Journal of Pharmaceutical Research International

33(21A): 50-65, 2021; Article no.JPRI.67009
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Toxicological Effects of Antituberculosic Chemotherapy in Adults: An Integrative Literature Review

Viviane Ferraz Ferreira de Aguiar[1], Dayara de Nazaré Rosa de Carvalho[2*], Dandara de Fátima Ribeiro Bendelaque[1], Lorena Nayara Alves Neves[3], Celice Ruanda Oliveira Sobrinho[3], Paula Sousa da Silva Rocha[1], Rafael Everton Assunção Ribeiro da Costa[4], Cidianna Emanuelly Melo do Nascimento[5], Susi dos Santos Barreto de Souza[1], Marcela Raissa Asevedo Dergan[2], Mioni Thieli Figueiredo Magalhães Brito[1] and Juarez Antônio Simões Quaresma[1]

[1] Federal University of Pará (UFPA), Belém, Pará, Brazil.
[2] State University of Pará (UEPA), Belém, Pará, Brazil.
[3] Metropolitan University Center of the Amazon (UNIFAMAZ), Belém, Pará, Brazil.
[4] University State of Piauí (UESPI), Teresina, Piauí, Brazil.
[5] University State of Ceará (UECE), Fortaleza, Ceará, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. The authors DFRB, LNAN, CROS, PSSR, REARC, CEMN, SSBS, MRAD contributed with the literature searches and wrote the first draft of the manuscript. Authors VFFA, DNRS, MTFMB and JASQ edited and finalized the manuscript. All authors read and approved the final manuscript

Article Information

DOI: 10.9734/JPRI/2021/v33i21A31368
Editor(s):
(1) Dr. Juan Carlos Troiano, University of Buenos Aires, Argentina.
Reviewers:
(1) Vladislav V. Fomenko, NIOCh SB RAS, Russia.
(2) Jorge Cervantes, TTUHSC, U.S.A.
Complete Peer review History: http://www.sdiarticle4.com/review-history/67009

Review Article

Received 22 January 2021
Accepted 27 March 2021
Published 07 April 2021

ABSTRACT

Objective: To analyze the toxicological effects of anti-tuberculosis chemotherapy in adults in national and international literature in the period from 2015 to 2020.

**Corresponding author: E-mail: dayara_twain@hotmail.com;*

Methodology: It is a qualitative descriptive research, of the type Integrative Literature Review (ILR). In the VHL databases PubMed / Medline, Arca, Web of Science, Microsoft Academic and Cochrane Library. Data analysis was performed with the aid of the IRaMuTeQ software.
Results: 36 articles were found in which the following categories were created: 1) Association of hepatotoxicity and appearance of liver damage; 2) The incidence of adverse events related to antituberculin therapy; 3) Risk factors of regular consumption of antituberculins; 4) Intensive renal treatment for patients with nephrotoxicity.
Conclusion: in our review we identified that the elderly, HIV positive and alcohol users are more likely to have toxicological effects during treatment, which can lead to a possible abandonment of treatment.

Keywords: Toxicity; antitubercular agents; drug therapy; adult.

1. INTRODUCTION

Tuberculosis (TB) is an infectious and contagious disease caused by Mycobacterium tuberculosis (MT), considered a public health problem due to its high incidence and prevalence, in addition to affecting more frequently populations that present low economic level, social inequality, malnutrition, alcoholism, smoking, pathologies and other conditions that reduce the immune capacity [1].

The treatment of TB, consisting of isoniazid, rifampicin, ethambutol and pyrazinamide, has great efficacy when associated with the correct doses and use for a sufficient time, aiming to avoid bacterial persistence, the development of drug resistance, ensuring the patient's cure [2]. However, it can cause undesirable side effects, either by the active ingredient itself or by its metabolites, such as the occurrence of toxicity in the patient [3].

Toxicological effects are the most recurrent adverse reactions associated with anti-TBs, which can lead to interruptions in treatment with resulting poor outcomes, including the risk of drug resistance. There are risk factors for the onset of these effects, such as patients with liver abnormalities, such as the chronic hepatitis B virus and the hepatitis C virus (HCV), disseminated tuberculosis, Asian ethnicity, female sex, significant use of alcohol, administration simultaneous use of other hepatotoxic drugs, being elderly and malnourished [4].

Side effects, especially the most serious ones, are related to a higher rate of treatment abandonment, resulting in longer therapy time and a greater number of hospitalizations and outpatient and home visits. In addition, changes in the therapeutic regimen resulting from these adverse effects lead to the inclusion of one or more less potent and more toxic drugs, an increased risk of treatment failure, recurrence of the disease and an increase in the duration of treatment [2].

Given the above, the present study aimed to analyze the toxicological effects of anti-tuberculosis chemotherapy in adults in national and international literature in the period from 2015 to 2020.

2. METHODOLOGY

This is a descriptive, qualitative research, such as Integrative Literature Review (ILR). The ILR is a research method that aims to conduct a comprehensive and systematic analysis of the literature. Thus, the ILR must be carried out in six stages, namely: 1) identification of the theme and selection of the research question; 2) delimitation of the eligibility criteria and identification of studies in the main banks and databases; 3) evaluation of the chosen studies and critical analysis; 4) categorization of the study; 5) evaluation and description of the results and 6) presentation of the results in an integrative review structure [5]. From the object of study, the following guiding question was developed: What are the toxicological effects of anti-tuberculosis chemotherapy in adults in national and international scientific research?

The collection of scientific material was carried out through online access in the following databases: VHL Regional Portal, PubMed / Medline (National Library of Medicine and National Institutes of Health / Medical Literature Analyzes Sand Retrieval System Online), Ark, Web of Science, Microsoft Academic Library and Cochrane. In order to improve, refine and guarantee the direction of all works relevant to the search for the theme, the choice of articles occurred from the combination of four descriptors

DeCS/MeSH (Health Sciences Descriptors), respectively: "Toxicity"; "Antituberculosis", "Adult" and "Chemotherapy" mediated by the Boolean operator "AND", in order to add restrictions to the number of studies.

The inclusion criteria determined for the selection of documents were: scientific articles published in the period from 2015 to 2020, free full text in Portuguese or English, and which address the topic of study. Studies outside the defined period, editorials, letters to the editor, incomplete articles, paid articles, reflective studies and those that did not address the theme suggested by the authors were excluded.

The articles were categorized based on the level of evidence by type of study, but levels 8 and 9 were not included in this study. The levels of evidence are divided into nine levels according to the type of study. At level 1, the evidence is named for systematic reviews; level 2, evidence from a randomized clinical trial; level 3, evidence obtained from a cohort study; level 4, evidence from case-control studies; level 5, evidence derived from cross-sectional study; level 6, evidence derived from case series research; level 7, evidence from a case report being an opinion and / or report; level 8, evidence from animal research and level 9 are evidence based on laboratory research [6].

After the critical analysis and the grouping of the selected studies, the articles were analyzed using the IRaMuTeQ software (Interface of R pour les Analyzes Multidimensionnelles de Textes et de Questionnaires), as it provides a more complex analysis of the articles researched by the author, having class formation according to the repetition of the words in the text. In addition, it is a tool that allows multiple forms of statistical analysis on the textual corpus and or the word tables in which this analysis is \anchored in software R. This program was developed in France by Pierre Ratinaud [7].

For the analysis of the data obtained through the IRaMuTeQ software, the text corpus was developed through the results and conclusion of the selected articles. Thus, we opted for the Descending Hierarchical Classification (DHC) method, which has the purpose of obtaining the formation of classes of text segments in different colors and may be with words similar to each other and also distinct from the segments of other textual classes [8].

At the end of the data collection, a total of 1105 articles were obtained in the referred databases. After this phase, the articles underwent an evaluation regarding the title and abstract, and of this total, 308 were excluded from the screening process. The assessment during this phase had the purpose of discarding articles that did not meet the eligibility criteria. At the end of the screening process, the final sample emerged from the reading of the full text composed of 36 articles that were evaluated regarding the title of the article, country, authors, year of publication and database, types of study, level of evidence, objective and synthesis of the results and those that answered the research question. The selection process for the selected articles is shown in the search flowchart below Fig. 1.

3. RESULTS AND DISCUSSION

At the end of this stage, the final sample emerged, consisting of 36 studies, which met the established criteria, as shown in the following table Table 1.

Based on the end of the sample, the analysis was performed using IRaMuTeQ software. The content analysis was done through the Descending Hierarchical Classification (DHC), which has the formation of classes, divided and identified, by colors and percentages. Class 1 (Red) corresponds to 35.34% of the words in the corpus, class 2 (Green) corresponds to 20.3% of the words, Class 3 (blue) corresponds to 20.3% of the word association in the corpus and class 4 (Purple) corresponds to 24.6% of the word association in the corpus.

Through the formation of the classes through the CHD, the IRaMuTeQ software provided information that would provide subsidies to build the filogram from the dendogram of the classes obtained from the text corpus. For the construction of the filogram, the words that obtained a frequency equal to or higher than the registered average were used, with the frequency (f) and the chi-square (x^2) of the most repeated words being placed, being organized into classes by the most significant words. After analyzing the identification of textual domains and interpretation, we sought to name their respective meanings in the classes described below: 1) Association between hepatotoxicity and the appearance of liver damage; 2) The incidence of adverse events related to antituberculin therapy; 3) Risk factors of regular consumption of antituberculins; 4) Intensive renal

treatment for patients with nephrotoxicity. The class filogram is shown below Fig. 2.

4. DISCUSSION

4.1 Class 1- Association of Hepatotoxicity and Appearance of Liver Disease

From the results, it was analyzed that the assessment of the risk of occurrence of hepatotoxicity in patients undergoing TB treatment becomes necessary, given the effects of the drugs used in anti-tuberculosis chemotherapy. Hepatotoxicity induced by antituberculosis drugs (ATDH) is one of the main complications resulting from antituberculin therapy with an incidence of 2% to 28%, being responsible for the increase in substantial morbidity and mortality and decrease in the effectiveness of the treatment due to its interruption. It may have different factors that contribute to its development, such as old age, female gender, malnutrition, HIVinfection and pre-existing liver disease [9,10].

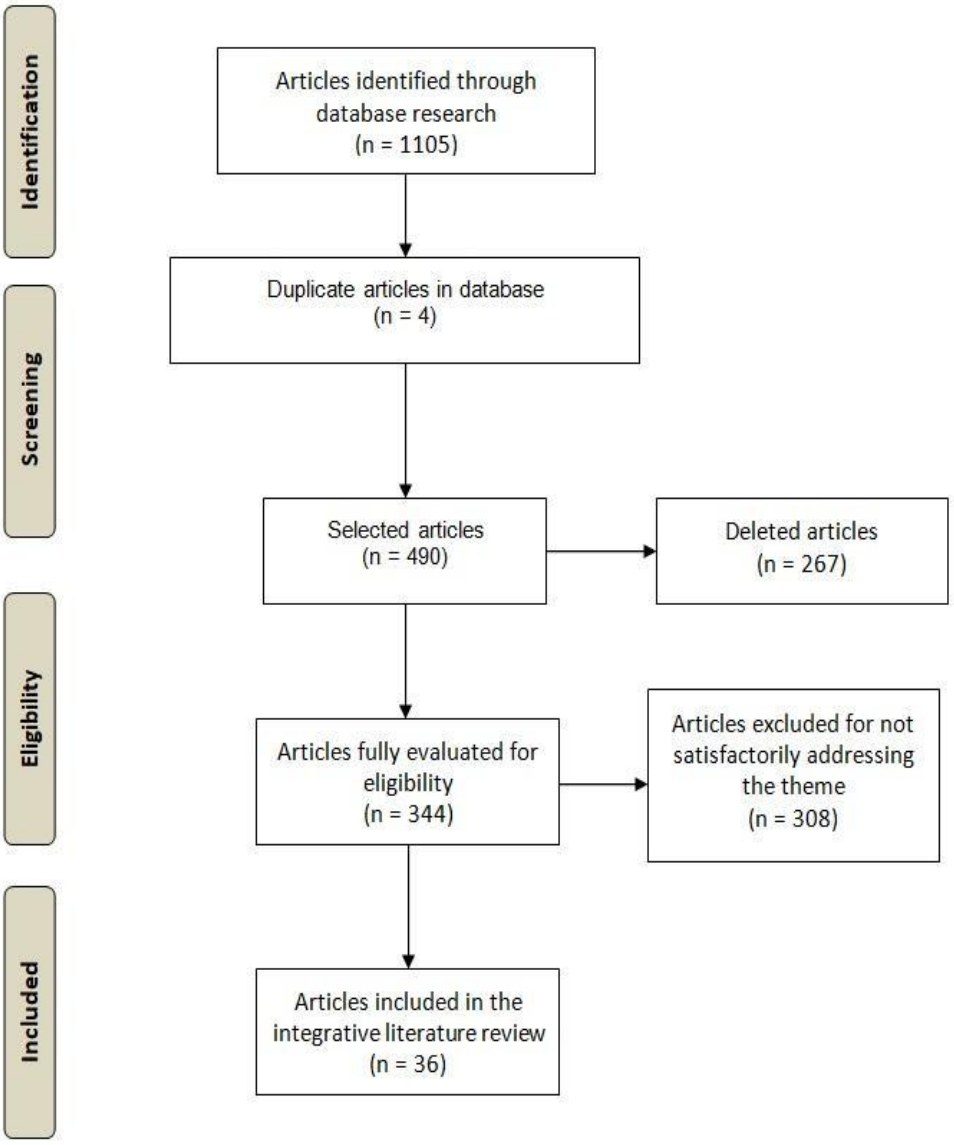

Fig. 1. Flowchart of search and selection of documents, Prisma (2009)
Source: Research authors, 2020

Table 1. The final sample emerged, consisting of 36 studies, which met the established criteria

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
Sequential analysis as a tool in detection of amikacin ototoxicity in treatment of multidrug-resistant tuberculosis. Brazil	Vasconcelos KA, Fleet SMMC, Netto AR, Kritski AL. 2018. [11] VHL.	Prospective cohort study. Level 3	Verify the early detection of ototoxicity caused by the use of amikacin in a population treated for multidrug-resistant tuberculosis (MDR-TB) by performing of three tests.	Changes in auditory thresholds were verified compatible with ototoxicity after two months of treatment through AAF and after six months of treatment through the ATL. However, these changes were not verified through the DPOAE search.
First line anti-tuberculosis induced hepatotoxicity: incidence and risk Factors. Africa	Bouazzi OE, Hammi S, Bourkadi JE, Tebaa A, Tanani DS, Bencheikh RS et al. 2016 [12] VHL	Retrospectivecohortstudy Level 3	Identify specific ATDH risk factors in the morocco population and assess the association between baseline plasma levels and the development of ATDH.	It was found that the incidence of hepatotoxicity is extremely high. And factors may be associated with the development of HDHD, such as genetic factors, combined forms of treatment and peak plasma levels.
Early monitoring for detection of antituberculous drug-induced hepatotoxicity. Korea	Lee CM, Lee SS, Lee JM, Cho HC, Kim WS, Kim HJ et al. 2016 [13] VHL	Retrospective cohort study Level 3	Investigate the time of onset of hepatotoxicity induced by antituberculosis drugs (ADIH) and related characteristics	It was observed among 108 patients who developed ADIH, 73 patients developed hepatotoxicity in 30 days
Might isoniazid plasma exposure be a valuable predictor of drug-related hepatotoxicity risk among adult patients with TB ? Italy	Cojutti P, Duranti S, Isola M, Baraldo M, Viale P, Bassett M et al. 2016 [14] VHL	Retrospective observational study Level 3	To investigate the relationship between isoniazid plasma exposure and the likelihood of ALT elevation among adult TB patients	The use of a logistic regression model estimated a probability of developing hepatotoxicity of 0.5 and 0.9 when in the presence of an AUC isoniazid
Drug-induced Hepatotoxicity of Anti-tuberculosis Drugs and Their Serum Levels. Korea	Jeong I, Park JS, Cho YJ, Yoon HL, Song J, Lee CT et al. 2015 VHL [15].	Retrospective cohort study. Level 3	To investigate whether anti-TB IHL is associated with baseline serum levels of the drug.	It was observed that 17 of the 195 patients had hepatotoxicity. Among the 17 patients with hepatotoxicity, 12 had anti-TB IHL. 10 patients had PZA-related hepatotoxicity and 2 had INH or RMP-related hepatotoxicity.
Ursodeoxycholic Acid Attenuates Hepatotoxicity of Multidrug Treatment of Mycobacterial Infections: A Prospective Pilot Study. Germany.	Lang SM, Ortmann J, Rostig S, Schiffl H. 2020. [16] VHL	Prospective cohort study. Level 3	To evaluate the hepatoprotective efficacy of oral ursodeoxycholic acid (UDCA) (250-500 mg TID) administered to	As a result, twenty-one of 27 patients showed normalization of elevated enzymes (alanine transferase and aspartate aminotransferase), alkaline phosphatase and bilirubin while continuing to treat TB and 5 patients demonstrated a significant reduction in liver enzymes.

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
			patients infected with TB or not with mycobacteria (NTM) with drug-induced hepatotoxicity and ongoing therapy.	No changes were observed in 1 patient.
A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. Asia	Luangchosiri C, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. 2015. [17] VHL	Randomized clinical study. Level 2	To evaluate the effectiveness of silymarin in preventing liver damage induced by antituberculosis drugs (antiTB-DILI) in patients with tuberculosis.	There were 1/27 (3.7%) and 9/28 (32.1%) of the patients who developed antiTB-DILI in the silymarin and placebo groups. That is, receiving silymarin had a 28% lower risk of antiTB-DILI than placebo.
Serious hepatotoxicity following use of isoniazid preventive therapy in HIV patients in Eritrea. East Africa	Russom M, Debesai M, ZeregabrM, BerhaneA, Tekeste T, TeklesenbetT. 2018. [18] VHL.	Retrospective descriptive study. Level 3	Evaluate the causal association of IPT and hepatotoxicity and identify possible risk factors in patients on highly active antiretroviral therapy (HAART)	In the period from June 2014 to June 2016, a total of 60 cases of hepatotoxicity were spontaneously reported to the Eritrean Pharmacovigilance Center, 31 of which were related to IPT in patients on HAART.
Genetic polymorphisms of N-acetyltransferase 2 & susceptibility to antituberculosis drug-induced hepatotoxicity. India	Sharma SK, Jha BK, Sharma A, Sreenivas V, Upadhyay V, JaisinghaniC et al. 2016 [19] VHL	Prospective cohort study. Level 3	To investigate the role of the NAT2 gene polymorphism in hepatotoxicity induced by anti-tuberculosis drugs (IHL).	The frequency of the slow acetylator genotype was commonly found and was not significantly different between patients with IDH (82.8%) and non-IDH (77.2%).
Nephrotoxicity and ototoxic symptoms of injectable second-line anti-tubercular drugs among patients treated for MDR-TB in Ethiopia: a retrospective cohort study. Africa	Shibeshi W, Sheth AN, Admasu A, Berha AB, Negash Z, Yimer G. 2019. [20] VHL	Retrospective cohort study. Level 3	To evaluate the prevalence, the management of nephrotoxicity and ototoxic symptoms and the results of the treatment of patients treated for MDR-TB with regimens based on injectables.	Based on clinical criteria, nephrotoxicity was detected in 62 (6.7%) and ototoxic symptoms in 42 (4.8%) participants.
The clinical impact of drug-induced hepatotoxicity on anti-tuberculosis therapy: a case control study. Korea	Song JH, Yoon SY, Park TY, Heo EY, Kim DK, Chung HS et al. 2019. [9] VHL	Retrospective cohort study. Level 3	Explore whether the development of IHL during TB treatment could affect the clinical	The relationship between treatment interruption time and total treatment duration and the proportion of hepatotonic users was significantly higher among patients with IDH

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
			course and results of TB.	
Characterization of 0Isoniazid-Specific T-Cell Clones in Patients with anti-Tuberculosis Drug-Related Liver and Skin Injury	Usui T, Meng X, Saide K, Farrell J, Thomson P, Whitaker P et al. 2016 [21] VHL	Retrospective cohort study. Level 3	Determine whether drug-specific T cells are detectable in patients with adverse reactions and, if so, characterize the nature of the T cell response	Transformation of positive lymphocytes and / or ELIspot were observed with all 6 patients. More than 3,400 T cell clones have been generated from isoniazid, rifampicin, pyrazinamide or PBMC treated with ethambutol. The CD4þ clones of all 3 patients were activated to proliferate and secrete cytotoxic mediators.
Association of adverse drug reaction to anti-tuberculosis medication with quality of life in patients in a tertiary referral hospital. Brazil	Valadares RMC, Carvalho WS, Miranda SS. 2020. [22] VHL	Cross-sectional study. Level 5	To evaluate anti-TB ADRs in patients admitted to a tertiary referral hospital in Belo Horizonte, Minas Gerais (MG) and to analyze their association with QOL.	All patients reported the presence of adverse reactions to medications, 71.6% of which are minor and 28.3% major and minor. The analysis of the global quality of life showed that patients with tuberculosis have a good average (67.3%).
Gender-Dimorphic Impact of PXR Genotype and Haplotype on Hepatotoxicity During Antituberculosis Treatment. China	Wang JY, Tsai CH, Lee YL, Lee LN, Hsu CL, Chang HC et al. 2015. [23] VHL	Prospective cohort study. Level 3	Evaluating certain genotypes and haplotypes in SNPs in the PXR regulatory region may be risk factors for HATT, and the distribution of these genotypes and haplotypes.	First study showing that 2 SNP PXR genotypes and 2 haplotypes influenced the risk of HATT only in women. Variants of the PXR gene have a sexual dimorphic impact that contributes to the increased risk of drug-induced HATT in women.
Correlation of CpG Island Methylation of the Cytochrome P450 2E1 / 2D6 Genes with Liver Injury Induced by Anti-Tuberculosis Drugs: A Nested Case-Control Study. China.	Zhang J. Zhu X, Li Y, Zhu L, LI S, Zheng G et al. 2016. [24]. VHL	Case control study. Level 4	To investigate the relationship between the hypermethylation of the CpG island of the CYP2E1 and CYP2D6 genes in the plasma cell-free DNA of patients with TB (under standard anti-TB therapy) and patients with ADLI.	In 114 pairs of cases, the CpG island methylation levels of the CYP2E1 and CYP2D6 genes in the plasma cell-free DNA were significantly correlated with the occurrence of anti-TB drug-induced liver injury (ADLI), with odds ratio (OR) values 2,429 and 3,500, respectively ($p < 0.01$)
N -acetyltransferase 2 (NAT2) gene polymorphism as a predisposing factor for phenytoin intoxication in tuberculous meningitis or tuberculoma patients having	Adole PS, KharbandaPS, Sharma S. 2016. [25] PubMed	Retrospective cohort study Level 3	To evaluate the effect of allelic variants of the N-acetyltransferase 2 (NAT2) gene as a predisposing factor for	Genotypic analysis showed that of the seven SNPs (single nucleotide polymorphisms) of the NAT2 gene studied, six mutations were found associated with phenytoin poisoning.

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
seizures - A pilot study. India			phenytoin toxicity in patients with TBM or tuberculoma with seizures and in simultaneous use of INH and phenytoin.	
Reduced Chance of Hearing Loss Associated with Therapeutic Drug Monitoring of Aminoglycosides in the Treatment of Multidrug-Resistant Tuberculosis. Netherlands	Altena RV, DijkstraALREADY, Meer MEVD, Howard JFB, Kosterink JGW, Soolingen DV et al. 2017. [26] PubMed	Retrospective cohort study. Level 3	Retrospectively evaluate the medical records of patients with tuberculosis (TB) treated with amikacin or kanamycin from 2000 to 2012.	The extent of hearing loss was limited and correlated with the cumulative dose of the drug per kg of body weight during daily administration.
Association and clinical utility of NAT2 in the prediction of isoniazid-induced liver injury in Singaporean patients	Chan SL, Chua APG, Aminkeng F, Chee CBE, Jin S, Loh M et al. 2017. [27] PubMed	Case-control study. Level 4	To assess the association between selected candidate SNPs and the risk of INH-DILI and to assess the clinical validity of associated variants in a population of Singapore.	Logistic regression was used to test the association between candidate SNPs and INH-DILI. The status of the NAT2 acetylator was inferred from the genotypes and tested for association with INH-DILI.
Antituberculosis drugs and hepatotoxicity among hospitalized patients in Jos, Nigeria	Isa SE, Ebonyi AO, Shehu NY, Idoko P, Anejo-okopiJA, Simji G et al. 2020. PubMed.	Retrospective cohort study. Level 3	To determine the incidence and clinical characteristics of hepatotoxicity in hospitalized patients receiving first-line anti-TB treatment.	Twenty patients developed symptomatic hepatotoxicity, with an incidence of 18.2%. In addition, 18 (16.4%) patients had hepatotoxicity according to the American Thoracic Society criteria.
Methionine and vitamin B-complex ameliorate antitubercular drugs-induced toxicity in exposed patients. Nigeria	Amagon KI, AwodeleO, Akindele AJ. 2017. [28] PubMed.	Prospective cohort studyLevel 3	To evaluate the modulating effect of co-administration of methionine and vitamin B complex on toxicity induced by antitubercular drugs in patients with tuberculosis	Hepatotoxicity was significantly higher, associated with the occurrence of adverse drug reactions. The hepatic, renal, hematological indices of antioxidants modulated by the vitamin B and methionine complex and adverse effects in patients administered antitubercular drugs
Longitudinal evaluation of visual function and structure for detection of subclinical Ethambutol-induced	Jin KW, Lee JY, Rhiu S, Choi DG. 2019. [29] PubMed.	Retrospective cohort study. Level 3.	Longitudinally evaluate the visual function and structure of patients	Subclinical toxicity was found in 22 eyes of 14 patients (that is, 13% of 168 eyes), in the forms of decreased VFI (VF index, 9 eyes of 6 patients), increased

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
optic neuropathy. Korea			taking ethambutol by various modalities and identify useful tests for detecting optical toxicity induced by subclinical ethambutol	thickness of RNFL in the quadrant (5 eyes of 4 patients) and FV pattern defect (12 eyes of 6 patients). The risk factors for the occurrence of subclinical toxicity were age, cumulative dose and duration of medication.
The use of optical coherence tomography for the detection of ocular toxicity by ethambutol. Europe	Taffner BMP, Mattos FB, Cunha MC, Saraiva FP. 2018 [30] PubMed.	Case control study. Level 4	Evaluate, by means of (OCT), changes in retinal thickness, secondary to the use of ethambutol in the treatment of patients with tuberculosis	A significant reduction in retinal thickness was observed in both groups at two months of treatment, and the percentage delta was greater in those patients who presented reduced visual acuity and / or changes in the Ishihara test.
Toxicity associated with tuberculosis chemotherapy in the REMoxTB study. England.	Tweed CD, Crook AM, Amukoye EI, Dawson R, Diacon AH, Hanekom M et al. 2018. Pub Med [31]	Double-early randomized study. Level 2.	Accurately characterize the patients at greatest risk, the incidence and the nature of toxicity related to standard therapy for TB.	The most common adverse events in standard therapy are related to hepatobiliary, musculoskeletal and metabolic disorders.
Anti-TB drug concentrations and drug-associated toxicities among TB / HIV-coinfected patients. East Africa.	Wiltshire CS, Braun AV, Scherrer AU, Manabe YC, Buzibye A, Muller D et al. 2017. [32] PubMed	Randomized clinical study. Level 2.	Determine the association between concentrations of anti-TB drugs and the occurrence of hepatotoxicity and peripheral neuropathy in co-infected TB / HIV patients	There was no association between rifampin concentrations and hepatotoxicity or concentrations of isoniazid and peripheral neuropathy in patients co-infected with TB / HIV.
Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis United States.	Song T, Lee M, Jeon HS, Park Y, Dodd LE, Dartois V et al. 2015. [9]	Randomized clinical study. Level 2.	Describe the adverse events associated with mitochondrial toxicity	The risk of mitochondrial toxicity increased with increasing concentrations of the linezolid valley, with all patients with a medium linezolid valley> 2 µg / ml developing an AE related to mitochondrial toxicity, either at 300 mg or 600 mg.
Rates and risk factors for nephrotoxicity and ototoxicity among tuberculosis patients in Tbilisi, Georgia	Buziashvili M, MirtskhulaVA V, Kipiani M, Blumberg HM, BaliashviliD, Magee MJ et al. Web of Science. 2019.	Retrospective cohort study. Level 3.	Assess prevalence and risk, factors for ADRs among patients with MDR-TB and widely drug-resistant	Eighty (54%) and 38 (26%) of 147 patients developed nephrotoxicity, and ototoxicity, respectively. Twenty five (17%) patients required permanent injection interruption enabled due to RAM.

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
			tuberculosis (XDR-TB).	
Hepatotoxicity from antituberculous therapy in the elderly: A systematic review. United States.	Hosford JD, Fricken MEV, LauzardoM, Chang M, Dai Y, Lyon JA et al. Web of Science. 2015.	Systematic Review Study. Level 2	Determine whether advanced age is a risk factor for hepatoxicity resulting from treatment with first-line drugs used to treat active and latent TB patients.	Our analysis revealed that patients over 60 years of age have a higher risk of developing hepatotoxicity. Studies suggest that a milder regime for this population can benefit and minimize risks to public health.
Risk assessment of hepatotoxicity among tuberculosis and human immunodeficiency virus / AIDS-coinfected patients under tuberculosis treatment. Cameroon.	Ngouleun W, Nya PCB, Pieme AC, Telefo PB. Web of Science. 2016. [33]	Prospective and retrospective cohort study. Level 3	Assess the risk factors for hepatotoxicity associated with anti-TB drugs.	The results showed that the status of the human immunodeficiency virus and alcohol consumption constitutes an aggravating factor for the occurrence of liver toxicity. In addition, the consumption of antioxidant foods simultaneously with TB medications helps to reduce the hepatotoxic effects of these drugs.
Hepatotoxicity during Treatment for Tuberculosis in People Living with HIV / AIDS. Brazil.	Mariz CA, Lopes EP, Santos BA, Maruza M, Montarroyos UR, Ximenes RAA, Lacerda HR et al. 2016. [34] Web of Science.	Prospective cohort studyLevel 3.	Determine the incidence of hepatotoxicity and identify predictive factors for the development of hepatotoxicity after people living with HIV / AIDS initiate treatment for tuberculosis.	The incidence of hepatotoxicity during treatment for tuberculosis in PLWHA was high. Those classified as phenotypically slow and malnourished acetylators should be directed to specific care to reduce the risk of hepatotoxicity during the treatment of tuberculosis. The use of fluconazole should be avoided during the treatment of tuberculosis in PLWHA.
Anti-TB drug concentrations and drug-associated toxicities among TB / HIV-coinfected patients. Uganda.	Wiltshire CS, Braun AV, Scherrer AU, ManabeYC, Buzibye A, Muller D et al. 2017. [32] Web of Science.	Prospective observational studyLevel 3.	Determine the association between anti-TB drug concentrations and the occurrence of hepatitis toxicity and peripheral neuropathy among patients co-infected with TB / HIV.	There was no association between rifampicin concentrations and hepatotoxicity or isoniazid concentrations and peripheral neuropathy among patients co-infected with TB / HIV.
First-line anti-tuberculosis drugs induce hepatotoxicity: A novel mechanism based on a urinary metabolomics platform. China.	Jun CAO, Yijun MI, Cuilin SHI, YicongBIAN, Chenrong HUANG, ZhijianYE et al. 2017. Web of Science.	Retrospective descriptive study. Level 3.	This study aimed to investigate the related mechanisms of liver damage in TB patients induced by tuberculostatic co-therapy based on the urine metabolomics platform	These results highlight that the generation of superoxide can aggravate the hepatotoxic effects of the HRZE regime. In addition, our metabolomics approach has the ability to predict hepatotoxicity for clinical applications.

Title of the article Country	Authors Year and Database	Type of Study and Level of Evidence	Objective	Condensation of results
A Case Series of Acute Kidney Injury During Anti-tuberculosis Treatment. Japan.	Sakashita K, Murata K,Takahashi Y, Yamamoto M, Oohashi K, Sato Y. 2019. [35] Web of science.	Retrospective descriptive study. Level 3.	Identify the incidence of Acute Kidney Injury (AKI) and the results of our management of AKI induced by anti-TB drugs in a single TB treatment center in the past 10 years.	Rifampicin is the main cause of AKI. Levofloxacin can be an alternative to rifampicin thanks to its safety and potency. Restarting anti-TB treatment without rifampin and steroid administration in the short term may be a viable management for AKI.
The impact of adverse events on healthrelated quality of life among patients receiving treatment for drug-resistant tuberculosis in Johannesburg, South Africa.	Sineke T, Evans D, SchnippelK, AswegenHV, Berhanu R, Musakwa N et al. 2019. [36] Web of Science.	Cross-sectional study. Level 5.	Describes the HRQoL of patients with TB-DR in Johannesburg, South Africa, stratified by self-reported AEs in the past 4 weeks.	The results show that drug-resistant tuberculosis (DR-TB) had a substantial impact on patients' quality of life, more than adverse events (AEs) during the first few months of treatment may be responsible for further reducing the health-related quality of life (HRQoL). Our findings highlight the negative effects of injectable agents on HRQoL.
Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases. Africa.	Jones J, Mudaly V, Voget J, Naledi T, MaartensG, Cohen K. 2019. [37] Web of Science.	Cohort study. Level 3	Describe adverse drug reactions (ADRs) in patients undergoing bedaquiline-containing tuberculosis who have been reported to the Western Cape Pharmacovigilance program.	The confirmed ADRs in patients receiving bedaquiline reflect the known safety profile of bedaquiline. Quantifying the incidence and clinical consequences of severe QT prolongation in patients receiving bedaquiline-containing regimens is a research priority to inform recommendations for patient monitoring during treatment programs for drug-resistant tuberculosis
Toxicity related to standard TB therapy for pulmonary tuberculosis and treatment outcomes in the REMoxTB study according to HIV status. UK.	Tweed CD, Crook AM, Dawson R, Diacon AH, Mchugh TD, Mendel CM et al. 2019. Web of Science	Cohort study. Level 3	Investigate the incidence of adverse events and cure rates according to HIV status for patients receiving standard TB therapy in the study	HIV-positive patients receiving standard TB therapy in the REMoxTB study were at a higher risk of adverse events during treatment, but cure rates were similar when compared to a compatible sample of HIV-negative patients.
Risk factors for acute liver failure among inpatients with anti-tuberculosis drug-induced liver injury. China.	Wang S, Shangguan Y, Ding C, Li P, Ji Z, Shao J. 2019. Web of Science	Retrospective cohort study. Level 3.	Analyze the clinical and laboratory characteristics and determine the predictors of Acute Hepatic Insufficiency (IHA) in hospitalized patients with induced liver injury (LHI) by antituberculosis drugs (TB).	The results of this study suggest that approximately half of all drug-induced liver injury cases occur within the first month, while 60% of (IHA) cases occur within 2 months. Elevated total bilirubin, aspartate aminotransferase, leukocyte count, pre-existing hepatitis and low platelet count are independent risk factors for the development of anti-TB drug-induced IHA.

It was analyzed that advanced age as a risk factor for hepatoxicity and found that patients over 60 years old had a prevalence in these cases, due to physiological changes and increased risk of drug toxicity [23]. In turn, it was assessed that the risk of hepatotoxicity in HIV-coinfected patients, concluding that advanced age (over 45 years), HIV / AIDS status and regular alcohol consumption were identified as factors that aggravate the occurrence of hepatotoxicity when taking TB medications [33].

The study showed that the decrease in the immune status of patients with HIV may be related to the increased risk of liver toxicity, indicating an acceleration of liver enzymes and progression to cirrhosis in coinfected patients compared to controls. In addition, these patients have a constant state of malnutrition, due to the depletion of glutathione reserves, making them vulnerable to oxidation and, therefore, to oxidative stress that is a mediator of hepatotoxicity [12].

4.2 Class 2- The Incidence of Adverse Events Related to Antituberculin Therapy

In the case of drugs most associated with hepatotoxicity [21], it was observed that Pyrazinamide has a well-recognized toxicity profile. The occurrence of hepatotoxicity and arthralgia are among the most common events and these are often reported to have side effects. The study by [34] showed the association of Isoniazid with the risk of occurrence of hepatotoxicity, leading to treatment interruption in 26 of the 60 cases, in addition to a decrease in efficacy in the others.

When assessing the incidence of hepatotoxicity in patients undergoing TB treatment, the literature shows a steady growth in which it is identified that the incidence of drug-induced hepatotoxicity (HDHD) in patients on antituberculosis therapy, with 24.6% of the patients having toxicity, being associated with the combined form of anti-TB drugs, genetic factors and peak plasma levels [12]. In turn, it was found in the study that among 108 patients who developed HDDH, 73 patients (67.5%) had hepatotoxicity within 30 days, emphasizing that monitoring of liver function during the first week in patients with extrapulmonary tuberculosis and function abnormal liver disease at baseline may be useful for very early detection of HDHD and better prognosis [13].

It is also observed that the incidence of symptomatic hepatotoxicity can vary from 15% to 18% in hospitalized patients, resulting in the prolongation of the individual and decrease in the effectiveness of the treatment, increasing the risk of being affected by morbidities and mortality rates [26].

4.3 Class 3- Risk Factors of Regular Consumption of Antituberculins

It appears that the success rate of TB treatment in patients with hepatotoxicity is lower compared to the group that does not have hepatotoxicity. The difference seems to be attributed to a higher mortality rate from all causes in the group, as it presents the largest number of elderly patients and / or with comorbidities, which may have negatively impacted treatment outcomes and mortality [9,38].

Early detection of the risk of hepatotoxicity in patients undergoing TB treatment is clinically important for several reasons, especially its association with decreased mortality and severe hepatotoxicity. In addition, early detection can allow for a shorter recovery time, from occurrence to normalization of AST, ALT and bilirubin, as the resolution of abnormal liver function tests is likely to be faster [13,10].

Therefore, monitoring liver function earlier in patients undergoing anti-tuberculosis treatment allows the identification of toxicological effects in patients associated with the completion of treatment with first-line anti-tuberculosis drugs, resulting in treatment efficacy and reduction of data caused by drug therapy [26].

4.4 Class 4- Intensive Renal Treatment for Patients with Nephrotoxicity and Toxicity

The occurrence of drug-induced nephrotoxicity for antituberculosis treatment is not yet well defined, but authors state that hepatotoxicity occurs in the first month, considered the intensive treatment phase. Thus, early detection of ADIH is extremely important for the maintenance of treatment, so it is recommended that a test be carried out on all users who use antituberculosis therapy, 2 weeks after the start of treatment [13,21].

Nephrotoxicity, identified in patients, is something that occurs in patients who use second-line injectable antituberculous drugs,

being aminoglycosides and capreomycin. The adverse events caused by minoglycoside medications are: acute tubular necrosis, activation of the renin-angiotensin systems and decreased glomerular filtration. This nephrotoxicity reveals renal failure that does not have a decrease in urine production. Thus, patients in the intensive phase of treatment for tuberculosis develop nephrotoxicity due to the long period of treatment. [20,38].

Ototoxicity is another adverse effect caused by second-line medications for the treatment of multidrug-resistant tuberculosis, which is why in the studies it is reported about the importance of being monitored through an evaluation, using the audiogram, vestibular test, Romberg test and measurement of serum creatinine, considering that it is also necessary to carry out a questionnaire on hearing symptoms in order to minimize the most severe hearing loss [26,20].

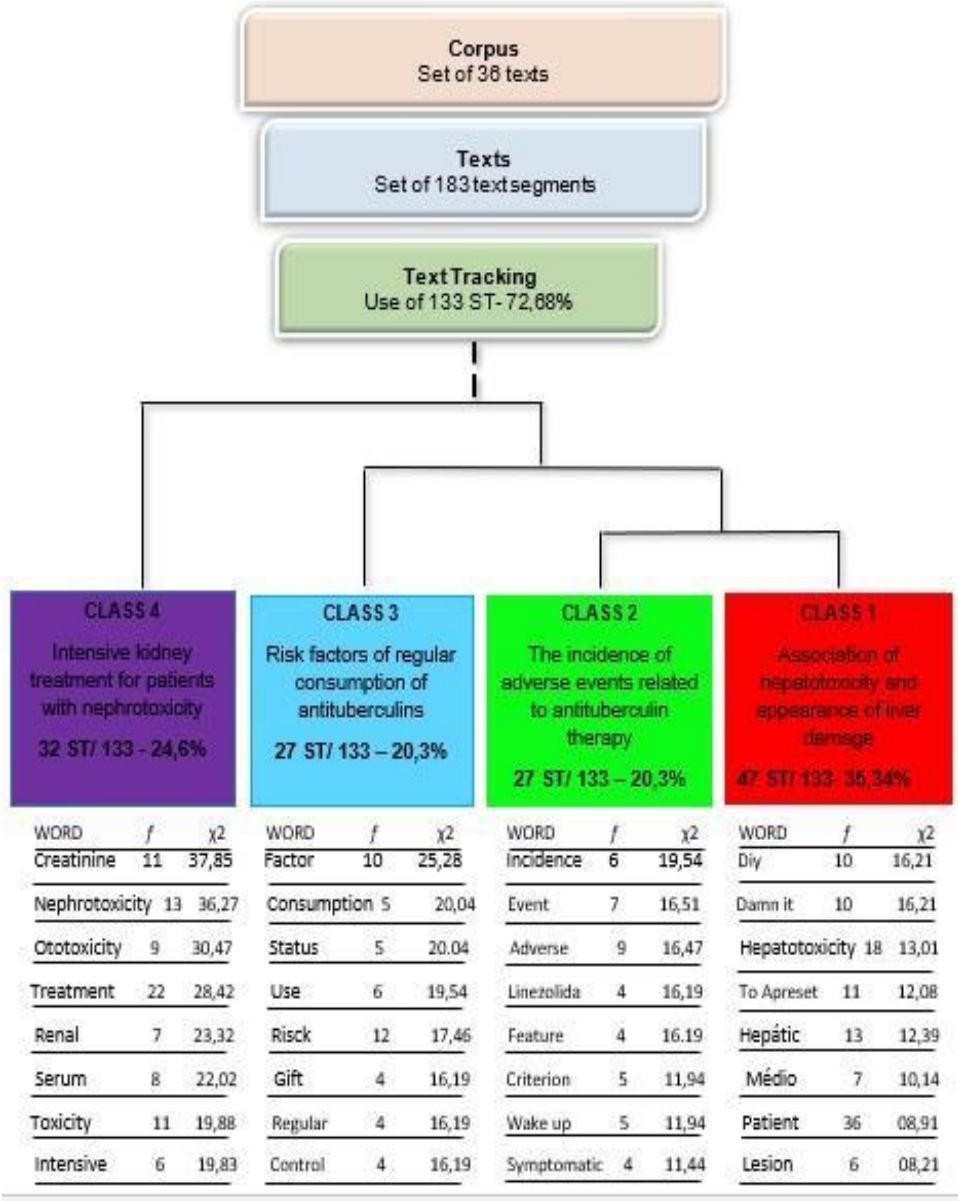

Fig. 2. Filogram made from the DHC analysis is shown in Fig. 1.
Source: Research authors, 2020

4. CONCLUSION

The treatment regimen for tuberculosis, despite being effective, can generate undesirable side effects for users due to the daily use of the four components of the drugs (isoniazid, rifampicin, ethambutol and pyrazinamide). In our review, we identified that elderly people, HIV positive and alcohol users are more likely to have toxicological effects during treatment, which can lead to a possible abandonment of treatment.

Given this, it is necessary for health professionals to be attentive and monitor the progress of therapy in order to identify these adverse effects early in order to intervene as soon as possible in the case and thereby reduce the patient's discomfort and increase the chances that he will complete the procedure treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable

ACKNOWLEDGEMENTS

We are grateful to the academic League of Nursing in Health of the Elderly - LAESI, for all the contribution to gerontological nursing and to the Department of Gerontological Nursing of ABEn/PA – DCEG-PA, for supporting the scientific production and dissemination in gerontological nursing.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Ciências. Tecnologias e insumos estratégicos. detectar, tratar e curar: desafios e estratégias brasileiras frente à tuberculose. Boletim Epidemiológico, Brasília, DF. 2015;46(9):1-19.
2. Chaves EC, Carneiro ICRS, Santos MIPO, Sarges NA, Neves EOS. Aspectos epidemiológicos, clínicos e evolutivos da tuberculose em idosos de um hospital universitário em Belém, Pará. Revista Brasileira de Geriatria e Gerontologia, Rio de Janeiro. 2017;20(1):47-58.
3. Silva LF,Silva EL, Silva TC, Caldas AJM. Tuberculose em idosos no Maranhão: contribuição para o programa de controle. Rev Fun Care Online. 2019;11(4):1088-1095.
4. Resende LSO, Santos-Neto ETS. Fatores associados às reações adversas a medicamentos antituberculose. J Bras Pneumol. 2015;41(1):77-89.
5. Olivência SA, Barbosa LGM, Cunha MR, Silva LJ. Tratamento farmacológico da dor crônica não oncológica em idosos: Revisão integrativa. Rev. bras. geriatr. gerontol.2018;21(3):383-393.
6. Pedrosa KKA, Oliveira ICM, Feijão AR, Machado RC. Enfermagem baseada em evidência: Caracterização dos estudos no Brasil. Cogitare Enferm. 2015;20(4):733-741.
7. Souza MAR, Wall ML, Thuler ACMC, Lowen IMV, Peres AM. O uso do software IRAMUTEQ na análise de dados em pesquisas qualitativas*. Rev Esc Enferm USP. 2018; 52(1): 1-7.
8. Salviati ME. Manual do Aplicativo Iramuteq (versão 0.7 Alpha 2 e R Versão 3.2.3); 2017.
   Acesso em: 16 de agosto de 2020. Disponível em:
   Available:http://www.iramuteq.org/documentation/fichiers/anexo-manual-do-aplicativo-iramuteq-par-maria-elisabeth-salviati.
9. Song JH, Yoon SH, Park TY, Heo EY, Kim DK, Chung HS et al. The clinical impact of drug-induced hepatotoxicity on anti-tuberculosis therapy: a case control study. Rev. Respiratory Research. 2019;20:283.
10. Jun CAO, Yijun MI, Cuilin SHI, Yicong BIAN, Chenrong HUANG, Zhijian YE. First-line anti-tuberculosis drugs induce hepatotoxicity: A novel mechanism based on a urinary metabolomics platform. Biochem Biophys Res Commun 2018;497(2):485-491.
11. Vasconcelos KA, Frota SMMC, Netto AR, Kritski AR. Análise sequencial como ferramenta na detecção da ototoxicidade da amicacina no tratamento da tuberculose multirresistente. J Bras Pneumol. 2018;44(2):85-92.
12. Bouazzi OE, Hammi S, Bourkadi JE, Tebaa A, Tanani DS, Bencheikh RS, et al. First line anti-tuberculosis induced

hepatotoxicity: Incidence and risk factors. Pan African Medical Journal. 2016;25-167.

13. Lee CM, Lee SS, Lee JM, et al. Early monitoring for detection of anti tuberculous drug-induced hepatotoxicity. The Korean Journal of Internal Medicine. 2016;31(1):65–72.
DOI: 10.3904/kjim.2016.31.1.65.
14. Cojutti P, Duranti S, Isola M, Baraldo M, Viale P, Bassetti M, Pea F. Might isoniazid plasma exposure be a valuable predictor of drug-related hepatotoxicity risk among adult patients with TB?. J Antimicrob Chemother. 2016;71(1):1323–1329.
15. Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT et al. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. Rev. Korean Med Sci. 2015;30(1):167-172.
16. Lang SM, Ortmann J, Rostig S, Schiffl H. Ursodeoxycholic acid attenuates hepatotoxicity of multidrug treatment of mycobacterial Infections: A prospective pilot study. Rev. International Journal of Mycobacteriology. 2020;19(1).
17. Luangchosiri C, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. BMC Complementary and Alternative Medicine. 2015;15(1):334.
18. Russom M, Debesai M, Zeregabr M, Berhane A, Tekeste T, Teklesenbet T. Serious hepatotoxicity following use of isoniazid preventive therapy in HIV patients in Eritrea. Pharmacol Res Perspect; 2018.
19. Sharma SK, Jha BK, Sharma A, Sreenivas V, Upadhyay V, Jaisinghani C, et al. Genetic polymorphisms of N-acetyltransferase 2 & susceptibility to antituberculosis drug-induced hepato-toxicity. Indian J Med Res. 2016;924-928.
20. Shibeshi W, Sheth AN, Admasu A, Berha AB, Negash Z, Yimer G. Nephrotoxicity and ototoxic symptoms of injectable second-line anti-tubercular drugs among patients treated for MDR-TB in Ethiopia: A retrospective cohort study. BMC Pharmacology and Toxicology. 2019;31 (20):1-10.
21. Usui T, Meng X, Saide K, Farrell J, Thomson P, Whitaker P. Characterization of isoniazid-specific T-cell clones in patients with anti-tuberculosis drug-related liver and skin injury. Rev. Toxicological sciences, 2017;155(2):420–431.
22. Valadares RMC, Carvalho WS, Miranda SS. Association of adverse drug reaction to anti-tuberculosis medication with quality of life in patients in a tertiary referral hospital. Rev. Soc. Bras. Med. Trop. on line. 2020;53.
23. Wang JY, Tsai CH, Lee YL, Lee LN, Hsu CL, Chang HC, et al. Gender-dimorphic impact of PXR genotype and haplotype on hepatotoxicity during antituberculosis treatment. Rev. Medicine. 2015;94(24).
24. Zhang J, Zhu X, Li Y, Zhu L, Li S, Zheng G. Correlation of CPG island methylation of the cytochrome P450 2E1/2D6 genes with liver injury induced by anti-tuberculosis drugs: A nested case-control study. Int. J. Environ. Res. Public Health. 2016;13:776.
25. Adole PS, Kharbanda P, Sharma S. N-acetyltransferase 2 (NAT2) gene polymorphism as a predisposing factor for phenytoin intoxication in tuberculous meningitis or tuberculoma patients having seizures - A pilot study. Rev. Indian J Med Res. 2016;143:581-590.
26. Altena RV, Dijkstra JA, Meer MEVD, Howard JFB, Kosterink JGW, Soolingen DV et al. Reduced chance of hearing loss associated with therapeutic drug monitoring of aminoglycosides in the treatment of multidrug-resistant tuberculosis. Rev Antimicrobial Agents and Chemotherapy. 2017;61(3):1-10.
27. Chan SL, Chua APG, Aminkeng F, Chee CBE, Jin S, Loh M. Association and clinical utility of NAT2 in the prediction of isoniazid-induced liver injury in Singaporean patients. Rev. Plos one; 2017.
28. Amagon KL, Awodele O, Akindele AJ. Methionine and vitamin B-complex ameliorate antitubercular drugs-induced toxicity in exposed patients. Rev. Noxious Effects of Antitubercular Drugs Modulated. 2017;5(5):360.
29. Jin KW, Lee JY, Rhiu S, Choi DG. Longitudinal evaluation of visual function and structure for detection of subclinical ethambutol-induced optic neuropathy. Rev. longitudinal evaluation of visual function and structure for detection of subclinical ethambutol-induced optic neuropathy. Rev. Plos one. 2019;1-12.
30. Taffner BMP, Mattos FB, Cunha MC, Saraiva FP. The use of optical coherence

tomography for the detection of ocular toxicity by ethambutol. Rev. Plos one. 2018;1-10.
31. Tweed CD, Crook AM, Amukoye EL, Dawson R, Diacon AH, Hanekom M, et al. Toxicity associated with tuberculosis chemotherapy in the REMoxTB study. BMC Infectious Diseases. 2018;18:317.
32. Wiltshire CS, Braun AV, Scherrer AU, Manabe YC, Buzibye AMD, et al. Anti-TB drug concentrations and drug-associated toxicities among TB/HIV-coinfected patients. J Antimicrob Chemother. 2017; 72(4):1172-1177.
33. Ngouleun W, Nya PCB, Pieme AC, Telefo PB. Risk assessment of hepatotoxicity among tuberculosis and human immunodeficiency virus/AIDS-coinfected patients under tuberculosis treatment. Rev. International Journal of Mycobacteriology. 2016;482–488.
34. Mariz CA, Lopes EP, Santos BA, Maruza M, Montarroyos UR, Ximenes RAA, et al. Hepatotoxicity during treatment for tuberculosis in people living with HIV/AIDS. Rev. PLoS One. 2016;11(6).
35. Sakashita K, Murata K, Takahashi Y, Yamamoto M, Oohashi K, Sato Y. A case series of acute kidney injury during anti-tuberculosis treatment. Intern Med 2019;58(4):521-527.
36. Sineke T, Evans D, Schnippel K, Aswegen HV, Berhanu R, Musakwa N. The impact of adverse events on healthrelated quality of life among patients receiving treatment for drug-resistant tuberculosis in Johannesburg, South. Health and Quality of Life Outcomes. 2019;17(1):94.
37. Jones J, Mudaly V, Voget J, Naledi T, Maartens G, Cohen K. Adverse drug reactions in South African patients receiving bedaquiline - containing tuber culosis treatment: An evaluation of spontaneously reported cases. BMC Infectious Diseases. 2019;19(1):544.
38. Isa SE, Ebonyi AO, Shehu NY, Idoko P, Okopi JAA, Simji G, et al. Antituberculosis drugs and hepatotoxicity among hospitalized patients in Jos, Nigeria. International Journal of My Cobacteriology. 2016: 21-26.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/67009