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# Clinical Features and Outcomes of Immune Checkpoint Inhibitor-Associated Cardiovascular Toxicities

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***Background:*** Despite the increasing prevalence of therapies utilizing immune checkpoint inhibitors (ICIs), the associated cardiovascular complications have been poorly reported. Given the fatality of ICI-related complications, especially myocarditis, optimal risk stratification to predict major adverse cardio- and cerebrovascular events (MACCEs) in patients receiving ICIs is mandatory.

***Methods:*** We collected clinical data from patients receiving ICIs, and the primary outcomes were MACCEs, including myocarditis, heart failure, and ischemic stroke. Other systemic immune responses relating to ICIs were also recorded. The median follow-up duration was 3 years.

***Results:*** Among 580 patients, the incidence of MACCEs was 3.9%. Older patients, male patients, and patients with lung cancer, liver cirrhosis, or diabetes had higher risks of MACCEs. There was no significant difference between the use of PD-1/PD-L1 inhibitors or CTLA inhibitors in terms of developing cardiovascular toxicities. The development of ICI-related MACCEs was associated with worse survival. Notably, after re-review by specialists, three patients eventually diagnosed with ICI-related myocarditis had not previously been identified. Only one was treated with pulse steroids, and none survived. The most common concomitant extracardiac immune-related adverse events were myositis/dermatitis, endocrine toxicity and hepatitis.

***Conclusions:*** Collectively, ICIs may lead to severe cardiovascular toxicities and require more attention. Early identification, proper diagnosis, and prompt treatment are pivotal for improving survival.

**Key Words:** Cardiovascular toxicity • Immune checkpoint inhibitor • Myocarditis • PD-1/PD-L1 inhibitor

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) belong to a novel drug class and help the immune system to efficiently recognize and target cancer cells.[1,2] ICIs have been shown to effectively improve the outcomes of patients with various cancer types.[1,3] Recent data suggest that up to 36% of cancer patients could be eligible for ICIs, and more than 3000 clinical trials have been conducted to evaluate the effectiveness of ICIs.[3-5] According to most randomized clinical trials of ICIs, cardiovascular complications are rare events with an incidence of 0.04% to 1.14%.[6] However, in contrast, observations in clinical settings indicate an increase in ICI-associated myocar-

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ditis.[7-9] Given the complexities associated with diagnosis, as well as the heterogeneous clinical presentation of ICI-associated myocarditis, the identification and ascertainment of myocarditis is challenging.[9,10] Although the epidemiology, diagnosis, and management of ICI-related cardiotoxicity have been reported previously, the results have been inconsistent among different cohorts.[7,9,11] Additionally, information regarding ICI-related cardiovascular complications is lacking in Asia. Most importantly, although high doses of steroids and immunosuppressant treatments are suggested as soon as ICI-related myocarditis has been diagnosed, it remains uncertain whether they have been detected early and managed properly in real-world practice. Thus, evidence is urgently needed for this rapidly expanding and vulnerable cohort of patients. Herein, through a multihospital registry, we investigated the incidence and characteristics of ICI-related major adverse cardio- and cerebrovascular events (MACCEs).

## METHODS

### Study design

The registry was specifically designed to collect suspected cases of MACCEs related to ICIs from 2015 to 2017 in three hospitals of Chi-Mei Medical Center. MACCEs, a composite of myocarditis, heart failure (HF) hospitalization and ischemic stroke, were identified by primary care physicians and confirmed by cardiologists, neurologists and oncologists. The diagnoses of HF and ischemic stroke were based on the definitions of clinical guidelines.[12,13] Myocarditis was diagnosed based on a guideline-recommended criteria that incorporate several variables, including clinical, biomarker, and imaging features.[14,15] Extracardiac immune-related adverse events were defined as pneumonitis, hepatitis, colitis, myositis/dermatitis, endocrine disorders such as hypophysitis, pituitary or adrenal insufficiency, and neurologic disorders.[7,16-18] The diagnosis was confirmed by one oncologist and subspecialists. Adverse events were graded using the Common Toxicity Criteria for Adverse Events (version 5.0).[19] This study was conducted in strict accordance with the Declaration of Helsinki on Biomedical Research involving human subjects, and was approved by the local ethics committee (IRB: 10811-010). The requirement for written informed consent was waived. The median follow-up duration was 3 years.

### Types of ICIs

The ICIs in this study included inhibitors targeting lymphocyte-associated protein-4 (CTLA-4), programmed cell death protein1 (PD-1), and programmed cell death-ligand 1 (PDL-1). The drugs used included pembrolizumab (anti-PD1), nivolumab (anti-PD1), ipilimumab (anti-CTLA4), atezolizumab (anti-PDL1), and durvalumab (anti-PDL1).

### Statistics

Continuous variables are presented as the mean ± SD or median (interquartile range), as appropriate, and categorical variables are presented as percentages. Continuous data were compared using unpaired Student's t-tests or Wilcoxon rank sum tests. Categorical data were compared using Fisher's exact test. Hazard ratios (HRs) for MACEs with 95% confidence intervals (CIs) were calculated using Cox regression analysis. Kaplan-Meier plots were applied for survival analysis. All statistical tests were two sided, and 5% was set as the level of significance. Statistical analyses were performed using IBM SPSS Statistics version 24 (IBM, Armonk, New York).

## RESULTS

### Patients' characteristics

In this registry, we retrospectively collected data from 580 patients who received ICIs, of whom 23 developed MACCEs following ICI treatment (Table 1). The incidence of MACCEs was 3.9%. In terms of each MACCE endpoint, three patients had myocarditis, 14 patients had HF hospitalization, and six patients had ischemic stroke. Among the 14 patients requiring hospitalization for HF, six had a reduced ejection fraction at diagnosis. The time intervals to events are shown in Table 1. Compared to the patients without ICI-related MACCEs, those who developed MACCEs were older (59.2 ± 12 vs. 72 ± 6.8 years, p = 0.01), more likely to be male (64.3% vs. 86.9%, p = 0.027), and more likely to have diabetes (28.4% vs. 69.5%, p = 0.001). In terms of cancer types, more of the patients who developed MACCEs had lung cancer (30.3% vs. 47.8%, p = 0.04). Regarding ICI treatment, more than 80% of the patients received anti-PD-1 therapies,

**Table 1.** Baseline characteristics of patients receiving immune checkpoint inhibitors (ICIs) (n = 580)

| Variable | Non-ICI-MACCEs (n = 557) | ICI-MACCEs (n = 23) | p value |
|---|---|---|---|
| Age at ICI initiation, yrs | 59.2 ± 12 | 72 ± 6.8 | 0.01 |
| Male, n (%) | 358 (64.3) | 20 (86.9) | 0.027 |
| Body mass index (kg/m$^2$) | 24.4 ± 32.5 | 23.1 ± 4.3 | 0.83 |
| Comorbidities, n (%) | | | |
| Hypertension | 214 (38.4) | 11 (47.8) | 0.24 |
| Diabetes | 158 (28.4) | 16 (69.5) | 0.001 |
| Heart failure | 16 (2.8) | 0 (0) | 0.71 |
| Coronary artery disease | 19 (3.4) | 1 (4.3) | 0.38 |
| Peripheral artery disease | 2 (0.3) | 0 (0) | 0.92 |
| Atrial fibrillation | 14 (2.5) | 1 (4.3) | 0.46 |
| Chronic kidney disease (≥ stage 3) | 30 (5.3) | 3 (13) | 0.25 |
| Old stroke | 24 (4.3) | 2 (8.6) | 0.56 |
| COPD | 14 (2.5) | 1 (4.3) | 0.45 |
| Liver cirrhosis | 80 (14.3) | 8 (34.7) | 0.04 |
| Autoimmune disease, n (%) | 4 (0.7) | 1 (4.3) | 0.4 |
| Smoking (current or ex), n (%) | 76 (13.6) | 4 (17.3) | 0.82 |
| Baseline SCr (mg/dl) | 1.02 ± 0.85 | 1.28 ± 1.34 | 0.17 |
| Baseline eGFR (ml/min per 1.73 m$^2$)* | 86.6 ± 33.2 | 75.9 ± 31.4 | 0.13 |
| Malignancy, n (%) | | | 0.84 |
| Breast cancer | 4 (0.7) | 0 (0) | 0.94 |
| GI tract cancers (HCC, colon cancer, others) | 209 (35.7) | 10 (43.4) | 0.64 |
| Lung cancer | 169 (30.3) | 11 (47.8) | 0.04 |
| Hematologic cancers | 9 (1.6) | 0 (0) | 0.47 |
| GYN cancers | 22 (3.9) | 0 (0) | 0.21 |
| Genitourinary cancers | 43 (7.7) | 1 (4.3) | 0.73 |
| Thyroid cancer | 7 (1.2) | 0 (0) | 0.52 |
| ENT cancers | 17 (3.1) | 1 (4.3) | 0.63 |
| Melanoma | 31 (5.5) | 3 (13) | 0.44 |
| Other cancers | 56 (10.1) | 0 (0) | 0.18 |
| Class of ICIs, n (%) | | | |
| Anti-CTLA-4 | 17 (3.1) | 1 (4.3) | 0.93 |
| Anti-PD-1 | 493 (88.5) | 20 (86.9) | 0.44 |
| Anti-PD-L1 | 47 (8.4) | 2 (8.7) | 0.83 |
| Extra-cardiac immune-related adverse events, n (%) | | | |
| Endocrine | 20 (3.6) | 5 (21.7) | 0.001 |
| Pneumonitis | 31 (5.6) | 1 (4.3) | 0.63 |
| Hepatitis | 29 (5.2) | 4 (17.4) | 0.03 |
| Colitis | 27 (4.8) | 2 (8.6) | 0.32 |
| Myositis or dermatitis | 29 (5.2) | 7 (30.4) | 0.001 |
| Neurologic disorders | 27 (4.8) | 3 (13) | 0.11 |
| MACCE (myocarditis + HF hospitalization + ischemic stroke) | | 23 | |
| Time to events, months (IQR) | | 3, 11 | |
| Myocarditis, n (%) | | 3 (13) | |
| Time to events, days (median)# | | 14 | |
| HF hospitalization, n (%) | | 14 (60.8) | |
| Time to events, months (IQR) | | 3, 16 | |
| Ischemic stroke, n (%) | | 6 (26.1) | |
| Time to events, months (IQR) | | 2, 12 | |

Data are shown as mean ± SD and n (%).

COPD, chronic obstructive pulmonary disease; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; eGFR, estimated glomerular filtration rate; ENT, ear, nose and throat; GI, gastrointestinal; GYN, gynecology; HCC, hepatocellular carcinoma; HF, heart failure; ICI, immune checkpoint inhibitor; IQR, interquartile range; MACCE, major adverse cardio- and cerebrovascular events; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; SCr, serum creatinine.

* Baseline eGFR calculated based on chronic kidney disease-epidemiology collaboration equation.

# Given only three patients diagnosed of ICI related myocarditis, the time to events of myocarditis was displayed in median value.

and there was no significant difference regarding the development of MACCEs among the patients receiving either anti-CTLA-4, anti-PD-1, or anti-PD-L1 regimens; none of the patients received a combination of anti-CTLA-4 and anti-PD-1 in this cohort. Extracardiac immune-related adverse events were also reported. Notably, the incidence rates of ICI-related endocrine disorders (21.7% vs. 3.6%, p = 0.001), hepatitis (17.4% vs. 5.2%, p = 0.03), and myositis/dermatitis (30.4% vs. 5.2%, p = 0.001) were significantly higher in the patients who developed MACCEs than in those who did not, while the incidence rates of ICI-related pneumonitis, colitis, and neurologic disorders were not significantly different.

### The predictors of ICI-related MACCEs

In Cox regression analysis, old age, male sex, and presence of diabetes or liver cirrhosis were associated with higher risks of ICI-related MACCEs (Table 2). Additionally, the patients who had concomitant extracardiac events, including ICI-related myositis/dermatitis and endocrine disorders, were at a higher risk of ICI-related MACCEs. In multivariable analysis, an age above 65 years (HR: 4.82, 95% CI: 1.54-15.08, p = 0.007), male sex (HR: 3.47, 95% CI: 0.99-12.1, p = 0.051), diabetes (HR: 3.32, 95% CI: 1.28-8.55, p = 0.013), ICI-related myositis/dermatitis (HR: 4.93, 95% CI: 1.97-12.31, p = 0.001), and endocrine disorders (HR: 3.68, 95% CI: 1.45-9.3, p = 0.006) were still significantly correlated with ICI-related MACCEs. Most importantly, the patients who developed ICI-related MACCEs had a significantly lower survival than those who did not develop MACCEs (Figure 1).

### The development and management of ICI-related cardiotoxicities

Among ICI-related MACCEs, myocarditis is the most fatal complication. One cardiologist and one oncologist reviewed the medical records and identified three patients with ICI-related myocarditis (Table 3). All three patients were above 65 years of age and were male. Two of them had lung cancer, and the other had hepatocellular carcinoma. Even though there is no significant difference between PD-1/PD-L1 inhibitors and CTLA inhibitors in terms of developing MACCEs, all three patients with myocarditis received anti-PD-1 therapy. Two

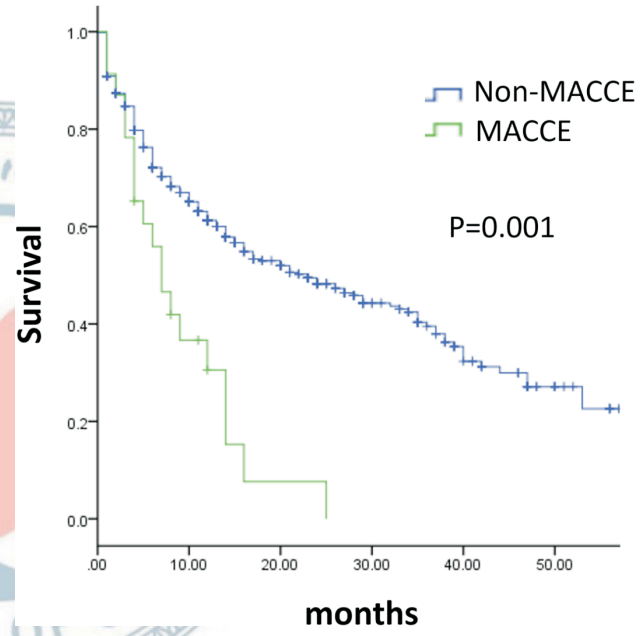


***Figure 1.*** *The Kaplan-Meier plot of the survival of immune checkpoint inhibitor (ICI) treated patients with and without developing major adverse cardio- and cerebrovascular events (MACCEs).*

**Table 2.** Univariate and multivariable predictors of MACCEs in patients receiving immune checkpoint inhibitors (ICIs)

| Parameters | Univariate | | Multivariable | |
|---|---|---|---|---|
| | HR | p | HR | p |
| Age | 1.09 (1.05-1.14) | 0.001 | | |
| Age ≥ 65 y/o | 8.75 (2.97-25.73) | 0.001 | 4.82 (1.54-15.08) | 0.007 |
| Male gender | 3.46 (1.03-11.65) | 0.045 | 3.47 (0.99-12.1) | 0.051 |
| Diabetes | 5.36 (2.21-13.05) | 0.001 | 3.32 (1.28-8.55) | 0.013 |
| Liver cirrhosis | 3.14 (1.29-7.64) | 0.012 | 2.12 (0.82-5.48) | 0.120 |
| Lung cancer | 1.96 (0.86-4.45) | 0.1 | | |
| ICI related myositis or dermatitis | 8.18 (3.59-18.67) | 0.001 | 4.93 (1.97-12.31) | 0.001 |
| ICI related endocrine disorders | 8.02 (3.53-18.17) | 0.001 | 3.68 (1.45-9.3) | 0.006 |

Abbreviation as Table 1.

**Table 3.** Clinical features of patients diagnosed with ICI related myocarditis

| Age/ sex | Cancer type | ICI regimen | Days from ICI | Initial presentations | Biopsy | ECMO/ IABP | Steroid/ immunosuppressants | Survival status | Days from ICI related myocarditis to Death |
|---|---|---|---|---|---|---|---|---|---|
| 76/M | Lung cancer | Pembrolizumab (anti-PD1) | 10 days | Dyspnea, fatigue | Nil | IABP | Nil | Died | 10 days |
| 65/M | HCC | Nivolumab (anti-PD1) | 14 days | Fatigue, shock | Nil | ECMO | Steroid | Died | 14 days |
| 78/M | Lung cancer | Nivolumab (anti-PD1) | 26 days | Dyspnea, palpitation | Nil | Nil | Nil | Died | 5 days |

Abbreviation as Table 1.

patients were prescribed nivolumab, and the other was prescribed pembrolizumab. All of them developed myocarditis after their first dose of ICIs. The duration from starting ICI therapy to the onset of myocarditis ranged from 10 to 26 days; all patients died 5 to 10 days from the initial diagnosis. The initial myocardial presentation was atypical; none had chest pain but instead presented with dyspnea, fatigue, or shock. Two of them received mechanical circulatory support, including intra-aortic balloon pump (IABP) and venoarterial extracorporeal membrane oxygenation (ECMO), but none of them had a myocardial biopsy. Regarding treatment specific for ICI-related myocarditis, only one of them was prescribed a high dose of steroids, but none were prescribed immunosuppressants. Notably, after medical review, the patients eventually diagnosed with ICI-related myocarditis had not been previously identified as having ICI-related myocarditis.

## DISCUSSION

Despite a significant improvement in cancer-free survival, ICIs are associated with immune-mediated adverse events affecting the neurological, endocrine, pulmonary, gastrointestinal, and renal systems.[7,10,16-18,20] Recently, in a small case series, cardiovascular complications including HF, myocardial infarction, stroke, and especially myocarditis, were identified as side effects of ICIs.[7,9,10] However, data on the presentations, risk factors, and outcomes are limited. In a pharmacovigilance study using the WHO global individual case safety report database, Salem et al. identified 31321 adverse events reported in patients who received ICIs.[9] They found that ICI treatment was associated with higher reporting of myocarditis, pericardial diseases, and vasculitis. In addition, myocarditis was more commonly reported in patients with melanoma, with a 50% risk of mortality.[9] Another retrospective and prospective multicenter registry in the United States indicated an incidence of 1.14% for developing myocarditis after starting ICIs.[21] In that study, the patients were approximately 65 years old, 29% were female, and 54% had no other immune-related side effects. Diabetes, sleep apnea, higher body mass index, melanoma, non-small cell lung, and a combination of ICIs with anti-CTLA-4 and anti-PD-1 regimens were more common in the cases with myocarditis relative to controls.[21] In the current study of a multihospital retrospective cohort, we found a relatively higher incidence of 3.9% of ICI-related MACCEs compared with previous reports. The patients who had MACCEs were prone to be older, male, and have lung cancer, liver cirrhosis, or diabetes. The development of ICI-related MACCEs was associated with higher mortality. In three patients eventually diagnosed with ICI-related myocarditis, none had been properly diagnosed initially. Only one of them was treated with pulse steroids, and none survived. To the best of our knowledge, this is the first article describing ICI-related cardiovascular complications in Taiwan, and it highlights the unmet need for awareness regarding immunotherapy-related cardiovascular toxicities. Given that early identification and prompt treatment with pulse steroids or immunosuppressants remain the standard of care, improving knowledge regarding ICI-related cardiotoxicities, especially myocarditis, is mandatory.

Even though the mechanism of ICI-related myocarditis is unclear, researchers have suggested a plausible pathophysiology in terms of shared antigens between

the tumor and myocardium. Several studies have identified the expression of PD-L1 in the myocardium of patients with ICI-related myocarditis.[6,7,11] In addition, a previous study showed that PD-1 knockout mice developed autoimmune dilated cardiomyopathy and increased mortality.[22] In addition, the hearts of the PD-1 knockout mice had decreased left ventricular systolic function and wall thinning with dilated right ventricles.[22] This suggests the critical role of PD-1 in regulating autoimmune responses, specifically with regards to the heart.[22] However, in contrast to the idea of off-target effects of ICI, Tay et al. studied embryonic stem cell-derived cardiomyocytes and found that in contrast to doxorubicin, ICIs alone did not induce inflammatory-related proteins, including PD-L1 expression, and did not induce apoptosis.[23] Instead, when cocultured with CD4+ T lymphocytes, ICIs exacerbated the immune response by increasing cytokine and inflammatory gene expressions and inducing apoptosis.[23] They concluded that blockade of PD-1 by ICIs enhanced cardiomyocyte inflammation and apoptosis by enhancing the T-cell response.[23] Further studies are needed to establish the exact mechanisms of ICI-related myocarditis.

In terms of the diagnosis of ICI-related myocarditis, there is wide variability in symptoms, including dyspnea, palpitation, and signs of congestive HF.[6,7,10] However, myocarditis can also present with asymptomatic cardiac biomarker elevation or pericardial diseases.[6,7] Echocardiography remains the first-line screening tool, as left ventricular systolic dysfunction has been reported in 79% of patients.[2] Troponin measurement is a sensitive initial test, whereas cardiac magnetic resonance imaging and endomyocardial biopsy are both gold standard components of the diagnostic criteria.[2,6] Approximately 30% of cases have been reported to have atrial or ventricular arrhythmia, and this was the major cause of death.[2,6] Among patients with ICI-related left ventricular systolic dysfunction, complete reversibility has been significantly associated with corticosteroid therapy.[2,7] Regarding the onset of cardiovascular complications after starting ICI therapy, Mahmood et al. reported a median time of 34 days (interquartile range, 21-75 days).[21] In another cohort, Escudier et al. reported a range of 2 to 454 days and a median of 65 days to a diagnosis of cardiotoxicity after the initiation of ICIs.[2] Upon current evidence, most cases of myocarditis will present within the first 2 months after initiating ICIs, although clinicians should still keep this diagnosis in mind during long-term ICI therapy.[2,17,24] Timely consultation with a cardiologist and decisions to stop ICIs are crucial for the diagnosis of ICI-related cardiotoxicities.[2,15] Following recommendations with regards to first-line management with pulse steroids and second-line therapy with immunosuppressants is also recommended as life-saving strategies.[2,15] In a previous study of 35 patients diagnosed with ICI-associated myocarditis, steroids were administered in 89%, and lower doses were associated with higher rates of MACCEs.[21] In contrast, in our cohort, only one of three patients was prescribed steroids in the group that was retrospectively diagnosed with ICI-related myocarditis. This highlights the lack of awareness of the need for a prompt and proper diagnosis regarding ICI-related myocarditis in real-world practice.

Compared with previous studies, the rate of concomitant extracardiac immune-related adverse events was relatively higher in our cohort.[16,18,25,26] The most common event was dermatitis, followed by endocrine toxicity and hepatitis. Among 35 patients with ICI-associated myocarditis, Mahmood reported that more than half of the patients had no other immune side effects.[21] Likewise, in a single center, retrospective study in Taiwan, Hsu et al. found that less than 4% of their patients had ICI-related immune events.[27] In contrast, in a global database of individual case safety reports, concurrent immune-related adverse events were reported to occur in 1 to 28% of patients.[5] Notably, patients diagnosed with ICI-related myocarditis were more prone to have concurrent myositis.[21] Taken together, given the heterogeneity of study designs and included populations, findings vary between studies. With the ever increasing number of patients receiving ICIs, more investigations are necessary for risk evaluation and mitigation strategies for ICI-associated immune adverse events.

There are some limitations to this study. First, in the setting of a retrospective study, the baseline characteristics of the patients and timing of monitoring may vary. In particular, some clinical information regarding echocardiographic parameters and biomarkers was missing. Given that the three hospitals in this study are affiliated with Chi-Mei Medical Center, the institutional standards are similar, and patient adherence is guaranteed. Second, the limited number of included patients may atten-

uate the statistical power, and large-scale studies are required in the future. Third, ICI-related MACCEs were diagnosed through chart reviews by clinical specialists, but the accuracy of diagnosis may need further validation. Despite these limitations, this study is the first to shed light on the epidemiology, clinical features, risk factors, and management of ICI-related cardiovascular complications in Taiwan. Our findings also highlight a lack of general awareness of ICI-related cardiovascular side effects. Early diagnosis and prompt intervention remain the key to mitigating the threat of ICI-related adverse effects in vulnerable cancer patients.

## CONCLUSIONS

Collectively, ICIs may cause severe cardiovascular toxicities and require more attention. Early identification, proper diagnosis and prompt treatment are pivotal for improving survival.

## DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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