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Prevalence and risk factors of tigecycline-induced liver injury: A multicenter retrospective study

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ABSTRACT

Objective: We conducted this multicenter retrospective study to evaluate the prevalence, clinical patterns, and risk factors for tigecycline-induced liver injury, which is a type of drug-induced liver injury (DILI).
Methods: Inpatients receiving intravenous tigecycline for ≥7 days were included. Patient information was collected to assess possible DILIs. The pattern and severity of tigecycline DILI were evaluated. A multivariable logistic regression model was used to identify the independent risk factors associated with tigecycline DILI.
Results: A total of 986 patients were identified and 397 patients were included in this study. The prevalence of tigecycline DILI was 10.3% (95% confidence interval [CI] = 7.51–13.7%). The most common type of tigecycline DILI was cholestatic, with mild severity observed in most cases. Abnormal baseline alanine aminotransferase levels (odds ratio [OR] = 3.11, 95% CI = 1.55–6.24, P = 0.001), intensive care unit admission (OR = 2.63, 95% CI = 1.32–5.36, P = 0.006), and treatment length (in weeks) (OR = 1.25, 95% CI = 1.05–1.49, P = 0.011) were independent risk factors for tigecycline DILI.
Conclusion: Our results indicate that the prevalence of tigecycline DILI is high, and that the patients at risk should receive special attention.

Introduction

Tigecycline shows promising in vitro activity against antibiotic-resistant gram-negative bacteria and various gram-positive organisms (Perdigão Neto et al., 2020; Pournaras et al., 2016; Yaghoubi et al., 2021). It also exhibits good efficacy for the treatment of skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia (Vardakas et al., 2012). Tigecycline alone or in combination with other antibiotics is used as a potential candidate for the treatment of carbapenem-resistant gram-negative bacterial infections (Doi, 2019). The consumption of tigecycline is high worldwide (Klein et al., 2018). Therefore, physicians are concerned about the safety of its use in clinical settings.

Drug-induced liver injury (DILI) is a common adverse drug reaction that can be demonstrated using impaired liver function tests. Antibiotics make a major contribution to the overall DILI events observed among all classes of drugs (Björnsson, 2017). Tigecycline therapy is sometimes accompanied by slight elevation in aminotransferase levels (Tasina et al., 2011). Liver injury during tigecycline therapy can also be caused by complications of sepsis and multiorgan failure rather than drug hepatotoxicity. LiverTox has a graded tigecycline hepatotoxicity likelihood of E, which is an unproven but suspected cause of clinically apparent liver injury (LiverTox, 2019). Accumulating case reports and retrospective data have indicated that tigecycline is associated with DILI (Kadoyama et al., 2012; Rossitto et al., 2014; Shi et al., 2021; Zha et al., 2020; Zhang et al., 2015). However, limited information is available on the prevalence and patterns of liver injury in cases of tigecycline-induced hepatotoxicity. Therefore, we performed this retrospective study to evaluate the frequency, clinical patterns, and risk factors for tigecycline DILI.

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Methods

Study design and ethics approval

This was a multicenter, retrospective study. This study was approved by the ethics committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (reference number 20210122-31). The requirement for obtaining informed consent from the patients was waived due to the retrospective nature of the study.

Patient inclusion

Inpatients receiving intravenous tigecycline from January 2019–December 2020 at three centers (Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; Affiliated Xiaoshan Hospital, Hangzhou Normal University; Second Affiliated Hospital, School of Medicine, Zhejiang University) were identified. We screened the medical records of patients and extracted the following clinical data: age, sex, body weight and height, intensive care unit (ICU) admission, tigecycline dosage regimen, and treatment length as well as baseline albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and alkaline phosphatase (ALP) levels, and the changing trends during and after tigecycline treatment. Patients who met the following criteria were excluded: (i) tigecycline treatment length less than seven days; (ii) age below 18 years; (iii) lack of essential laboratory examinations to identify the presence of DILI; and (iv) patients with ALT $\geq$ 5 $\times$ upper limit of normal (ULN), ALP $\geq$ 2 $\times$ ULN, or ALT $\geq$ 3 $\times$ ULN and TBIL $\geq$ 2 $\times$ ULN before receiving tigecycline (Andrade et al., 2019; Tuohutaerbieke et al., 2021).

Evaluation of tigecycline DILI

Patients who met one of the following criteria during tigecycline treatment were recognized as having possible tigecycline DILI: (i) ALT $\geq$ 5 $\times$ ULN; (ii) ALP $\geq$ 2 $\times$ ULN; or (iii) ALT $\geq$ 3 $\times$ ULN and TBIL $\geq$ 2 $\times$ ULN (Aithal et al., 2011; Raul J. Andrade et al., 2019). For patients exhibiting biochemical abnormalities before tigecycline treatment, the baseline value was used instead of the ULN.

The causality of liver injury and tigecycline use was assessed according to the updated Roussel Uclaf Causality Assessment Method (RUCAM) (Danan and Teschke, 2016). Patients with RUCAM scores $\geq$ 6 were defined as having tigecycline DILI. For patients with RUCAM scores below 6, it was unreliable to attribute the liver injury to tigecycline treatment; therefore, these patients were excluded from further risk factor analysis.

Clinical patterns and severity of tigecycline DILI

The R value was calculated using the following equation to determine the clinical type of DILI: R = [ALT / (ALT ULN)] / [ALP / (ALP ULN)]. There are three clinical types of DILI: (i) R $\leq$ 2.0, cholestatic; (ii) R $\geq$ 5.0, hepatocellular; and (iii) 2.0 $<$ R $<$ 5.0, mixed (Aithal et al., 2011; Andrade Raúl et al., 2019; Andrade Raul et al., 2019).

The severity of DILI was classified into two grades. Mild levels indicated DILI cases with ALT $\geq$ 5 or ALP $\geq$ 2 and TBIL $<$ 2 ULN, whereas the other cases were moderate or extremely severe (Aithal et al., 2011; Andrade Raúl et al., 2019; Andrade Raul et al., 2019).

Statistical analysis

All continuous results are presented as the mean $\pm$ standard deviation, and categorical results are presented as numbers and percentages. Statistical differences between continuous results were tested using Student *t* test. The chi-square test or Fisher exact test was used for categorical results. Variables with P $<$ 0.2 in single-variable comparisons were included in a multivariable logistic regression model. Backward stepwise multivariable logistic regression analysis was performed to identify the independent risk factors for tigecycline DILI. A two-tailed P $<$ 0.05 was considered to be statistically significant. Relative risk was estimated using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All statistical tests were performed using the SPSS software (Version 26.0).

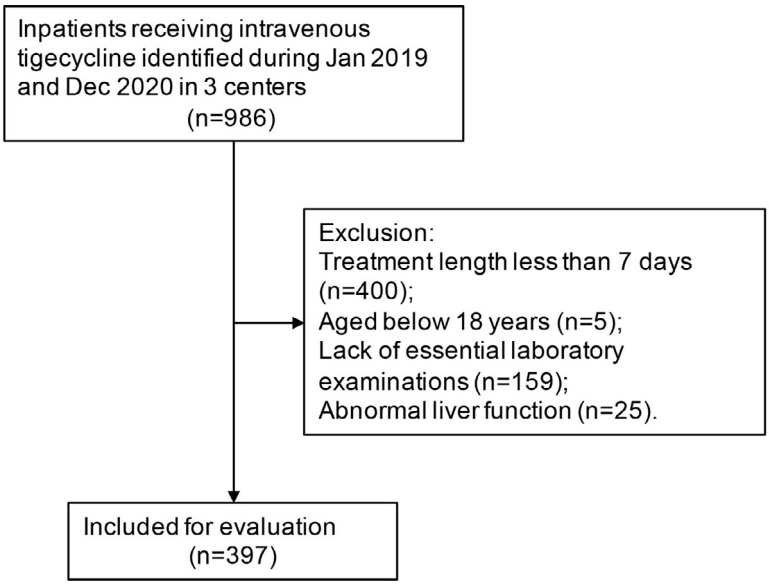

Fig. 1. Flowchart of patient exclusion and inclusion.

Table 1
Demographic characteristic of included patients with or without tigecycline-induced liver injury.

	Total (n=397)	DILI (n=41)	Non-DILI (n=326)	*P*
Male	271(68.3)	29(70.7)	221(67.8)	0.697
Female	126(31.7)	12(29.3)	105(32.2)	0.697
Age (year)	64.0±15.4	64.7±14.0	63.6±15.7	0.643
BMI (kg/m^2)	22.1±3.7	22.3±3.9	22.1±3.7	0.789
ICU admission	164(41.3)	26(63.4)	123(37.7)	0.001
Baseline ALB (g/L)	29.1±4.7	27.8±4.0	29.3±4.7	0.033
Baseline ALB>30 g/L	160(40.3)	11(26.8)	136(41.7)	0.080
Baseline Infection site				
Pulmonary infection	206(51.9)	26(63.4)	162(49.7)	0.087
Intra-abdomen infection	80(20.2)	7(17.1)	68(20.9)	0.547
Skin and soft tissue infection	28(7.1)	1(2.4)	25(7.7)	0.336
Blood stream infection	29(7.3)	3(7.3)	24(7.4)	>0.999
Other or undefined	54(13.6)	4(9.8)	47(14.4)	0.631
Pathogen				
CRAB	131(33)	18(43.9)	102(31.3)	0.122
CRKP	137(34.5)	13(31.7)	113(34.7)	0.702
Other or undefined	129(32.5)	10(24.4)	111(34)	0.180
Underlying liver disease				
Liver cirrhosis*	6(1.5)	0(0)	6(1.84)	>0.999
Cholecystitis or gallstones	69(17.4)	6(14.6)	56(17.1)	0.666
Fatty liver	35(8.8)	5(12.2)	24(7.4)	0.350
HBV infection	18(4.5)	2(4.9)	14(4.3)	0.696
Loading dose applied	164(41.3)	14(34.1)	137(42)	0.318
Maintenance dose				
50 mg every 12h	215(54.2)	22(53.7)	179(54.9)	0.880
100 mg every 12h	181(45.6)	18(43.9)	147(45.1)	0.885
Other	1(0.3)	1(2.4)	0(0)	-
Treatment length/ day	16.2±10.4	20.6±14.4	15.7±10.0	0.040
Baseline TBIL (μmol/L)	15.1±8.7	17.0±11.2	14.9±8.4	0.261
Baseline normal TBIL	321(80.9)	30(73.2)	264(81)	0.282
Baseline ALT (U/L)	29.1±25.7	39.7±34.9	27.8±24.2	0.040
Baseline normal ALT	308(77.6)	23(56.1)	262(80.4)	0.003
Baseline ALP (U/L)	100.5±48.9	101.6±36.6	100.4±42.1	0.845
Baseline normal ALP	254(64)	25(61)	211(64.7)	0.642
Baseline AST (U/L)	29.1±23.1	42.2±37.7	27.4±20.3	0.017
Baseline normal AST	315(79.3)	29(70.7)	263(80.7)	0.181

Data are expressed as patient number (percentage) or mean value ± standard deviation; Statistical differences between continuous results were tested by Student *t* test; chi-square test or Fisher exact test were used for categorical results; DILI, drug-induced liver injury; BMI, body mass index; ICU, intensive care unit; ALB, albumin; CRAB, carbapenem resistant *Acinetobacter baumannii*; CRKP, carbapenem resistant *Klebsiella pneumoniae*; HBV, hepatitis B virus; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase. * Patients with liver cirrhosis were all in Child-Pugh class A.

Results

Patient inclusion and characteristics

A total of 986 patients who received tigecycline treatment were identified and checked to determine if they met the inclusion criteria. The inclusion and exclusion process are presented in Fig. 1. Finally, 391 patients were found to be eligible and were included in the analysis; their demographic characteristics are shown in Table 1.

Prevalence of tigecycline DILI

As shown in Table 2, 71 patients met the criteria of DILI. A total of 12 patients stopped tigecycline treatment because of possible DILI. The RUCAM scale was used to measure the causality of tigecycline and liver injury. Among patients who met the criteria for DILI, 41 had RUCAM scores ≥ 6, and liver injury in these patients was considered to be induced by tigecycline. The prevalence of tigecycline DILI was 10.3% (95% CI = 7.51–13.7%). The demographic characteristics of the patients with tigecycline DILI and non-DILI are also shown in Table 1. The other 30 patients with RUCAM scores < 6 were excluded from further risk factor analysis. Elevated liver enzyme and TBIL levels were common in patients receiving tigecycline treatment. Nearly half of the patients had increased ALP levels above the ULN or baseline after tigecycline treatment (Table 2).

Table 2
Liver injury in patient receiving tigecycline.

	Patients	Percent (%)	95% CI
Meet the criteria of DILI	71	17.9	14.3-22.0
RUCAM score ≥6	41	10.3	7.51-13.7
RUCAM score 3-5	30	7.56	5.16-10.6
Liver function test			
TBIL≥1×ULN	81	20.4	16.5-24.7
TBIL≥2×ULN	43	10.8	7.95-14.3
ALT≥1×ULN	65	16.4	12.9-20.4
ALT≥ 3×ULN	17	4.28	2.51-6.77
ALP≥1×ULN	186	46.9	41.9-51.9
ALP ≥2×ULN	35	8.82	6.22-12.0

DILI, drug-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method, TBIL, total bilirubin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal, baseline value is used instead of ULN for patients with abnormal liver function test before tigecycline treatment.

The clinical patterns and severity of tigecycline DILI are shown in Fig. 2. Among the patients with tigecycline DILI, most cases were identified to be cholestatic, and DILI at mild grade was 85.4% (95% CI = 70.8–94.4%).

Risk factors of tigecycline DILI

The results of direct comparisons of single variables are shown in Table 1, and the variables with P < 0.2 were used in the back-

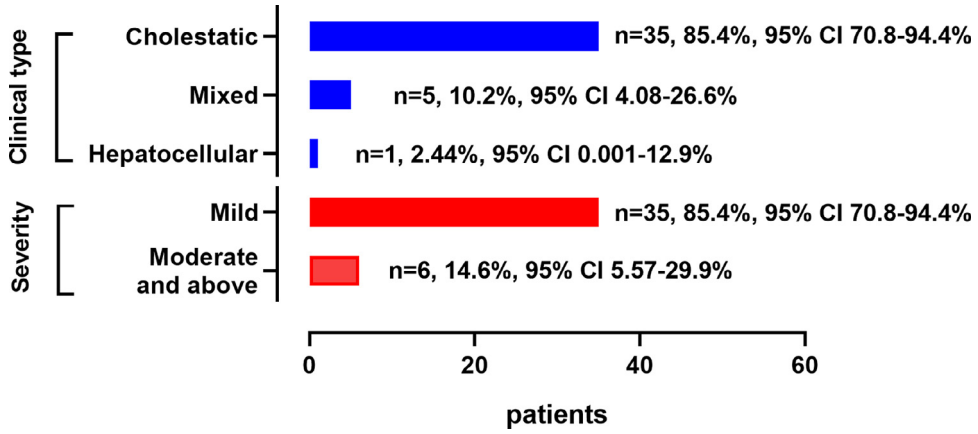

Fig. 2. Type and severity of tigecycline-induced liver injury.

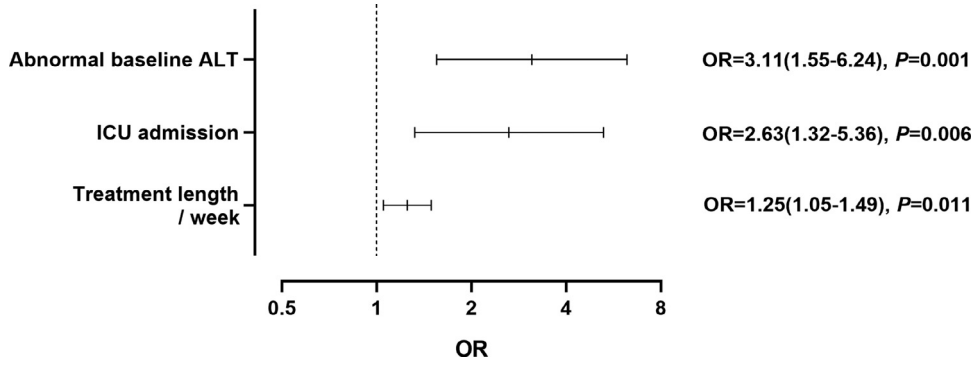

Fig. 3. Independent risk factor for tigecycline-induced liver injury.

ward stepwise logistic regression model. Interestingly, the maintenance dose (standard dose of 50 mg or high dose of 100 mg every 12 hours) was not a risk factor for tigecycline DILI (Table 1). The results of the final logistic regression analysis are presented in Fig. 3. ICU admissions, abnormal baseline ALT levels, and treatment length were found to be independent risk factors for tigecycline DILI.

Discussion

To the best of our knowledge, this is the first multicenter study to evaluate the prevalence, clinical patterns, and severity of tigecycline DILI. Risk factors of tigecycline DILI were also identified here, and the results of this study will be helpful for the clinical application of tigecycline.

In this study, the prevalence of tigecycline DILI was found to be 10.3%. The well-accepted inclusion criteria for DILI were used to screen for patients with DILI, and the RUCAM scale was used to assess the causality of tigecycline and DILI in this study. Thus, the reported prevalence is reliable for the study population. Although there is little data on the prevalence of DILI in patients receiving tigecycline treatment, the prevalence of 10.3% is higher than anticipated. The ALT and ALP elevation rates were 16.4 and 46.9%, respectively. A summary of phase I, II, and III studies of tigecycline concluded that elevated ALT or AST levels were reported in 1%–2% of tigecycline recipients (Rello, 2005). A systematic review and meta-analysis of the safety of tigecycline treatment for various infections included 15 trials and 7654 patients before 2010 and found that the rate of ALT elevation was only 76/3103 (Yahav et al., 2011), which may be due to the lower severity of illness in patients included in these trials (Babinchak et al., 2005; Postier et al., 2004). High rates of abnormal liver function are observed in patients receiving tigecycline treatment who are critically ill and drug-resistant bacteria-infected. A retrospective study comparing the clinical efficacy and safety of high-dose and standard-dose tigecycline in critically ill patients infected with multidrug-resistant bacteria reported an impaired liver function rate of 18% (De Pascale et al., 2014). However, impaired liver function has not been clearly defined in the literature. Fan et al conducted a prospective study to explore the relationship between tigecycline concentration and hepatotoxicity. The overall reported that the frequency of hepatotoxicity was 28.9% (11/38 patients) (Fan et al., 2020). However, the definition of hepatotoxicity in this literature was ALT $>$ 3 ULN or TBIL $>$ 1.5 ULN, which is not widely accepted. Thus, hepatoxicity could be overestimated. Moreover, the causality of impaired liver function and tigecycline use was not assessed in any of these studies. It should be noted that infection is a common risk factor associated with liver injury that is always observed in tigecycline recipients (Surewaard et al., 2018). A recently published retrospective study reported a frequency of 5.7% for tigecycline DILI (Shi et al., 2021). It included patients receiving tigecycline treatment for more than 72 hours; however, DILI caused by antibiotics usually occur after 1 week of treatment (Björnsson, 2017). Moreover, the treatment length of drug-resistant bacterial infections, the most common indication of tigecycline use, is usually not less than 1 week (Kalil et al., 2016).

Our study also revealed that the most common type of DILI is cholestatic, which is consistent with the reports of other studies (Kadoyama et al., 2012; Shi et al., 2021). To date, the specific mechanism of tigecycline DILI remains unclear. Understanding the pattern of tigecycline DILI will be helpful in the prevention and treatment of liver injury (Stine and Lewis, 2016). As ICU patients and patients with severe infections were included in this study, it was difficult to assess the relationship between international

normalized ratio elevation or organ failure and drug hepatotoxicity. This made the grading of severe DILI inaccurate (Aithal et al., 2011). Thus, we only categorized severity into two grades: mild and moderate and above. Most DILI cases are of mild severity. Patients with mild DILI usually recover when the drug is discontinued (deLemos et al., 2016; Zoubek et al., 2020).

Abnormal baseline ALT levels are an independent risk factor for tigecycline DILI. Abnormal baseline ALT levels have also been associated with other DILIs (Hidaka et al., 2020; Wong and Graudins, 2017). It is interesting that ALP elevation is common in tigecycline DILI, whereas abnormal baseline ALP is not an independent risk factor for it. ICU admission is also an independent risk factor. This indicates that patients with severe illnesses are more likely to develop DILI. The Acute Physiology and Chronic Health Evaluation II score, another variable that indicates the severity of illness, was identified as a risk factor associated with tigecycline-related hepatotoxicity in another study (Fan et al., 2020). It may be because ICU patients are more likely to experience hypoperfusion, inflammation, and the use of multiple drugs (Horvatits et al., 2019). Treatment length is associated with tigecycline DILI, which was also found in another study (Shi et al., 2021). This indicates that patients receiving tigecycline should be carefully monitored to assess the efficacy and safety of the drug to avoid unnecessary long-term use of tigecycline. Pharmacologists have attempted to find a safe range of tigecycline concentrations for treatment (Fan et al., 2020). Our study suggests that treatment length should be taken into consideration in future studies to identify a safe range for the use of tigecycline. The results also emphasize that when comparing the prevalence rates of tigecycline DILI with other reports, treatment length should be taken into consideration because this study only included patients receiving tigecycline for $\geq$ 7 days.

It is important to note that dose is not an independent risk factor for tigecycline DILI. A high dose of tigecycline ($\geq$ 100 mg, every 12 hours) is suggested on the basis of the results of pharmacokinetic/pharmacodynamic analysis (Horvatits et al., 2019). However, the safety of high-dose tigecycline remains controversial. In a systematic review and meta-analysis, Xu et al concluded that high-dose tigecycline was associated with more adverse events (Xu et al., 2016), whereas subsequent research studies suggest that there are no statistical differences in the distribution of adverse events between the two groups (Zha et al., 2020). There is limited data on liver injury. The aforementioned retrospective study reported comparable rates of impaired hepatic function in both groups (De Pascale et al., 2014). However, trough concentration was related to hepatotoxicity in a small prospective study, and drug dose was found to be indirectly involved (Fan et al., 2020). A recent retrospective study reported that a high tigecycline dose was associated with DILI; however, the OR was only 1.028 (Shi et al., 2021). Our study indicates that the prevalence of tigecycline DILI is similar in the high-dose and standard-dose groups, and high doses are recommended for the treatment of patients with severe or drug-resistant bacterial infections.

This study had some limitations. Some bias may have existed because of the retrospective nature of this study. The recovery from hepatotoxicity and the contribution of hepatotoxicity to total mortality were not analyzed. Pharmacological treatments against DILIs were not considered and should be evaluated in future studies.

Conclusions

This is the first multicenter, retrospective study to evaluate the prevalence, clinical patterns, and risk factors for tigecycline DILI. The prevalence of tigecycline DILI in this study population was 10.3%, and the most common type was found to be cholestatic. Abnormal baseline ALT levels, ICU admissions, and treatment length were found to be independent risk factors for tigecycline DILI. These findings may aid in the clinical application of tigecycline.

Author contribution

Conceptualization, LY and GH; data curation, ZY, YZ, LY, JJ, and JZ; formal analysis, ZY, YZ, JJ, and LY; funding acquisition, ZY; investigation, ZY, YZ, and LY; methodology, ZY; project administration, LY and GH; resources, ZY, YZ, and LY; supervision, LY and GH; validation, ZY, YZ, JJ, and LY; visualization, ZY and LY; roles/writing: original draft, ZY; writing: review and editing, ZY, LY, and GH. All authors have read and approved final manuscript.

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Ethical approval statement

The study was approved by ethics committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (reference number 20210122-31). Informed consent was waived as part of the approval due to the retrospective nature of the study.

Data availability

All data are shown in the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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