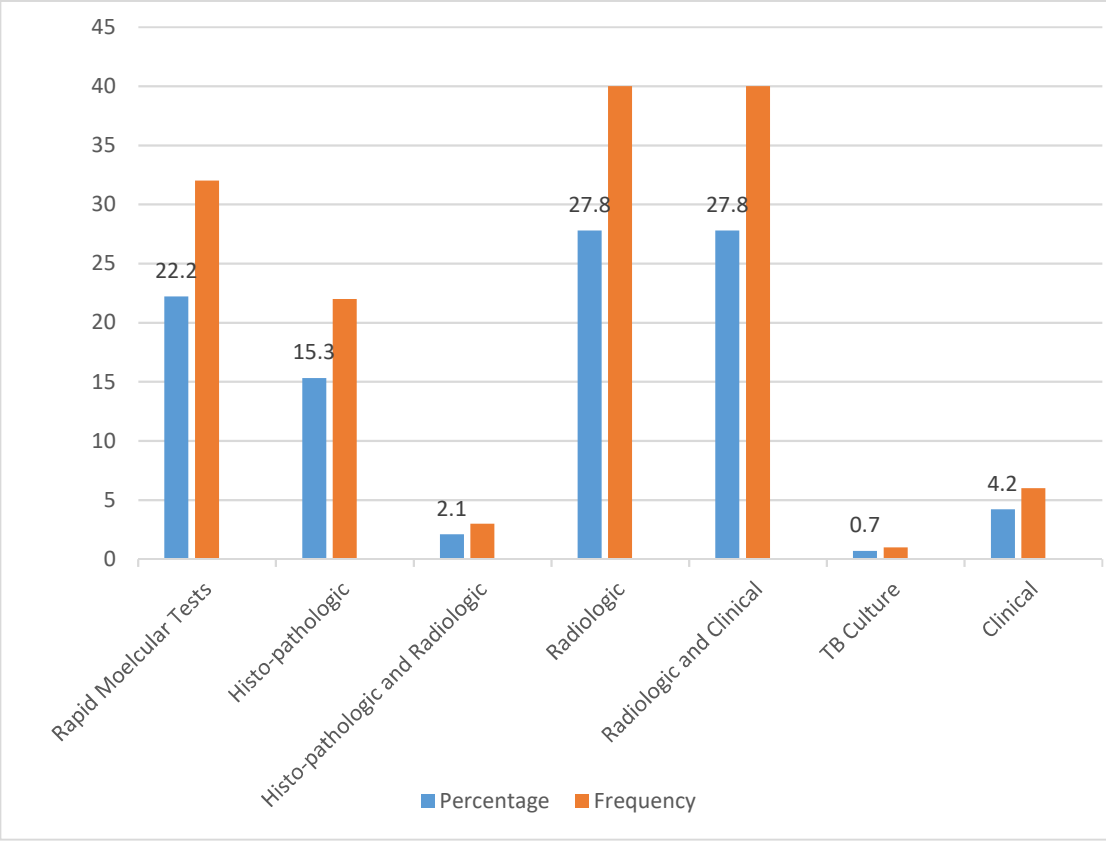

Figure 6. Method of diagnosis

Concomitant hepatotoxic medications were used by 12 (8.3%) patients. Half (50%) of the cases used different combinations of anti-epileptic drugs, while the remaining half used chemotherapeutic drugs, antimicrobials or a combination of both.

		Frequency	Percentage
Chemotherapy	6-Mercapropurine, Cyclophosphamide, Cytarabine, L- Asparginase	1	8.3
	Cyclophosphamide	3	25.0
Antimicrobial& Chemotherapy	6-Mercaptopurine, Methotrexate, Cotrimoxazole	1	8.3
Antimicrobial	Ciprofloxacin, Fluconazole	1	8.3
Anti-epileptic Drugs	Phenobarbitone	1	8.3
	Phenobarbitone, Phenytoin	2	16.7
	Phenytoin, Valproic acid	1	8.3
	Valproic acid, Carbamazepine	2	16.7
Total		12	100%

Table 2. Hepatotoxic comedications

5.3. Prevalence of ATLI and clinical findings

Among the 144 cases, 8 (5.6 %; 95% CI: 2.4, 10.7) patients developed ATLI, with equal number of male and female patients. Age group 5 to 15 years accounted for 25% of the total cases, while 75% of the cases were under five years old, with infants age <1 year and those with age 1 to 5 years, each accounting 37.5% of all cases with ATLI. Mean age of patients who developed ATLI was 3.21 ±3.39 SD years, and ranged from 6 months to 9 years.

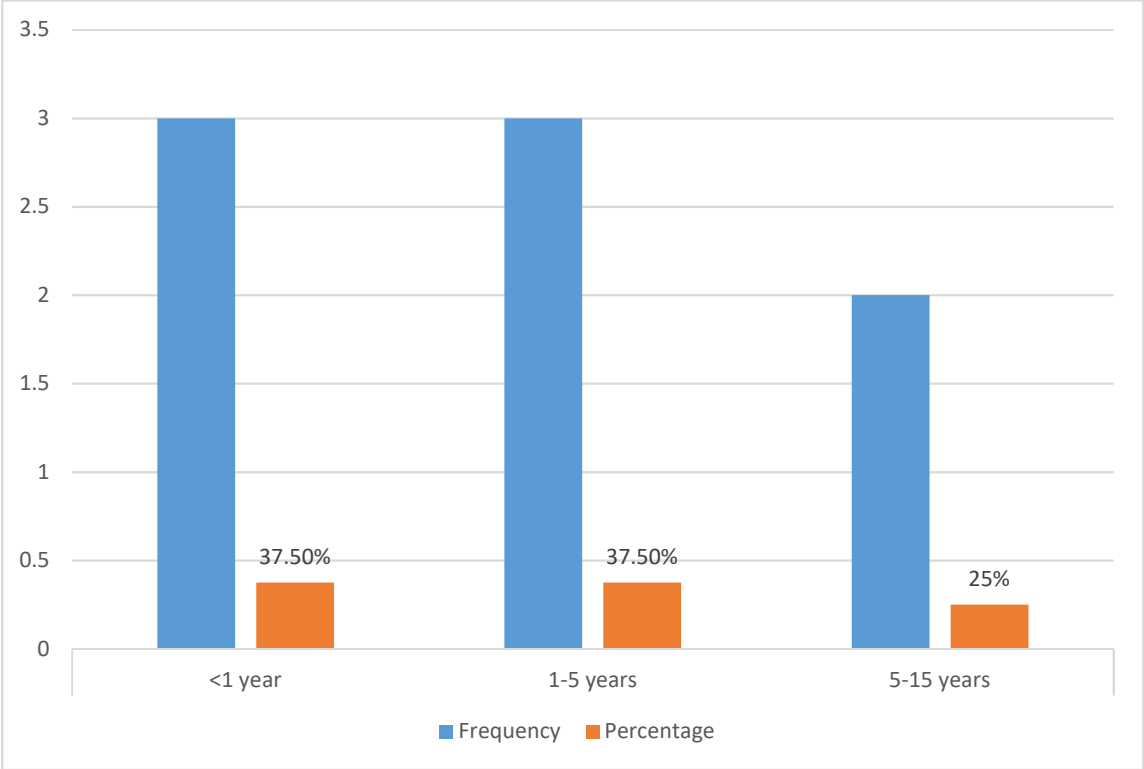

Figure 7. Age distribution in patients with ATLI

Of the total eight cases with ATLI, three fourth (n=6) of the patients were severely malnourished, while moderately malnourished and well nourished cases each accounted for 12.5%.

Based on distribution of anatomical site of TB, majority 7 (87.5%) patients had extrapulmonary TB, with the rest 12.5% having pulmonary TB. Of the 7 extrapulmonary TB cases, more than half (62.5%) of the cases were disseminated TB, while 25% were TB of the central nervous system.

Half of the cases were diagnosed with Rapid molecular tests (3 with Xpert® MTB/ RIF assay and 1 with LF-LAM assay), while 25% were diagnosed with radiologic methods together with a clinical diagnosis, and only 1 (12.5%) patient had Histo-Pathologic diagnosis.

Majority (75%) of cases were on intensive phase of therapy while developing ATLI, whereas, 25% were on continuation phase. Of the eight cases only one patient had concomitant use of hepatotoxic co-medication with combinations of anti epileptic drugs. Detail of clinical characteristics of patients with ATLI are shown on table 3.

		Frequency	Percent
Nutritional status	Well nourished	1	12.5
	MAM	1	12.5
	SAM	6	75
	Total	**8**	**100**
Anatomic site of tuberculosis	➢ **Extrapulmonary TB**		
	• TB Meningitis	1	12.5
	• Tuberculoma	1	12.5
	• Disseminated TB	5	62.5
	➢ **Pulmonary TB**	1	12.5
	Total	**8**	**100**
Use of hepatotoxic co-medication	No	7	87.5
	Yes (Phenytoin, Carbamazepine)	1	12.5
Duration of therapy during development of ATLI	Intensive phase	6	75
	Continuation phase	2	25

Table 3. Clinical characteristics of patients with ATLI

On the diagnosis of ATLI, one patient with pulmonary TB was asymptomatic with only elevation of liver enzymes (AST ≥ 5X ULN and ALT ≥ 3X ULN), while the rest 7 (87.5%) showed elevated liver enzymes with clinical symptomatology, 5 patients had nausea, vomiting and loss of appetite, and 2 patients developed vomiting, icteric sclera & anorexia.

All cases were managed inpatient, with serial reintroduction of regimen with all of them completing treatment.

Serum liver enzyme levels	Frequency	Percentage
Elevated AST > 5X ULN and ALT > 3X ULN	1	12.5%
Elevated AST ≥ 3-4X ULN	1	12.5%
Elevated AST >3-4X ULN and Total Bilirubin > 2mg/dl	3	37.5%
Elevated ALT and AST ≥ 3X ULN and Total Bilirubin > 2mg/dl	3	37.5%
Total	**8**	**100%**

Table 4. Pattern of liver enzymes elevation

5.4. Factors associated with ATLI

During bivariate analysis, variables such as, age, sex, nutritional status, anatomic site of tuberculosis, use of hepatotoxic comedications and phase of anti-TB therapy were analyzed. Based on the p-value (< 0.25), age and nutritional status were the two candidate variables identified for multivariate analysis.

In the multivariate analysis, age and nutritional status were the statistically significant (p-value < 0.05) variables associated with ATLI .

	Category	ATLI presence		Bivariate analysis (COR)	Multivariate analysis (AOR)	p-value
		No	Yes			
Age	<1 year	6	3	1	1	
	1 to 5 years	19	3	0.31[0.05, 1.99]	0.34[0.042, 2.82]	0.32
	5 to 15 years	111	2	0.036[0.05, 0.25]	**0.061[0.007, 0.52]**	**0.011***
Nutritional status	Well nourished	74	1	1	1	
	MAM	42	1	1.7[0.10, 28.9]	0.16[0.05, 0.48]	0.81
	SAM	20	6	22.2[2, 195.1]	**13.2 [1.38, 126.3]**	**0.025***

Table 5. Factors associated with ATLI

Result of the multivariate analysis revealed that, the risk of ATLI was 93.9% lower in age group 5-15 years as compared to age group <1 year [AOR= 0.061; 95% CI: 0.007, 0.52].

The odds of ATLI was 13 times higher in severely malnourished patients as compared to those who were well nourished [AOR=13.2; 95% CI: 1.38, 126.3].

6. DISCUSSION

One hundred forty four cases were enrolled in this study, with data showing equal number of male and female patients being affected with ATLI, with no association between gender and the occurrence of ATLI, which is similar to other studies.[4, 5, 10, 13, 24]

The occurrence of ATLI in the current study was found to be 5.6 %, which is comparable with previous studies carried out in the United States (3.3%), Indonesia (7%), and Japan (8.1%).[4, 10, 12]

The frequency of ATLI in the current study is higher than a cross-sectional study done in Nigeria, with 6.5% children noted to have three-fold elevation of ALT after 2 mo of therapy with normalized levels in all children when rechecked after 3 months, with the study concluding ATLI to be uncommon in children. [6]

Our study's number is also higher than that of seen in India (2.3%) and China (1.84%).[14, 24] The variation seen may be due to, a relatively small sample size (n=62) used in the Nigerian study, and the inclusion of latent TB cases in the Indian study.

In contrast, the present study's figure is significantly lower than those seen in Pakistan (13.9%, 14%), India (15.2%) and Indonesia (27%).[5, 8, 9, 25] The higher magnitude seen in the Indonesian study was attributed to the limitation of study period used, which was the first two months of intensive phase of therapy. In addition, the probable cause considered for the first hepatotoxic event was, livers' initial adaptation.[5]

Possible cause for the disparity seen between our study and the Pakistanis and Indian case series may be due to the prospective nature of the studies and the method used for following patients, which was, a baseline test followed by serial scheduled monitoring of both liver enzymes and clinical symptoms, which was not applied in our study.

Although statistical significance could not be established, majority (7/8) of patients with ATLI in our study had extrapulmonary TB, which is similar to findings seen in Pakistan, Indonesia & Japan. [4, 10, 25]

Regarding the phase of therapy during the development of ATLI, 75% of our cases were on intensive phase of treatment, which is in agreement with various previous studies.[8, 9, 12, 16, 23, 24, 25]

Our analytical study found nutritional status to be significantly associated with ATLI, with severely malnourished patients having 13 times higher risk than those with normal nutritional status. This finding is consistent with studies from Gabon, Peru and Indonesia, who also reported SAM as a statistically significant factor increasing the risk of ATLI in children.[15, 22, 23] This could be attributed to the multiple pathophysiological changes in malnutrition that alter the pharmacokinetics of drugs contributing to drug toxicity.[26]

Another factor found to be associated with ATLI in our study was, age group 5-15 years. As compared to age group < 1 year, age group 5-15 years had significantly lower risk (93.9 %) of developing ATLI [AOR= 0.061; 95% CI: 0.007, 0.52]. This finding could be explained by changes seen in livers' drug metabolism with enzymes showing different stages for different development stage.[10]

7. CONCLUSION AND RECOMMENDATION

This study revealed that ATLI is common (5.6%) among children who received first-line anti-TB therapy at TASH, PIDC. Sex, anatomical site of TB and phase of anti-TB therapy were not associated with ATLI.

According to the findings of this study, the predominant factor with a negative impact was severe acute malnutrition, which showed a greater likelihood for the development of ATLI. The other factor which revealed a significantly lower risk for ATLI was age group 5-15 years as compared to age group < 1 year.

Based on the findings of this study we urge clinicians in care of pediatric patients to be aware of the commonness of the problem particularly in those with severe acute malnutrition, and propose close monitoring of these patients. We also suggest a national guideline for the diagnosis, management and monitoring of ATLI in pediatric patients.

Uniform and strict documentation of valuable information is also of great importance so as to limit the bias towards factors associated with ATLI. A wider scale study, with a prospective nature is also needed to investigate other risk factors further.

8. Limitations and strengths of the study

Strengths

Assessment on the prevalence and associated factors of ATLI among children seen in TASH is conducted in a setting were pediatric infectious disease specialists are available and is the an initial study to be done in our setup.

Findings are informative and can aid as a pioneer for further studies on the area of interest.

Limitations

Its retrospective nature with the collection of data through chart review may affect its quality. Additionally, as a single-center study, representation of a wider population could be limited.

Use of different laboratories for determination of liver function tests could affect results and subsequently lead to misinterpretation.

Sample size could not be attained due to some cards being incomplete and patients being lost to followup.

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10. ANNEX: Data Collecting Questionnaire

Title: Prevalence and associated risk factors of anti-TB induced liver injury among children seen at Tikur Anbessa Specialized Hospital

Code number _____ Date ____/___/___ MRN _____

Section I: Socio-demographic data

1. **Age____** months / years
2. **Sex:** A. Male B. Female

Section II: Clinical data

1.Method of TB diagnosis:

A. AFB smear microscopy

B. Rapid molecular tests

i. Xpert® MTB/ RIF assay

ii. Line-probe assays (LPAs) (GenoType® MTBDRplus and GenoType® MTBDRsl)

iii. Lateral flow lipoarabinomannan assay (LF-LAM)

iv. Loop-mediated isothermal amplification (TB-LAMP)

C. Histo-Pathologic

D. Radiologic

E. Clinical

F. TB culture

2. Anatomical site of TB disease

A. Pulmonary tuberculosis (PTB)

B. Extra-pulmonary tuberculosis (EPTB), Specify _____

3. Nutritional status

A. Normal **B.** Moderate acute malnutrition **C.** Severe acute malnutrition

4. Use of any hepatotoxic comedications

A. No **B.**Yes, if yes specify _____

5. Was ATLI present

A. No **B.**Yes

6. Duration of therapy during developing ATLI____ days

7.Were symptoms of hepatitis present

A. No

B. Yes, if yes:

a. nausea b.vomiting c. icteric sclera

d. tea-colored urine e. pale stool f. diminished appetite

8. Peak LFTs

A. Elevated ALT

i. ≥3-4 times the ULN

ii. ≥5 times the ULN

B. Elevated AST

i. ≥3-4 times the ULN

ii. ≥5 times the ULN

C. Total bilirubin >2mg/dl

9. Treatment intervention after development of ATLI

A. All drugs were withdrawn

B. One drug was withdrawn

C. Two drugs were withdrawn

D. Three drugs were withdrawn

E. No alteration