EXPERT OPINION

Anti-tuberculosis drugs adverse reactions: a review of the Iranian literature

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Introduction: Tuberculosis (TB) treatment, in particular therapy for multidrug-resistant TB (MDR-TB), is associated with toxicities and adverse drug reactions (ADRs).

Areas covered: This paper reviews Iranian literature reporting ADRs which occurred during tuberculosis treatment. English language papers were sourced from PubMed, ScienceDirect, Wiley, Ovid and Proquest, with Google Scholar searched for Persian language articles. Reported ADRs, proportion of patients with ADRs, risk factors and determinants, as well as the characteristics of the studies were reviewed. 21 articles were included; about 60% of them were in English and three included patients with MDR-TB. The ratio of ADR per capita was 1.9 (in 6 studies) and 33.63% of patients developed an ADR (in 7 studies). Hepatitis (2.5 – 45.3%) was reported in nearly all of the studies. The mean time from initiation of medication to development of hepatitis ranged from 4.67 to 25.25 days (in 6 studies). Most cases of mortality were due to hepatotoxicity. Except for comorbidities and female gender, other risk factors such as HIV and length of hospitalization were only reported in one article.

Expert opinion: The pattern of ADRs in Iranian articles was found to be similar to many other studies in the present review. We suggest that future studies resolve the confounding factors in this area that are mentioned in this review.

Keywords: adverse drug reaction, drug induced hepatotoxicity, Iran, multidrug-resistant tuberculosis, side effect, tuberculosis

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1. Introduction

Tuberculosis (TB) as one of the major causes of mortality due to a curable infectious disease [1,2] was responsible for 20 deaths per 100,000 populations in 2011 [3]. Even though it is an endemic disease in developing countries [4], developed countries are also encountering resurgence of this disease [5]. Increase in the number of HIV-positive individuals has led to a significant increase in the number of TB patients over the last decade in both developing and developed countries [6,7]. During the course of HIV infection, TB is the most important opportunistic infection that can happen at any point [6]. Moreover, HIV-positive patients have a high risk of transformation of latent TB to active from [6] and this makes patients more vulnerable for development of adverse drug reactions (ADRs) [8]. Multidrug-resistant TB (MDR-TB) is another challenge for health systems, which is treated with second-line agents. These agents are often less effective [9-11], cause more ADRs and toxicities [9,10] and also need longer treatment duration [9,10].

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Article highlights.

- Few original articles are published from Iran that mainly focused on ADRs of anti-anti-tuberculosis medications.
- As many as almost one-third of patients participating in seven studies experienced at least one ADR during the treatment course.
- Drug-induced hepatotoxicity was the most widely concern of all of the included studies, whereas the definitions varied considerably between studies.
- The second most frequent reported ADR was rash (reported in seven studies), followed by ototoxicity and pruritus.
- The major causes of mortality during TB treatment course were hepatotoxicity and neuropsychiatric events.

This box summarizes key points contained in the article.

Even though active TB can be successfully managed with the completion of anti-TB therapy [12], it seems that completion of the full course of therapy without significant ADRs is achieved only by a minority of patients [13]. These ADRs may be mild or life-threatening [5,14]. Occurrence of severe ADRs is common particularly in hospitalized patients with pulmonary tuberculosis [12].

ADRs can generally decrease treatment effectiveness through negative impact on patients' adherence [1], which is an extremely important determinant of treatment outcome [13].

Morbidity and mortality can increase when patients experience severe ADRs to first-line anti-TB medications, which may lead to discontinuation of the culprit drug [5,9]. Meanwhile, administration of an alternative agent may increase toxicity and may eventually increase the risk of treatment failure and relapses [5]. One of the most prevalent ADRs of these drugs is hepatotoxicity [1]. In fact, the leading cause of treatment interruption is liver enzyme elevation [15].

Like many other countries, Iran has some difficulties with TB, especially due to increasing drug-resistant strains, which complicates the control of disease [7]. According to the World Health Organization (WHO), 14.12 new cases per 100,000 populations were diagnosed with TB in Iran in 2011 [3]. The prevalence of severe complications of anti-TB medications is not still well known, despite more than 30 years of their utilization. This can be probably attributed to lack of awareness and under-reporting [13].

Several studies that focused on ADR of the anti-TB medications have been performed in Iran. But there was not a concluding review on these articles. Therefore, we decided to review the published ADRs reported in Iranian patients, current proportion of patients who experienced different ADRs, the determinants and risk factors in patients with TB, as well as the evaluation of the characteristics of the studies. To the best of our knowledge, this is the first review of anti-TB ADRs in the Middle East and developing countries.

2. Methods

2.1 Data sources and searched terms

For the purpose of doing this review, we searched the literature in both English and Persian language to find papers related to ADRs caused by anti-TB medications in Iran. The English resources searched were PubMed, Ovid, Wiley, ScienceDirect and ProQuest. In order to find Persian articles, we performed search in Google Scholar, which has a wide coverage for Persian articles. The time span was up to October 2013. Relevant references of articles were traced manually by referring to the cited journals. We decided to search extensively to find all the articles that were published related to different aspects of TB in Iran and among them we selected the related ones according to the abstracts and full texts. We used these English terms and their corresponding Persian equivalents: 'tuberculosis', 'adverse drug reaction', 'side effect' 'Iran', 'isoniazid' (INH), 'rifampin' (RIF), 'pyrazinamid' (PZA) and 'ethambutol' (ETM). The mentioned resources were searched within title, keywords, abstracts or MeSH terms whichever were appropriate.

2.2 Inclusion/exclusion criteria

We included all of the studies on adults and children, that are, cross-sectional, case–control, clinical trial and cohort studies. All the studies on patients with active or latent TB regardless of the resistance pattern and also on patients with other comorbidities were considered. Studies were excluded if they were not concerned with any specific ADR or laboratory abnormalities due to anti-TB medications. We also excluded letters, case reports and abstracts of seminars, organizational reports, opinions or editorial papers, book chapters, as well as articles in languages other than English or Persian. Moreover, studies that only included non-Iranian patients, addressed general outcome of TB treatment and studies that reported ADRs due to BCG vaccination were excluded from this review.

2.3 Data extraction

Two authors independently selected the articles according to the inclusion and exclusion criteria by reading the titles and abstracts and whenever necessary the full texts. We extracted and summarized the important issues reported in most of the articles in two sections and in five tables. The reason of separating these sections was different focus of the articles. In the first section, articles that assessed ADRs in general are discussed. In **Table 1**, we abstracted the studies designs, total number of patients and their demographics (age, sex), number of patients who developed ADR, therapy regimen, total number of events, associated factors and strategies to manage ADRs, and, finally, severity, causality or preventability of ADRs if reported. In **Table 2**, we reported specific ADRs and their proportions. We mentioned the ADRs in descending order, based on the number of articles in which the

specific ADR were stated. In this table, the percentages were calculated by dividing number of patients who developed an ADR to total number of patients recruited in each study. We also calculated the ratio of ADRs per capita by dividing the number of events to the total number of patient who developed ADR from the studies that reported both numbers. Additionally, we calculated the proportions of each ADR by dividing the total number of patients experiencing ADR to the total number of patients included in the study.

Because of the importance of the drug-induced hepatotoxicity (DIH) by anti-TB drugs, we separately extracted these data in the second section of the findings. We summarize the definitions used for DIH throughout the studies in **Table 3**. We extracted details regarding hepatotoxicity in two tables. In **Table 4**, general study characteristics such as publication year, design, location and also participants' characteristics, exclusion criteria, comorbidities and treatment protocol and so on, are summarized. The percentage of DIH development, patients age, onset, symptoms, severity, management, length of time needed for the resolution of symptoms, associated factors, process of re-challenge and so on, are extracted and summarized in **Table 5**. Wherever the authors only reported increases in liver enzymes, we used the general definition of DIH regarding rise of > 5 times upper limit of normal (ULN) of liver enzymes for hepatotoxicity (> 200 IU) and the definition of the WHO for the severity of DIH based on liver enzymes and extracted the data in **Table 5**. Studies that lacked most parts of the mentioned characteristics are pointed in the text.

3. Findings

Our search process yielded 599 and 659 English and Persian papers, respectively (**Figure 1**). Removing the duplicate articles resulted in 314 and 146 articles in English and Persian, respectively. Among these articles many were identified to be irrelevant and were excluded. Therefore, ultimately we found 21 studies suitable to be included in the present review. According to the corresponding authors, 16 studies were conducted by physicians (in one study the evaluation was based on the first author due to undefined corresponding author) and the remaining by pharmacists. Two-thirds of the studies were in English language.

3.1 ADRs in general

3.1.1 *Study characteristics and definitions*

A total of 11 studies were included in this section of our review. Among them five studies were in Farsi. The time span of the publications was from 2002 onward. The main characteristics of studies are shown in **Table 1**. Most of the study designs were cross-sectional (63.6%), including four prospective studies, followed by cohort design in three studies (27.3%) and one clinical trial. Only two studies by pharmacists specified a definition for ADR (WHO definition) and criteria for assessment of causality, severity and preventability [16,17]. The most common corresponding authors were physicians (nine studies) followed by clinical pharmacists (two studies).

3.1.2 *Anti-TB regimen*

The majority of studies only included patients diagnosed with drug-sensitive TB (60%) [16-22]. Two studies reported the data of MDR-TB patients [2,23]. There was only one study that included both patients with sensitive TB and MDR [24]. Only one study evaluated the treatment of latent TB [25]. Details of the treatment regimens are summarized in **Table 1**.

3.1.3 *Patients*

All studies except three [22,25,26] were conducted in hospitalized patients. The mean age of patients was calculated to be 46.72 years in 889 patients from six studies. There was only one study that exclusively included the pediatric patients that assessed INH prophylaxis. None of the children in this study experienced ADRs [25].

3.1.4 *ADRs categorization*

Except three, all other studies reported the ADRs as a result of an integrated regimen. Javadi *et al.* reported that 32.4% of detected ADRs could be attributed to the combination of INH, RIF and PZA [17]. Gholami *et al.* reported ADRs for each anti-TB medication [16]. The third study was the mentioned study on pediatric patients.

All studies reported ADRs by symptoms. However, two studies additionally reported the ADRs based on WHO organ system classification. In these studies, the most frequent involved organs were 'gastrointestinal system' and 'liver and biliary system,' which were together responsible for almost 60% of total ADRs (58% [16] and 61.1% [17] of ADRs). As mentioned previously Aminzadeh et al. did not report any ADR.

3.1.5 *Proportions of ADRs*

The ratio of ADRs per capita was 1.9 based on the data obtained from six studies that reported both the number of ADRs and the total patient population. We also figured out the total proportion of patients who developed an ADR to be 33.63% based on the data derived from seven studies. When we excluded studies of MDR-TB, the results were nearly the same: proportion of patients with ADR and the ratio of ADRs per capita were 30.5% and 1.94, respectively. Among ADRs, hepatitis was reported in nearly all of the studies (except the study on the treatment of latent TB) [25] with the proportion of 2.5 – 45.3% in different studies. The second most frequent reported ADR was rash, which was reported in seven studies, followed by ototoxicity and pruritus, both of which were reported in 54% of studies. The highest prevalence ADR reported in these studies, regardless of the number of articles reporting ADRs, was arthralgia (66.7%), followed by headache (58.7%) and neuropathy (50.7%). There is also one report of hyperglycemia in diabetic patients (4.41% of total participants) (**Table 2**) [17].

Table 1. Characteristics of studies that reported different ADRs.

Author year	Study design	Patients		Therapy regimen	ADR				
		N (F%:M%)	Age (years) ± SD (range)		N (F%:M%)	N Events	Associated factors		Severity/ causality/ preventability	Action taken
							Significant	Nonsignificant		
Taramian *et al.* 2012 [19]	Retrospective cross-sectional	387 (39:61)	45.5 ± 19.3	1st line regimen	56 (35.71:64.28)	185	Hospitalization length (days) TB site	–	–	DC 14.2%§
Baghaei *et al.* 2011 [23]	Retrospective cross-sectional	80 (45:55)	40.64 ± 17.53 (14 – 81)	MDR PTH,CS,OFX, ETM,PZA,AMK	45 (48.9:51.1)	90	Comorbidity	Age > 65 Y Type of TB HIV DM	–	DC 37.77%¶
Tabarsi *et al.* 2011 [24]	Prospective cohort	100 (38:62)	45.6 ± 19.75	Non MDR/MDR INH,RIF,PZA,ETM, PTH,CS, OFX	36	–	MDR-TB	–	–	DC 100%¶ Replaced 66.66%
Rasoulinejad *et al.* 2010 [20]	Historical cohort	75 (21.3:78.7)	46.9 ± 17.2 (22 – 78)	INH,RIF,PZA ETM,STR	–	–	HIV **	–	–	–
Masjedi *et al.* 2008 [2]	Retrospective cohort	43 (37.2:62.8)	44.38 ± 19.05 (15 – 83)	MDR ETM,PZA,CLR PTH,CS,OFX, AMC,AMK	25	41	–	–	–	Regimen modified 80%¶
Javadi *et al.* 2007 [17]*	Prospective cross-sectional	204 (58.8:41.2)	52.4 ± 5.2	INH,RIF,PZA ETM	92 (63.04:36.95)	136	Female Previous history of ADR	(Higher chance for severe ADRs) Previous use of anti-TB drugs History of drug allergy Nationality Smoking Comorbidity	In 136 events Causality Certain 14% Probable 21.30% Severity Mild 25% Moderate 56.6% Severe 18.4% Preventability Preventable 34.6%	Continue + symptomatic therapy 46.3%§ No change 28.7% DC 20.6% Dose adjustment 4.4%

*Only included patients with pulmonary TB.

‡Study setting: outpatient.

§The percentages of different actions taken are calculated based on the total number of events.

¶The percentages of different actions taken are calculated based on the total number of patients who developed ADR.

#The study reported seven severity levels that we modified based on Modified Hartwig and Siegel severity scale [57].

**HIV-positive patient experienced peripheral neuropathy, arthralgia, vomiting, headache, dizziness, nephrotoxicity, rash, trombocitopenia, neutropenia, leucopenia significantly higher than HIV-negative patients.

ADR: Adverse drug reaction; AMC: Amoxicillin/Clavulanic acid; AMK: Amikacin; CLR: Clarithromycin; CS: Cycloserine; DC: Discontinued; DM: Diabetes mellitus; ETM: Ethambutol; F: Female; HIV: Human immunodeficiency virus; INH: Isoniazid; M: Male; MDR-TB: Multi-drug resistant tuberculosis; N: Number; OFX: Ofloxacin; PT: Prothionamide; PZA: Pyrazinamide; RIF: Rifampin; STR: Streptomycin.

Table 1. Characteristics of studies that reported different ADRs (continued).

Author year	Study design	Patients		Therapy regimen	ADR					
		N (F%:M%)	Age (years) ± SD (range)		N (F%:M%)	N Events	Associated factors		Severity/ causality/ preventability	Action taken
							Significant	Nonsignificant		
Gholami *et al.* 2006 [16]*	Prospective cross-sectional	83	–	INH,RIF,PZA ETM	44 (52.3:47.7)	81	–	Age	In 81 events Causality Certain 8.6% Possible 43.2% Probable 48.2% Severity# Mild 40.7% Moderate 55.6% Severe 1.9% Lethal 2.5 %	DC 34.5%¶ Continue + symptomatic therapy 21% Dose adjustment 7.4% No specific symptomatic therapy 33.4% (didn't cause a serious problem, for example, headache or constipation)
Ayatollahi *et al.* 2004 [22]‡	Prospective cross-sectional	325 (44:56)	–	–	113 (53.98:46.01)	174	Female	Age Nationality Weight	In 113 patients Severity Minor 29.8% Major 5% (10 patient had also minor ADRs)	DC and restart 11.5%¶ (all patients with Hepatitis) DC PZA 0.88% (Due to arthralgia lead to RA)
Ataei *et al.* 2004 [26]‡	Clinical trial	200 (47:53)	15 – 50	Denver & Standard INH,RIF,PZA, ETM,STR	–	18	–	–	–	–
Afzali *et al.* 2002 [21]	Prospective cross-sectional	190 (49:51)	–	INH,RIF,PZA, ETM,STR	–	–	–	–	–	–

*Only included patients with pulmonary TB.

‡Study setting: outpatient.

§The percentages of different actions taken are calculated based on the total number of events.

¶The percentages of different actions taken are calculated based on the total number of patients who developed ADR.

#The study reported seven severity levels that we modified based on Modified Hartwig and Siegel severity scale [57].

**HIV-positive patient experienced peripheral neuropathy, arthralgia, vomiting, headache, dizziness, nephrotoxicity, rash, trombocitopenia, neutropenia, leucopenia significantly higher than HIV-negative patients.

ADR: Adverse drug reaction; AMC: Amoxicillin/Clavulanic acid; AMK: Amikacin; CLR: Clarithromycin; CS: Cycloserine; DC: Discontinued; DM: Diabetes mellitus; ETM: Ethambutol; F: Female; HIV: Human immunodeficiency virus; INH: Isoniazid; M: Male; MDR-TB: Multi-drug resistant tuberculosis; N: Number; OFX: Ofloxacin; PT: Prothionamide; PZA: Pyrazinamide; RIF: Rifampin; STR: Streptomycin.

Table 2. Incidence of specific ADRs in studies.

ADR	Incidence %
Hepatitis	2.5 [26], 3 [24]#, 3.38 [22], 3.68 [21], 5 [23]¶, 6.97 [19], 7.7 [29], 9.2 [2]¶, 10.78 [17], 14.5 [30], 20 [6], 25.3 [16], 45.3 [20]
Rash	0.5 [26], 0.51 [19], 1.3 [23], 1.96 [17], 4.81 [16], 14.7 [20],16.92 [22]*
Ototoxicity/hearing loss and tinnitus	0.31 [22], 0.6 [21], 1.3 [20], 14.5 [23], 19 [24], 46 [2]
Pruritus	0.5 [19], 0.6 [21], 1 [26], 7.5 [23], 8.8 [17], 16.92 [22]*
Ocular toxicity	0.25 [19], 0.49 [17], 0.6 [21], 1.23 [22], 2.4 [16]
Neuropathy	0.5 [26], 4.92 [22], 6.02 [16], 1.96 [17], 50.7 [20]
Hyperuricemia	1.25 [23], 1.47 [17], 2.7 [20], 3.61 [16], 7.4 [21]
Nausea	1.5 [26], 11.36 [19], 11.27 [17]‡,12 [22]§, 16.3 [23]
Arthralgia	0.5 [26], 6.3 [23], 6.46 [22], 66.7 [20]
Vomiting	11.36 [19], 12.5 [23], 11.27 [17]‡, 37.3 [20]
Vertigo	1.5 [26], 6.3 [23], 7.7 [22], 41.3 [20]
Headache	2.5 [23], 4.9 [17], 8.43 [16], 58.7 [20]
Anorexia	2.5 [23], 3.92 [17], 7.75 [19], 12 [22]§
Diarrhea	0.25 [19], 1.96 [17], 3.61 [16], 12 [22]§
Fever	5 [23], 10.6 [21], 36 [20]
Nephrotoxicity	0.6 [21], 3.8 [23], 5.3 [20]
Constipation	4.9 [17], 17.3 [16]
Hyperglycemia	4.41 [17], 8.43 [16]
Jaundice	0.61 [22], 2.58 [19]
Psychosis/suicide	6.9 [2], 7 [24]
Abdominal pain	0.49 [17], 13.8 [23]
Prolonged PT	2.04 [16], 7.36 [21]
Thromcytopenia	17.3 [20]
Thromcytopenia and prolonged PT	0.98 [17]
Epigastric pain	6.45 [19]
Dysuria	4.81 [16]
Weakness	3.8 [23]
Dry mouth	1.47 [17]
Hypothyroidism	1.25 [23]
Pigmentation	1 [26]
Gastric indigestion	0.98 [17]
Mood change	0.49 [17]
Neurologic (depression, suicide, convulsions, consciousness, psychosis)	7.5 [23]

*Ayatollahi *et al.* reported rash and pruritus 16.92% together.

‡Javadi *et al.* reported nausea and vomiting 11.27% together.

§Ayatollahi *et al.* reported gastrointestinal side effects (nausea, anorexia and diarrhea) 12% together.

¶MDR-TB patients [23,24].

#MDR-TB/drug-sensitive TB [2].

3.1.6 *Onset of ADRs*

Unfortunately, most of the studies did not report the onset of events. However, Baghaei *et al.* reported that major side effects appeared after the median of 21 days from the medication initiation [23]. Also, Gholami *et al.* reported the occurrence of almost 90% of ADRs in the first 20 days [16].

3.1.7 *Management of ADRs*

Drug discontinuation was one of the strategies in six studies and ranged from 34.5 to 100% in five studies, which reported interventions for patients who developed an ADR [2,16,22-24]. Other interventions were symptomatic therapy along with continuation of the regimen and also regimen modification (drug replacement or dose adjustment).

3.1.8 *Complications of ADRs*

Some of the studies reported the need for admission and length of hospitalization due to ADRs. The rate of hospitalization as estimated by Javadi *et al.* was 5.4% [17]. Gholami *et al.* reported prolonged hospitalization in 59% of patients. They also mentioned that ADRs, which led to admission, occurred on days 21 – 30. However, 71.6% of patients improved at last [16]. Likewise, significant extended hospital stay was reported by Taramian *et al.* [19]. Tabarsi *et al.* reported more cases of mortality or treatment failure in patients with ADR. They also found that less ADRs were experienced by patients with successful TB treatment [24]. Most of the cases of mortality were due to hepatitis that is described later. Mortality due to other ADRs was

observed in two patients with MDR-TB as a result of suicide [2]. Moreover, in another study on patients with MDR-TB, it was suggested that neurological side effects (depression, convulsions, consciousness and psychosis) can be associated with increased mortality [23].

3.2 Hepatotoxicity

3.2.1 Studies' characteristics

Twenty articles reported hepatotoxicity or changes in liver function tests (LFT). Ten studies were among the previously mentioned articles that evaluated hepatotoxicity besides other ADRs. Among other studies, six articles were mainly focused on the aspects of hepatotoxicity or LFT changes. Among them there was a clinical trial that evaluated the protective effects of N-acetylcysteine on DIH. We only extracted data of the control group of this study [27]. The remaining four studies were as follows: one study evaluated the pattern of LFT changes in different time spans [28], another study focused on the risk factors of mortality due to TB in which authors reported total number of DIH [29]. Other studies included a case series [6] and a short report [30], both of which recruited patients coinfected with HIV and only reported the incidence of DIH without other details. Among the latter 10 studies, the most common corresponding authors were physicians (seven studies), followed by clinical pharmacists. All of them were published after 2002.

3.2.2 Diagnosis and definition of DIH

Eleven studies defined DIH as shown in **Table 3**; however; the definitions varied widely, for example, the definition used by Gholami *et al.* [16] versus the one used by Afsharian *et al.* [31]. Also, studies were not in consensus about minimum elevated enzyme levels according to which the symptomatic patients would be included as DIH. Additionally, cholestatic hepatitis was defined and considered only in a limited number of studies.

3.2.3 Patients

The 20 studies together recorded the data of 4849 patients (prospectively or retrospectively). Their eligibility criteria varied widely. For example, Tabarsi *et al.* in their studies only included TB patients coinfected with HIV [6,30], but these patients were excluded from the studies by Ghasemi Barghi *et al.* [32] and Baniasadi *et al.* [27]. The details of studies characteristics are summarized in **Table 4**. All of the 10 studies, which focused on hepatotoxicity, included patients with drug-sensitive TB. However, in studies that included MDR-TB patients that were mentioned earlier, hepatotoxicity was also pointed.

3.2.4 Proportion of DIH

Among the total 4849 cases, 450 cases of DIH were defined with the proportion of 9.28%. Due to the limited number of cases with cholestatic hepatitis, we could not obtain an incidence for this kind of hepatotoxicity separately. Baniasadi *et al.* reported three cases of hyperbilirubinemia [27]. Additionally, in the study by Afzali *et al.,* 16 cases (8.5%) experienced a rise in bilirubin (> 1.2 mg/dl) [21]. They also reported rise in ALP in 24 (18.4%) patients (in 11 patients ALP raised > 4 ULN) [21]. [33]. Only two studies reported cases of jaundice [19,22]. The study by Sharifzade *et al.* was the only study that characterized hepatotoxicity based on causality, preventability and predictability. They noted that all of the DIH cases were category A and none of them were preventable or predictable [18].

Three studies reported hepatitis in patients with MDR-TB: 5% by Baghaei *et al.* [23], 9.2% by Masjedi *et al.* [2] and 3% by Tabarsi *et al.* [24]. In the latter study, both patients with drug-sensitive and -resistant TB were included. By excluding these studies from the total number of patients, the proportion of patient developed DIH reaches 9.49%, which is slightly higher than the previously mentioned percentage.

3.2.5 Onset of DIH

The mean time from initiation of the anti-TB medications to the development of DIH ranged from 4.67 to 25.25 days (reported in six studies). As reported by Sharifzade *et al.,* the cumulative incidence of DIH during the first month of treatment was 22%. It increased in the second month to 25% and was constant through the next two months. Finally, in the sixth month of treatment, it reached 27.7% [18].

3.2.6 Management of DIH

Only seven studies mentioned the management strategies for cases of hepatitis. In these studies after confirmation of the DIH, all of the anti-TB medications were discontinued. However, in the study by Baniasadi *et al.* [27] and Sharifzadeh *et al.* [18], only INH, RIF and PZA were discontinued and the latter was the only study in which patients received an alternative regimen during the time needed to elapse for normalization of the enzymes. The mean time passed for recovery and decreasing enzymes was between 7.5 and 23.45 days after discontinuation of the medications and was reported in five studies.

3.2.7 Reinitiation of anti-TB regimen

Restarting the anti-TB medications was considered based on the normalization of the transaminase enzymes in 4 out of 6 studies that addressed this issue. In another study, resolution of symptoms was the criteria for reinitiation of the anti-TB medications [22]. In contrast, in the study by Khalili *et al.*, returning of the enzymes to < 2 ULN was acceptable to restart the medications [33]. In three studies, the protocol of gradual drug initiation was described. The reinitiation of the regimen was successfully tolerated in most of the DIH cases. However, in 29 patients out of 178, in whom the process was noted (from four studies), this led to re-experiencing the DIH (16.29% of all re-challenged patients). In the only study that mentioned treatment strategy for the second DIH episode, permanent discontinuation of the culprit agent and

Table 3. Different definitions of drug-induced hepatotoxicity in studies.

Definitions of DIH	Studies
AST/ALT > 5 UNL	Ghasemi Barghi *et al.* [32], Khalili *et al.* [33], Sharifzadeh *et al.* [18], Afsharian *et al.* [31], Baniasadi *et al.* [27], Rasoulinejad *et al.* [20], Taramian *et al.* [19], Alavi-Naini *et al.* [29]
Symptoms of hepatitis	Ghasemi Barghi *et al.* [32], Sharifzadeh *et al.* [18]
ALT & AST > 5UNL + symptoms of Hepatitis	Gholami *et al.* [16]
ALT/AST > 3 UNL + symptoms of Hepatitis	Khalili *et al.* [33], Sharifzadeh *et al.* [18], Javadi *et al.* [17], Taramian *et al.* [19], Alavi-Naini *et al.* [29]
ALT & AST > 2 UNL + symptoms of Hepatitis	Rasoulinejad *et al.* [20]
AST/ALT > ULN + symptoms of Hepatitis	Baniasadi *et al.* [27]
AlP > 2 UNL + jaundice or hyperbilirubinemia, pruritus	Khalili *et al.* [33]
jaundice ± abdominal sign and symptom	Sharifzadeh *et al.* [18]
Total bil > 1.5 mg/dl	Baniasadi *et al.* [27]
Based on definition of the American Thoracic Society	Baghaei *et al.* [23]
No definition	Baghaei *et al.* [34], Hajibagheri *et al.* [28], Tabarsi *et al.* [24], Masjedi *et al.* [2], Afzali *et al.* [21], Ayatollahi *et al.* [22], Ataei *et al.* [26], Tabarsi *et al.* [30], Tabarsi *et al.* [6]

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase, Bil: Bilirubin; DIH: Drug-induced hepatotoxicity.

replacing a drug or prolongation of the treatment duration was implemented [33].

3.2.8 Outcome and mortality due to hepatotoxicity

Khaili *et al.* noted that DIH was the leading cause of treatment interruption (31.37%) and modifying treatment regimen (13%) [33]. Mortality was reported in four studies. Baghaei *et al.* reported that 13 patients (13.4% of total DIH cases) died, which was significantly higher than those who did not experience hepatotoxicity (21 cases, 3.2%) [34]. In the study by Sharifzade *et al.,* two patients died as a result of DIH complications (6.45%) [18]. Gholami *et al.* reported two deaths among 21 DIH patients (9.52%) [16]. In a 9-year retrospective study on 715 patients, 55 cases developed DIH (7.69%). Seventy-five deaths were reported, among which 22 patients had experienced DIH (40% of total cases with DIH). Multivariate analysis revealed DIH as one of the major risk factors for mortality [29].

4. Discussion

4.1 Summary of general findings

Although there are many studies reporting minor to life-threatening side effects [14], TB treatment with directly observed treatment short-course (DOTS) strategy is still the most cost-effective of all the healthcare interventions [35]. In this review, we gathered the results of published articles related to the anti-TB medications in Iran. Commonly reported ADRs in our review such as hepatitis, skin rash and pruritus, nausea/vomiting, arthralgia, neuropsychiatric symptoms, ototoxicity and peripheral neuropathy were similar to those reported by other investigators [5,36-39]. In accordance with other studies, we found DIH to be the most common reported ADR [36,37,39].

Following hepatitis, rash was the second most frequent ADR, which is similar to other studies [38-40]. Pruritus was also reported commonly in included studies (0.51 – 8.82%), which are close to the results of other studies (0.4 – 6%) [39,41,42].

We calculated a ratio of 1.9 ADR per patient for about 75% of total patients included in this review, which is comparable and close to other reports. For example, Marra *et al.* detected 646 ADRs in 318 patients (2.03 ADR per patient) [39]. Likewise, this ratio was 1.09 [37] and 1.18 [5] in other studies. All these mentioned studies are selected because of large sample size consisting of > 1000 TB patients and reporting both the number of events and patients. Total proportion of patients who developed at least one ADR was 30.7% based on seven studies in the present review, which is higher than that reported in a systematic review of Chinese articles [43]. Yin yin *et al.* indicated that the total incidence of anti-TB-induced ADR was 12.62% [43]. We found that the two largest studies included in our review tended to report relatively lower proportion of ADRs [19,22], which is consistent with previous observations [44]. However, we did not notice a relationship between the study design (retrospective vs prospective) and proportion of ADRs reported. It should be noted that this number was calculated based on the data of about 30% of all the studies and cannot be extrapolated to the total patient population with certainty. Notably, most of the patients in the reviewed studies were hospitalized at the initiation of the medications. This might potentially be due to the more complex and serious condition and can increase the probability of detecting ADRs as a result of close monitoring. It is suggested that population-based studies report lower incidence of ADRs [39].

WHO estimates that 3.7% of new TB cases and 20% of previously treated patients were infected with MDR mycobacterium [3]. Fortunately according to the 2012 global TB report, Iran is not among the 27 high MDR-TB burden

Table 4. Characteristics of studies that mainly assessed drug-induced hepatotoxicity.

Author Year of publication	Study design	City/ duration	Treatment protocol	Exclusion criteria	Participants					Definitions	
					N (F%, M %)	Age Year ± SD	Nationality	% of pulmonary TB	Comorbidities	DIH	Other
Hajibagheri *et al.* 2002 [28]	Prospective cross-sectional	Kurdestan 1999	–	–	309	Range 15 – 91 y (Mostly > 64)	–	–	–	–	–
Sharifzadeh *et al.* 2005 [18]	Prospective	Tehran 1999 – 2002	INH RIF PZA ETM	Chronic HCV Chronic HBV	112 (46.42,53.57)	47.5 ± 19.1	Ir 84.8% Non-Ir 15.2% (most Afghanian)	71.4%	DM 6.25% Previous anti-TB treatment0.9% Chronic liver disease :0.9% concomitant use of hepatotoxic drug 0.9% IDU 0.9% Alcohol consumption 0.9%	ALT/AST > 3 UNL + symptoms of hepatitis OR ALT/AST > 5 UNL OR Symptoms of Hepatitis OR jaundice ± abdominal sign and symptom	Causality European Union classification Preventability Schumock & Thornton Severity Hartwig Predictability WHO
Afsharian *et al.* 2007 [31]	Retrospective cross-sectional	Kermanshah 1375 – 1383	–	–	723 (38%, 62%)	47.44‡	–	84.8%	HBV 1.52% HCV 5.25% HIV 1.93% HCV + HBV 0.41% HIV + HBV 0.55% HIV + HCV 1.24% HIV + HCV + HBV 1.24%	ALT/AST > 5UNL	–
Khalili *et al.* 2009 [33]	Prospective cohort	Tehran 2007 – 2008	INH RIF PZA ETM	Patients < 18 Years History/Evidence of Liver Dysfunction Suspected MDR, XDR	102 (33.3, 66.7)	43.21 ± 18	Ir: 100%	–	CVD 13.72% GI upset 6.66% DM 6.86% Rheumatologic disease 2.94% HIV 31.37% HBV 7.84% HCV 27.45% IDU: 31.37% Alcohol Consumption: 9.8% Smoking: 48.03%	ALT/ AST > 3 UNL + Symptoms of Hepatitis OR ALT/AST > 5 UNL Cholestatic Hepatitis ALP > 2 UNL + jaundice or hyperbilirubine-mia, pruritus	ADR Definition WHO Severity† WHO toxicity classification
Baghaei *et al.* 2010 [34]	Prospective cross-sectional	Tehran 2006 – 2008	INH RIF	–	761 (52,48)	52.44 ± 21.43	Ir 81.2% Afghan 18.2% Other 0.6%	100%	HIV : 5.65% DM: 19.71% HBV: 1.31%	–	–

ALT: Alanine transaminase; AST: Aspartate aminotransferase; Bil: Bilirubin; DIH: Drug-induced hepatotoxicity; DM: Diabetes mellitus; ETM: Ethambutol; INH: Isoniazid; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IDU: Intravenous drug use; Ir: Iranian, GI: Gastrointestinal; ALP: Alkaline phosphatase; LFT: Liver function tests; M: Male; MDR-TB: Multidrug resistant TB; N: Number; PZA: Pyrazinamide; RIF: Rifampin; STR: Streptomycin; ULN: Upper limit of normal; WHO: World Health Organization; XDR- TB: Extensively drug resistant.

Table 4. Characteristics of studies that mainly assessed drug-induced hepatotoxicity (continued).

Author Year of publication	Study design	City/ duration	Treatment protocol	Exclusion criteria	Participants					Definitions	
					N (F%, M %)	Age Year ± SD	Nationality	% of pulmonary TB	Comorbidities	DIH	Other
			PZA ETM						HCV: 1.7% Alcohol Consumption 0 Smoking: 27.59%		
Baniasadi *et al.* 2010 [27]	Open-label clinical trial	Tehran	INH RIF ETM PZA	Alcohol consumption Viral hepatitis Hemoptysis Abnormal baseline LFT Chronic disease (asthma, liver, kidney) Use of other hepatotoxic drug HIV Liver TB Moribund state	32 (46.87,53.13)	73.41 ± 6.72	Ir 96.87%	100%	–	AST/ALT > 5 ULN OR Total bil > 1.5 mg/dl OR AST/ ALT>ULN+hepatitis symptoms	–
Ghasemi Barghi *et al.* 2011 [32]	Retrospective cross-sectional	Qazvin 2004 – 2010	INH RIF PZA ETM/STR	Baseline abnormal LFT Chronic liver diseases or cirrhosis History of alcohol/drug abuse HBV HCV HIV Use of other hepatotoxic drug Non-Ir patients Nonclassic treatment Cases of treatment failure MDR TB	324 (59.8,41.2)	42 ± 12.1	Ir: 100%	100%	–	Symptoms of hepatitis (N/V, abdominal pain or jaundice) OR ALT > 5 UNL	–

ALT: Alanine transaminase; AST: Aspartate aminotransferase; Bil: Bilirubin; DIH: Drug-induced hepatotoxicity; DM: Diabetes mellitus; ETM: Ethambutol; INH: Isoniazid; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IDU: Intravenous drug use; Ir: Iranian, GI: Gastrointestinal; ALP: Alkaline phosphatase; LFT: Liver function tests; M: Male; MDR-TB: Multidrug resistant TB; N: Number; PZA: Pyrazinamide; RIF: Rifampin; STR: Streptomycin; ULN: Upper limit of normal; WHO: World Health Organization; XDR- TB: Extensively drug resistant.

Table 5. Different aspects of hepatotoxicity in studies that mainly focused on hepatotoxicity.

Ref.	% of DIH (F%, M %)	Age (year ± SD)	Onset mean (day) (range)	Symptoms/ LFT rise	Severity (% in DIH patients)	Management/ mean days to enzyme reduction	Re-challenge process	N patients with second episode of DIH after re-challenge	Comorbidities	Associated factors	
										Significant	Nonsignificant
[28]	5.50% experienced 5 – 15 ULN On day 15 0.6% : 15UNL On day 30th	–	–	With LFT rise ALT/AST rise 22% On day 15th 4.2% On day 30th	Mild 27.94%‡ Moderate 60.29% Severe 10.29% Very severe 1.47%	–	–	–	–	–	–
[18]	27.7% (45.16,54.83) Pulmonary TB: 58.6%	46 ± 3	16.7 ± 3.2 (80.6% in 1st m, 6.45% after 6 m)	–	§Moderate 16.12% Severe 77.41% Lethal 6.45%	DC of hepatotoxic drugs/ alternative regimen ETM, CIPX and AMK or STR until LFT normalization	INH: gradually over 1st w RIF: gradually over 2nd w PZA: gradually over 3rd w	0	–	–	Age Sex Nutrition Nationality Use of other hepatotoxic drugs
[31]	5.1% (45.94,54.05) Pulmonary TB 75.6%	49.71 ± 18.19	12.4 ± 3.3	–	–	–	–	–	HBV 2.7% HCV 10.8% HIV 2.7% HCV + HBV 2.7% HIV + HBV 2.7% HIV + HCV 2.7% HIV + HCV + HBV 2.7%	Age > 65 y	Sex TB type HIV HCV HBV
[33]	31.37%	–	14.17 ± 9.67	Symptom/LFT rise ALT > 3 – 5 ULN + GI symptoms 56.25% With LFT rise (ALT > 5 ULN) 43.75 %	*Moderate 59.37% Severe 25% Very Severe 15.6%	DC 7.5 ± 4.6	ETM full dose from the 1st day plus RIF (gradually in 3 days from initiation) INH from 4th day gradually in 4 days PZA: after INH, gradually in 3 days	13 patients 40.6% RIF 1 INH 3 PZA 9	–	HIV HCV Abnormal LFT baseline Concomitant Hepatotoxic drug use (ranitidine, MTX, CMX, nevirapine, lovastatin, methyldopa, pioglitazone)	Age HBV Alcohol ingestion

*Based on WHO Toxicity Classification Standards: mild (ALT/AST < 2 × ULN), moderate (ALT/AST 2.5 – 5 × ULN), severe (ALT/AST 5 – 10 × ULN), very severe (ALT/AST > 10 × ULN).
‡For these studies, the severity of hepatotoxicity is calculated based on WHO definition.
§Based on Hartwig and Siegel questionnaire.
AMK: Amikacin; CIPX: Ciprofloxacin; CMX: Cotrimoxazole; CVD: Cardiovascular disease; DC: Discontinued; DIH: Drug-induced hepatitis; DIH: Drug induced hepatotoxicity; DM: Diabetes mellitus; DM: Diabetes mellitus; ETM: Ethambutol; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus positive; IDU: Intravenous drug use; INH: Isoniazid; LFT: Liver function test; LFT: Liver function test; M: Male; m: Month; MDR-TB: Multidrug resistant TB; MTX: Methotrexate; PZA: Pyrazinamid; RIF: Rifampin; STR: Streptomycin; ULN: Upper limit of normal; W: Week.

Table 5. Different aspects of hepatotoxicity in studies that mainly focused on hepatotoxicity (continued).

Ref.	% of DIH (F%, M %)	Age (year ± SD)	Onset mean (day) (range)	Symptoms/ LFT rise	Severity (% in DIH patients)	Management/ mean days to enzyme reduction	Re-challenge process	N patients with second episode of DIH after re-challenge	Comorbidities	Associated factors	
										Significant	Nonsignificant
[34]	13.0% (57.6,42.4)	54.84 ± 22.91	17.53 ± 19.42 (1 – 125) (most in the first 2 w, 4.0% after 2 m)	Symptoms significantly higher in DIH Anorexia 48.5% Nausea 75.8% Vomiting 61.6% Abdominal pain 27.3% Jaundice 22.2% Diarrhea 4% Decreased level of consciousness 7.1% Fever 12.1%	-	DC 10.26 ± 6 5.95 (0 – 32)	ETM,INH,RIF,PZA initiated one by one and increased gradually	16 patients 16.2% DIH 3 times relapsed in 2 patients 2.0%	HIV 7.1% DM 18.2% HBV 5.1% HCV 9.1%	Age > 65	Sex Nationality Smoking Opium abuse HIV HBV HCV DM Use of other hepatotoxic drugs (NSAIDs, steroids, anticonvulsants)
[27]	37.5%	–	4.67 ± 4.58	Symptomatic:100% LFT rise (AST/ALT > 5 ULN) 50% Total bil > 1.5 mg/dl 25%	–	DC 8.17 ± 3.76	–	–	–	–	Age Sex Weight DM
[32]	4.9% (62.5,37.5)	52	25.25(13 – 45)	Symptomatic :31.25%	Severe: 56.25‡ Very sever: 43.75	DC 23.45 (14 – 43)	–	0	–	–	Sex Age

*Based on WHO Toxicity Classification Standards: mild (ALT/AST < 2 × ULN), moderate (ALT/AST 2.5 – 5 × ULN), severe (ALT/AST 5 – 10 × ULN), very severe (ALT/AST > 10 × ULN).

‡For these studies, the severity of hepatotoxicity is calculated based on WHO definition.

§Based on Hartwig and Siegel questionnaire.

AMK: Amikacin; CIPX: Ciprofloxacin; CMX: Cotrimoxazole; CVD: Cardiovascular disease; DC: Discontinued; DIH: Drug-induced hepatitis; DIH: Drug induced hepatotoxicity; DM: Diabetes mellitus; DM: Diabetes mellitus; ETM: Ethambutol; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus positive; IDU: Intravenous drug use; INH: Isoniazid; LFT: Liver function test; LFT: Liver function test; M: Male; m: Month; MDR-TB: Multidrug resistant TB; MTX: Methotrexate; PZA: Pyrazinamid; RIF: Rifampin; STR: Streptomycin; ULN: Upper limit of normal; W: Week.

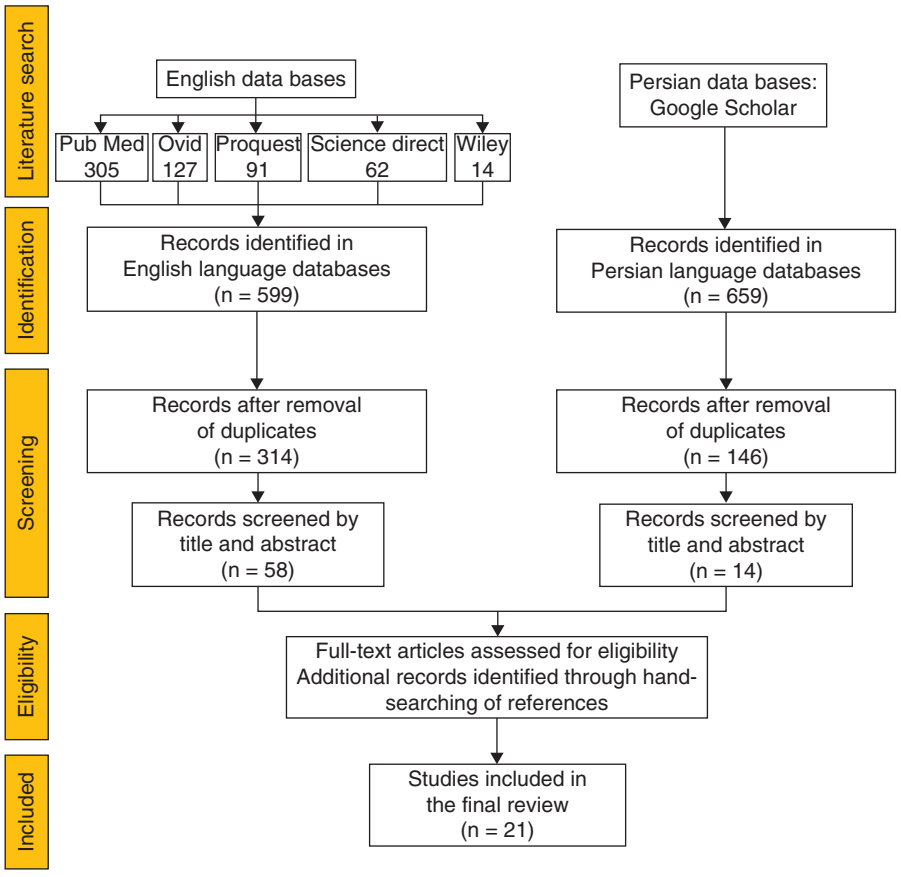

Figure 1. Search process and number of eligible studies.

countries [3]. In our review, only three studies included MDR cases and none assessed extensively drug-resistant TB. Due to the heterogeneities in treatment of MDR cases regarding medications, treatment duration and whether the administered drugs are supervised or not, the comparison of different studies is difficult [45]. In these studies, the three most reported ADRs were hearing loss, hepatitis and psychosis/suicide attempts. However, the orders of frequency were not the same through these studies [2,23,24]. The proportion of patients who developed ototoxicity varied widely throughout our studies and was between 0.31 and 46%. This wide range can be attributed to the differences in treatment regimens. The upper limit of this range (14.5 – 46%) belonged to studies on MDR-TB cases in which patients received amikacin. The lower side was reported in sensitive TB cases (0.31 – 1.3%), among them limited number of patients received streptomycin as an alternative to ethambutol. This pattern is in agreement with previous literature in which ototoxicity was more prevalent in the treatment of MDR-TB patients (41.8%) [46] compared with drug-sensitive TB (1.7%) [5]. However, patients with MDR-TB in our review received neither capreomycin nor kanamycin both of which are known to have auditory adverse effects [41]. Psychosis and suicide ideation were among common ADRs in studies on MDR-TB patients [2,23,24]. The proportions reported in our reports were comparable to Shin *et al.* [47] but were lower than Törün *et al.* [48].

4.2 Factors associated with ADR

Seven studies evaluated factors that may potentially increase the susceptibility to ADRs. However, in some of the articles only factors with significant correlation were mentioned and the evaluated factors (without regard to the significance of association with ADRs) were not clearly mentioned. Demographic factors were evaluated as risk factor in a number of studies. In contrast to other studies [38,39,49], none of our articles found increased age as a significant risk factor. Female gender was found to be a significant determinant of ADRs [17,22], which is in line with other studies [38,39,44,49]. Several studies reported that MDR-TB cases are more vulnerable for ADRs [3,39]. This was determined in the study that included both patients with drug-sensitive and MDR-TB cases [24]. In one of the included studies, HIV-positive status significantly enhanced the chance of specific ADRs [20]. Lack of significance of this factor in other studies might be attributed to unavailability of HIV serostatus for many patients [16,17,22] and the low number of HIV-positive patients in studies [19,23,24]. Nutritional status, which was

shown to be a risk factor for developing ADR [37], within the Iranian study population.

4.3 DIH determinates, associated factors and management

Hepatotoxicity is shown to be one of the most frequent side effects of anti-TB treatment [1]. DIH is also the leading cause of treatment interruption in this patient population [50,51]. Heydari *et al.*, in a retrospective study of 534 pulmonary TB patients, found that DIH was responsible for 25.5% of treatment interruptions or delay [52]. This was also reported by Khalili *et al.* [33]. In almost all of the studies (20 out of 21) included in our review, hepatotoxicity was addressed. According to our review, 9.28% of patients who received anti-TB regimen ultimately developed DIH. Although a wide variation in proportion of patients (from 2.5% [26] to 45.3 [20]) and definitions exist. During the standard TB treatment, the range of incidence of DIH is reported to be between 2 and 28% [1,53], which represents the variation across studies all over the world. The incidence is reported to be 3% in Canada and the USA, 4% in the UK, 11% in Germany, 5% in Hong Kong, 5.3% in Singapore, 16.1% in Taiwan, 36% in Japan, 8 – 36% in India, 9.9% in Argentina [50,53] and 15% in Egypt [4]. In a systematic review of the published literature in China, the overall incidence of hepatic injury was 11.9% [43]. These diversities in the rate of hepatotoxicity can be attributed to the lack of uniformity in the definition of hepatotoxicity, the population [1], treatment regimens and types of monitoring [4].

In six studies of the present review, the investigators evaluated the factors associated with development of DIH. None of these studies found female sex as a risk factor. However, this was a risk factor for hepatotoxicity in several other studies [1,35,50]. Nevertheless, this factor was not revealed to be treatment limiting or statistically significant and some of the studies did not show an increased risk of DIH in women [4,54]. Two of our studies found that patients older than 65 years were significantly at higher risk for DIH [31,34]. Despite the fact that increasing age is among risk factors for DIH [1,4,35,50], there are studies like some of our reports in which no association was determined in this regard [4,18,27,32,33,54]. The correlation between concomitant use of other hepatotoxic agents and DIH was evaluated in three studies but a significant association was recognized in only one [33]. Lack of finding a correlation between this factor and DIH may be due to the differences in concomitant agents among studies [33,34]. Coinfection with HBV [1,50,54], HCV [1,4,50] and HIV [50] are suggested to be the risk factors for DIH. These coinfections were evaluated in three studies, and only in the study by Khalili *et al.* [33] it was demonstrated that patients with HCV and HIV coinfections were significantly more susceptible to DIH. Lack of this association in other two studies [31,34] may be somehow due to the fact that viral hepatitis and HIV serostatus were not checked for all of the patients and the frequency of positive patients was not representative of a real distribution of these infections. It was also proposed that lack of association between hepatotoxicity and viral hepatitis coinfection might be due to the sole consideration of being positive or negative for viral markers without considering the chronic liver injury or chronic hepatitis [31]. In two studies that only included TB patients coinfected with HIV, the frequency of DIH was 14.5% [30] and 20% [6]. Unfortunately, none of the studies exactly determined the number of HIV patients receiving antiretrovirals while they were under TB treatment. It should be noted that the impact of HIV in development of DIH cannot be separated from that of antiretroviral therapy or viral hepatitis coinfections in these patients [34]. Three studies could not identify any specific risk factor for DIH despite evaluating the role of age and sex in this regard [18,27,32]. The mean onset of the DIH was between 4.67 and 25.25 days after treatment initiation (as mentioned is six studies), which is consistence with other studies that reported most of the cases of DIH in the first two months of treatment [1,53]. It is assumed that the majority of patients recover spontaneously from the DIH by discontinuation of the culprit drugs [35], and this was the modality mentioned in six studies that addressed the management of DIH in our review. It is an accepted method to reintroduce the medications after resolution of the DIH [53]. Based on the data of four studies, it was found that 16.26% of patients re-experienced the DIH after reinitiation of the anti-TB medications. This is higher than the study by Sharma *et al.*, in which they found that DIH reoccurred in 10.9% of the patients [51]. The low frequency of recurrence found by Sharma *et al.* might be attributed to the differences in patient population because they excluded patients at high risk for hepatotoxicity [55]. However, the prevalence of DIH recurrence was 24% in another study [56]. Finally, it is worth mentioning that this serious adverse effect can result in considerable morbidity and mortality [1] and can decrease the effectiveness of treatment [1,53]. In our review, the major cause of ADR-induced mortality was DIH and it was shown that death rate was higher in patients who developed DIH [16,29,34].

5. Conclusion

The review of Iranian studies shows that patients receiving anti-TB medications are vulnerable to a variety of adverse effects. Among them, the most frequently reported ones were hepatotoxicity, rash and ototoxicity. To the best of our knowledge, this is the first review of the published literature on adverse reactions of anti-TB treatment regimen in Iran. However, the limitation of this review is particulary related to the paucity of well-designed studies that mainly concern ADR. Many of the studies lacked some of the data regarding patients' characteristics. Also, discrepancies were noted about the categorization of ADRs, definitions, patient populations, concomitant medications and so on. The causality assessments were conducted in limited studies, which might have led to the misclassification of diagnosis.

6. Expert opinion

The ADR pattern in general was comparable to other studies in terms of frequently reported ADRs, the most common ADRs and number of ADRs per patients. But we faced the higher proportion of patients experiencing ADRs to the total patients undergoing TB treatment. Because of the aforementioned heterogeneities of the studies on MDR-TB cases in the text, it was difficult to compare the results within MDR-TB population. But the whole pattern of common ADRs with slight difference was also comparable to other studies. Associated factors with ADRs in the first section were almost similar to other studies (e.g., female gender, MDR-TB, and HIV-positive patients), except the age of patients that was not found to have significant association in none of our studies. Majority of the studies were similar in considering the characteristic and quality of studies. Many studies did not include any specific definition for ADR and they did not assess causality, preventability and severity of ADRs. Most of the authors only reported ADRs of the combinations of anti-TB medications rather than reporting for individual agents. Moreover, a large amount of articles did not report the onset and duration of ADRs. Additionally, the studied populations were mostly sensitive TB cases and were hospitalized. Many of the articles lacked some necessary explanations and details. All of the above-mentioned points could be considered as confounding factors. These factors make the comparison between the studies difficult or evan sometimes unreliable because the available data do not provide enough informative bases for the comparison of the results. These can also lead to studies with lower quality. Nevertheless, we did our best to extract the data mentioned in the articles in a way to be similar as much as possible in order to eventually achieve some conclusions. Another consideration is that different approaches of physicians and pharmacists in conducting studies can make the results of the studies somehow different. All of the included studies in this review were concerned about DIH. This shows the high importance of this ADR in patients receiving anti-TB medications. Among the causes of drug-related mortality in TB patients, DIH stands first, followed by neuropsychiatric events associated with second-line agents used for the treatment of MDR-TB. This finding emphasizes on the roll of anti-TB medication-induced DIH. We calculated the proportion of Iranian patients who developed DIH; however, these data need to be interpreted cautiously. One of the most important points that facilitate pooling data of different studies together is the consistency between the studies' inclusion and exclusion criteria. Historically several risk factors are suggested to be associated with increased incidence of DIH. The different approaches of the articles with the inclusion of patients with these risk factors along with the different definition of DIH can make the conclusion difficult. Currently, the only intervention that is recommended for the management of the DIH is discontinuation of the regimen that interrupts treatment as was noted in the included studies. However, most of the authors did not address the consequences of this interruption. Finally, it worth mentioning that the included studies did not focus on the differences of the ethnicities among Iranians in the development of ADRs and none were multicentral. Therefore, the authors suggest that researchers follow these areas.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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