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Anti-tuberculous Drug-induced Hepatotoxicity: A Retrospective Look onto Abu-Dhabi Tertiary Health Care Center Sheikh Khalifa Medical City (SKMC) Tuberculosis Patients Over a 7 Years' Period

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The most effective tuberculosis treatment currently available is the 6-months course regimen utilizing isoniazid (INH), rifampicin (RIF), Ethambutol (ETB) and pyrazinamide (PYZ). The most serious side effect, which limits the use of these first line anti-tuberculosis medications, is hepatotoxicity, which may be fatal. TB is one of the commonest infectious diseases in the United Arab Emirates (UAE), due to the large number of immigrant workers from countries endemic for TB. Sheikh Khalifa Medical City (SKMC) is the largest tertiary care hospital in the UAE and cares for a majority of tuberculosis patients in Abu-Dhabi.

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The Purpose: To find our incidence of DIH, risk factors for developing DIH and which drug of the known 4 anti-tuberculous medications caused more hepatotoxicity. We also looked at the patterns of AFB drug-resistance on cultures to report the incidence of single-drug and multi-drug resistant strains.
Design: A retrospective observational study of all tuberculosis patients admitted to SKMC in UAE between 2005-2011.
Results: 1047 tuberculosis patients admitted between 2005-2011, 450 were excluded and 597 were included in this study. The incidence of DIH was 3.2%, the risk factors for DIH were ethnicity (Asians were 63.2%), female gender (47%) and diabetes as a comorbidity. The majority of DIH cases happened in the first 2 weeks of treatment (58%), and INH was the commonest drug causing DIH among anti-TB medications (57%).
Conclusion: Tuberculosis remains more common in Asian immigrants among any diverse population like UAE and USA. Incidence of DIH in tuberculosis patients in our diverse, multi-national population was similar to that reported from USA, supporting the recommendation of liver function testing every two weeks from initiating ATT treatment up to one month, then monthly follow up until the end of the treatment course or if any new symptoms occur.

Keywords: Tuberculosis (TB); Acid Fast Bacilli (AFB); Drug-induced Hepatitis (DIH); Latent Tuberculosis Infection (LTBI); Antituberculosis Drug-induced Hepatotoxicity (ATDH).

1. INTRODUCTION

Over the past decade, the incidence of Tuberculosis (TB) has been increasing in different areas of the world, especially in the Gulf Cooperation Council (GCC) countries (Saudi Arabia – Qatar – Oman – UAE – Kuwait – Bahrain). For example, in Kuwait there has been an increase in the annual incidence of TB by 2.3% between 1989-1999 [1]. More recent regional data on the complications and toxicity of anti-tuberculosis medications are not available.

According to WHO latest updates, tuberculosis is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2012, 8.6 million people developed symptomatic TB and 1.3 million died from it. The majority of deaths were among population aged 45 years or younger, which indicates the persistence of a problem in early recognition and timely treatment of this potentially fatal infection [2].

Nowadays, we are well equipped with sensitive, specific and readily available diagnostic tools, as well as very effective therapies. These advances has been reflected in the latest data published by WHO emphasizing that the mortality rate of TB has declined by 45% over the past 22 years [2]. However, we are somewhat limited by side effects of these medications, most pronounced is hepatotoxicity. Other limitations are loss of follow-up during patient treatment, patient incompliance, and the coexistence of TB and immunosuppression, like in AIDS and cancer patients, making cure more difficult and side effects more prevalent.

The most frequent adverse effects of antituberculosis treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders. Hepatotoxicity is the most serious one and is the focus of the present review. Antituberculosis drug-induced hepatotoxicity (ATDH) causes substantial morbidity and mortality and diminishes treatment effectiveness. Asymptomatic transaminase elevations are common during antituberculosis treatment, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time.

Most international published data collected from major institutions have reported that DIH is relatively becoming more common, and there are some identified risk factors like pre-existing liver disease and low body mass index [3]. However, there is very limited research done about DIH in our gulf region, especially in United Arab Emirates (UAE). The focus of this retrospective study would be: finding the incidence of DIH, its risk factors, the most hepatotoxic drug among different ethnicities, and most prevalent time of onset of DIH.

2. METHODS

A retrospective study of all tuberculosis admissions at our institution during a 7 years period: from January 2005 until January 2011. The excluded patients were those younger than 13 years of age, those who had insufficient

laboratory follow up (defined as less than 4 weeks from starting anti-tuberculous therapy (ATT)), patients who had atypical mycobacteria on culture, as well as any patient who had acute viral hepatitis or decompensated liver disease. The software used for data analysis was MedCalc statistical software, version 13.0.6.

Data on patients' demographics (age, gender, and ethnicity), co-morbidities (presence of diabetes mellitus, pre-existing liver disease, renal failure, organ transplant and cancer), body weight, body mass index (BMI), and baseline transaminases/bilirubin were captured for the cohort of patients in the 7 years.

Also, we captured the clinical course (including DIH and other complications), methods of diagnosis and treatment outcome.

Important definitions used in this study analysis and discussion: drug-induced hepatitis (DIH) is defined as elevation of serum alanine aminotransferase (ALT) enzyme level >2 times above the upper limit of normal (> 100 IU/L as per our institution's lab normal reference values) in symptomatic patients, or elevation of serum ALT enzyme level > 3 times above the upper limit of normal (>165 IU/L as per our institution's lab normal reference values) in asymptomatic patients. Multi-drug resistant (MDR) TB is defined as resistance to isoniazid (INH) and rifampicin (RIF), with or without resistance to other first-line ATT drugs (WHO).

2.1 Laboratory Data

Acid fast bacilli are identified from clinical samples by auramine immuno-fluorescent (RAL diagnostics) microscopy, liquid and solid media culture and the GenXpert MTB/RIF (Cepheid) molecular assay. Patient samples are decontaminated as described previously [4]. Liquid media from the BACTEC MGIT 960 system (Becton Dickinson) is inoculated in incubated for 42 days [5]. Consecutively BBL Lowenstein Jensen solid media (Becton Dickinson) is also inoculated and incubated at 36'C for the same period of time. Mycobacterium tuberculosis positive cultures are confirmed with Ziehl Neelsen stain and the BD MGIT TBc identification test (Becton Dickinson). Antibiotic sensitivities to isoniazid, rifampicin, ethambutol and pyrazinamide are performed on all Mycobacterium tuberculosis isolates with the BACTEC MGIT 960 system (Becton Dickinson) [6,7].

3. RESULTS AND DATA ANALYSIS

3.1 Demographics

The number of patients found admitted with TB between 2005-2011 was 1047, while the cohort of patients included in our study was 597 patients. We excluded the patients who were younger than 13 years of age, and who had atypical mycobacteria on culture. Those who had confirmed acute viral hepatitis were excluded from the study of anti-tuberculous therapy-induced hepatotoxicity (Flowsheet 1).

All diagnosed patients were started on the classic four first-line ATT medications, doses adjusted by body weight, with vitamin B6 50 mg daily.

3.2 Patient Characteristics (Table 1)

Majority of the patients – 73% - were males (437 males versus 160 females). Average age of the patients was 34 years (range: 13-83 years). The mean body mass index (BMI) was 20.8 kg/m^2 (range: 10-45 kg/m^2).

Upon reviewing the nationalities of the patients with tuberculosis studied at SKMC over the past 7 years, we decided to group them into 5 main groups: Asia – Middle East & North Africa (MENA) – Africa – Europe - Americas – Australia.

Of note, the majority of our tuberculosis cases (75.5%, n= 450) were from Asia, in descending order: 163 patients from India, 153 patients from Bangladesh and Pakistan, 73 patients from Philippines, 26 patients from Indonesia, 24 patients from Nepal, 7 patients from Sri Lanka, and 1 patient from each of: Afghanistan, China, Malaysia, Uzbekistan. Our MENA region listing included the following countries: GCC countries (Saudi Arabia – Qatar – UAE – Kuwait – Bahrain - Oman), Palestine, Syria, Lebanon, Jordan, Iraq, Iran, Yemen, Morocco, Tunisia, Algeria, Libya, Egypt, Sudan, Mauritania, and Somalia.

3.3 Co-morbidities

Among the comorbidities we documented in our tuberculosis patient population at SKMC were: diabetes, organ transplant, HIV status, viral hepatitis B and C status, End-Stage Renal Disease (ESRD) patients requiring hemodialysis, and confirmed cancers. Only 0.3% (n=2) and 0.5% (n=3) of the patients had organ transplants

Table 1. Clinical characteristics of the patients

Characteristics	Total
Age-yr	
Median	34
Range	13-83
Gender- no (%)	
Male	437 (73)
Female	160 (27)
Body Mass Index-kg/m^2	
Mean	20.8
Ethnic group-no (%)	
Asia:	450 (75.5)
India	163
Pakistan	153
Bangladesh	153
Phillipines	73
Indonesia	26
Nepal	24
Srilanka	7
Afghanistan	1
China	1
Malaysia	1
Uzbekistan	1
MENA	81 (13.5)
Africa	60 (10.05)
Europe	2 (0.003)
Americas	2 (0.003)
NOS	2 (0.003)
Comorbidities-no (%)	
Diabetes	73 (12.2)
HBV	11 (1.8)
HCV	5 (0.8)
HIV	3 (0.5)
Cancer	3 (0.5)
Organ transplant	2 (0.3)
Hemodialysis	8 (1.3)
Culture results- no (%)	
INH-R	14 (2.3)
MDR	9 (1.4)
RIF-R	2 (0.3)
PYZ-R	5 (0.8)
Streptomycin-R	4 (0.7)
INH & Streptomycin-R	2 (0.3)
INH & PYZ-R	2 (0.3)
ETB-R	0
Cultures sensitive to all drugs	559 (93.6)
Baseline liver enzymes- IU/L	
ALT	
Mean	26.66
Range	6-557
AST	
Mean	27.52
Range	10-509
Bilirubin	
Mean	12.23
Range	1-219
Albumin	
Mean	32.13
Range	9-49

and confirmed cancers, respectively. Among the total of 597 patients recorded at our tuberculosis registry, only 1.8% (n=11) had positive hepatitis B serology, 0.8% (n=5) had positive hepatitis C serology, and 0.5% (n=3) had confirmed HIV infection. As expected in our patient population, diabetes mellitus was the most prevalent co morbid condition in our studied population; constituting 12.2% (n=73) of the TB patients.

3.4 Multi-drug Resistance

Multi-drug resistant (MDR) TB, as defined by WHO, is resistance to isoniazid (INH) and rifampicin (RIF), with or without resistance to other first-line ATT drugs. In our patient population, only 7 patients (1.2%) had confirmed MDR mycobacterium tuberculosis on culture and sensitivity testing at SKMC laboratory. Of note, none of these patients died during the follow up period, but 2 patients had ATT-induced hepatotoxicity. The highest single drug resistance was to Isoniazid (INH); in 14 cultures (2.3%), while there was no resistance to Ethambutol (ETB) in our patient population (Table 1).

3.5 Drug-Induced Hepatotoxicity (DIH)

The incidence of hepatotoxicity in our 597 patients studied was found to be 3.2% (n=19). The most hepatotoxic drug was *isoniazid*, responsible for 57% of the DIH cases (n=11 out of 19), followed by *pyrazinamide* (n=5), then rifampicin and ethambutol at equal rates (n=2). The most likely time of onset of DIH was at the second week from starting ATT (57.9%), and to a lesser extent up to 4 weeks from initiating therapy (26.3%) (Flowsheet 1).

One patient out of the 11 who developed DIH due to isoniazid was on concurrent Fluconazole therapy for 2 weeks. Also, one patient from the 2 who developed DIH due to rifampicin was on Voriconazole therapy. Other medications used during ATT administration were less likely to cause hepatotoxicity: Prednisolone, piperacillin / tazobactam, Azithromycin, and second line ATT drugs including Moxifloxacin, Amikacin.

Five out of the nineteen patients who developed DIH were symptomatic (nausea, vomiting, abdominal pain), that is 26.3% of the patients who had DIH. Mortality was 1.7% in this group.

3.6 Characteristics of Patients with DIH (Flowsheet 1)

Among the 19 patients who developed DIH, 10 patients were males, 9 patients were females. The median age among these patients was 29 years, which was not very different from the median age of our total study population (30 years). Also, the mean BMI in these patients was 21 kg/m^2, which is similar to the mean BMI of the total study population**.** Patients' nationalities were: 6 Indians, 3 Pakistanis, 3 Middle Eastern, 3 Ethiopians, 2 Bangladeshis, 1 Somali and 1 Filipino. So the 63.2% of patients were from Asia (n=12, RR= 0.83, 95% CI 0.6-1.2, P-value = 0.3), concurring with the total study population.

Among this group of patients, 3 patients had laboratory testing that confirmed HBV infection, one patient had laboratory testing that confirmed HIV infection, and one patient had laboratory testing that confirmed HCV infection (Table 2). Diabetes mellitus was among the significant risk factors for DIH in this patient population (RR = 2.4, 95% CI 1.0-5.4, P-value = 0.04, NNT = 5.48) (Fig. 1).

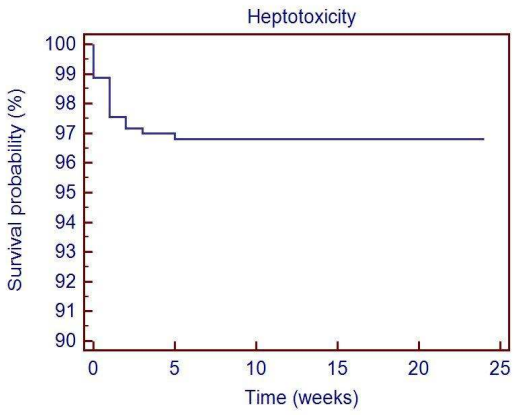
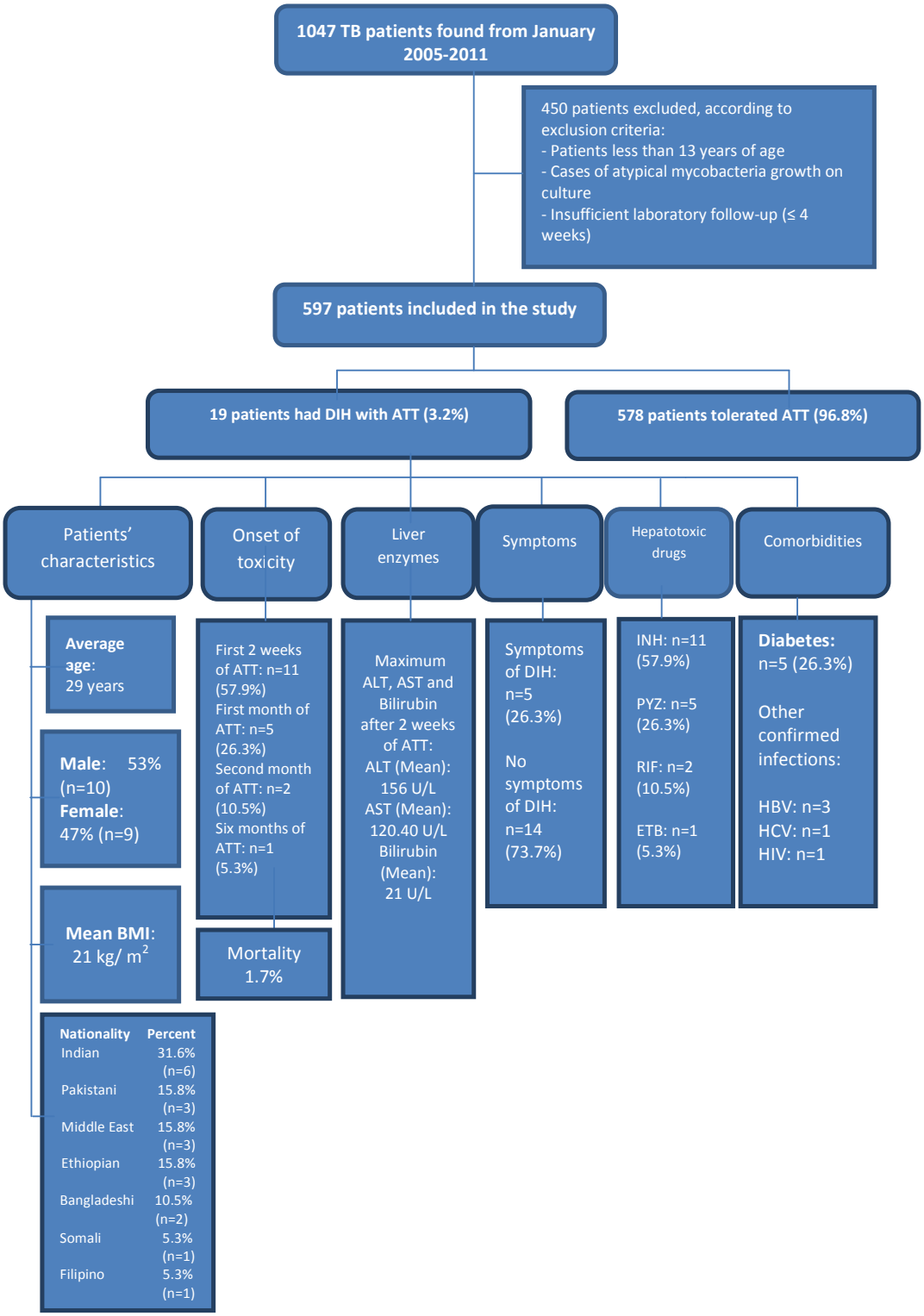


Fig. 1. Kaplan-Meier survival curve

Table 2. Statistical significance of DIH risk factors

	RR	95% CI	P value	NNT
Asian	0.83	0.6-1.2	0.3	7.9
DM	2.4	1.0-5.4	0.04	5.48
HBV	1.9	0.4-9.5	0.43	7.7
HCV	0.86	0.16-4.7	0.86	18
HIV	0.92	0.17-4.8	0.92	33

RR: Relative Risk, CI: Confidence Interval, NNT: Number Needed to Treat



Flowsheet 1. Enrolment and outcomes

Patients could have more than one reason for exclusion. TB denotes tuberculosis, DIH Drug-induced hepatitis, ATT Anti-tuberculous Therapy, BMI Body Mass Index, ALT Alanine Aminotransferase, AST Aspartate Aminotransferase, INH Isoniazid, PYZ Pyrazinamide, RIF Rifampicin, and ETB Ethambutol

4. DISCUSSION

The development of DIH during TB chemotherapy is the most common reason leading to interruption of therapy [8]. The reported incidence of antituberculosis drug-induced hepatotoxicity (ATDH), the most serious and potentially fatal adverse reaction, varies between 2% and 28%. Risk factors are advanced age, female gender, slow acetylator status, malnutrition, HIV, and pre-existent liver disease.

However, it remains difficult to predict what patient will develop hepatotoxicity during tuberculosis treatment. The exact mechanism of ATDH is unknown, but toxic metabolites are suggested to play a crucial role in the development, at least in the case of isoniazid [9].

The reported incidence being 3% in the USA, 4% in the UK, 11% in Germany, 9.9% in Argentina, 13% in Hong Kong, 36% in Japan, 26% in Taiwan and 8-36% in India [10,11,12,13,14,15]. The higher incidence of DIH in the Asian countries might be the result of ethnic susceptibility [9].

Also, the lack of uniformity in the definition of DIH as well as in the use of different anti-TB regimens in different studies might be responsible for this difference. The reported mortality from DIH after the development of jaundice varies from 4-12% [16].

Our incidence in UAE matches that of USA (3.2% and 3% respectively), where hundreds of nationalities live in USA just like UAE [17]. The demographics of our study showed 75.5% of TB cases were from Asia and 11/19 patients who had DIH were from Asia, mainly India.

Several studies have reported that the risk of ATDH increases with advancing age with a few failing to prove it [18,19,20,21]. The majority of our study population was young males, who come to work in UAE, so median age was 29 years in the DIH group.

Previous studies have also shown an increased risk of DIH in women [18,19,22,23]. Despite that female gender was not found to be a predictor for the development of ATDH in other studies [9], our study population showed more DIH in females. We had 437 male patients (73%), 10 patients only developed DIH. On the other hand, out of 160 female patients (27%), 9 patients developed DIH. This indicates clear female predominance 5.6% versus 2.3% in males.

Poor nutritional status has been considered to be one of the factors contributing to a higher incidence of DIH in the developing countries [24,25,26,27]. Drug metabolism pathways, including acetylation pathways, have been showing derangements in states of protein energy malnutrition [28]. In our study we evaluated nutritional status using BMI, where mean BMI in these patients was 21 kg/m^2, which does not support that BMI is a predictive cause for DIH.

The most likely time of onset of DIH in our population was noted at the second week from starting ATT (57.9%), and to a lesser extent up to 4 weeks from initiating therapy (26.3%), in agreement with Makhlouf et al. [3] where toxicity occurred 15–60 days (median: 30 days) after initiation of therapy. In contrast, another study reported that hepatotoxicity occurs generally within weeks to months rather than days to weeks from onset of anti-tuberculous therapy [3,29,30].

The most hepatotoxic drug in our study was isoniazid*;* responsible for 57% of the DIH cases (n=11 out of 19). This corresponds to 1.8% of all the studied population. INH hepatotoxicity has been demonstrated since long time with TB treatment experiences [31,32]. A study of isoniazid for treatment of LTBI involving more than 11,000 patients in Seattle–King County, Washington, reported that symptomatic transaminase elevation of more than five times the upper limit of normal occurred in 0.1% of treatment initiations. Percentage of toxicity in this study was less; as these LTBI patients were otherwise healthy people [33].

Recent smaller treatment studies have reported significant transaminase elevation in 1 to 4% of those treated with isoniazid for LTBI, whereas in other recent large reviews, the incidence of INH–induced hepatotoxicity ranged between 0.1 to 0.56% [33,34,35,36]. Differences among these studies may be due to variations in sample size, differences in the definitions of hepatotoxicity, patient selection criteria, and potential confounding causes of hepatotoxicity.

5. CONCLUSION

To conclude, ATDH in our study population was 3.2%, in agreement with USA DIH incidence, as

it has a multi-national population similar to that of UAE. Risk factors for ATDH in our study population were Asian ethnicity, female gender, and diabetes as comorbidity. The onset of toxicity was mostly in the first 2 weeks of receiving therapy, and INH was the most hepatotoxic medication causing DIH in 1.8% of our patients.

We strongly support the recommendation of liver function testing every two weeks from initiating ATT treatment up to one month, then monthly follow up until the end of the treatment course or if any new symptoms occur.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Approval of our institution research ethical committee was attained.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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