Assessment of prognostic factors in previously treated Japanese patients with metastatic renal cell carcinoma who received nivolumab: An observational multi-institute study

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Abstract. The aim of the present study was to evaluate the prognosis of Japanese patients with metastatic renal cell carcinoma (mRCC) receiving nivolumab and to identify factors predicting the overall survival (OS) in this cohort of patients. This study retrospectively assessed the outcomes of 77 consecutive Japanese patients with mRCC who were treated using either 1 or 2 molecular-targeted agents followed by nivolumab in routine clinical practice. The best responses to nivolumab observed were as follows: Complete response in 3 patients, partial response in 27, stable disease in 33 and progressive disease in 14; therefore, the objective response rate in the 77 patients was 39.0%. During the median follow-up period of 11 months after the introduction of nivolumab, the median progression-free survival and OS were 7 months and not reached, respectively. On multivariate analysis of several parameters, age, Karnofsky Performance Status (KPS) and neutrophil counts were demonstrated to be independently associated with OS in the 77 patients. By dividing these patients into 3 groups according to 3 risk factors, it was possible to stratify the OS; however, the International Metastatic Renal Cell Carcinoma Database Consortium model was unable to classify the OS. These results suggested that age, KPS and neutrophil counts were useful predictors of OS in previously treated patients with mRCC who received nivolumab.

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Introduction

The introduction of molecular-targeted agents notably improves the prognosis of patients with metastatic renal cell carcinoma (mRCC) (1). Furthermore, immune checkpoint inhibitors (ICIs), such as programmed cell death protein-1, programmed death-ligand 1 and cytotoxic T-lymphocyte antigen 4 antibodies, were demonstrated to be effective against mRCC through a unique mechanism of action of restoring T cell-mediated immune responses and have become novel treatment options for mRCC (2). Amongst these, nivolumab initially resulted in significant improvements in OS compared with everolimus in previously treated patients with mRCC (3), which led to the approval of ICI-based combination therapies for treatment-naïve patients with mRCC, including nivolumab plus ipilimumab, avelumab plus axitinib and pembrolizumab plus axitinib (4-6).

To date, well-designed models, such as the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification systems, have been widely accepted as prognostication tools for both previously treated and treatment-naïve patients with mRCC (7-10). However, the MSKCC and IMDC systems were developed based on patients who received cytokine and molecular-targeted therapies, respectively (7-10); therefore, it remains unclear whether these two conventional prognostication models can be applied to patients with mRCC treated using ICIs. In addition, several parameters differing from those adopted in the MSKCC and IMDC models were identified as useful prognostic factors for patients with mRCC receiving ICIs (11-16). For example, Suzuki *et al* (11) reported that a high C-reactive protein level and neutrophil-to-lymphocyte ratio (NLR) were significantly associated with a poor overall survival (OS) in patients with mRCC treated using nivolumab.

As such, a multicenter retrospective study was used to identify reliable predictors of OS in previously treated patients with mRCC who received nivolumab.

Patients and methods

Patients. Between October 2016 and November 2019, 114 patients with mRCC received nivolumab after treatment using molecular-targeted agents at one of the following four institutions belonging to the Tokai Urologic Oncology Research Seminar: Hamamatsu University School of Medicine (Hamatsu, Japan), Gifu University Graduate School of Medicine (Gifu, Japan), Fujita Health University School of Medicine (Toyoake, Japan) and Nagoya City University Graduate School of Medical Science (Nagoya, Japan). After excluding 37 patients who were diagnosed with non-clear cell mRCC and/or received nivolumab as later than a fourth-line therapy, the present study included 77 patients with clear cell mRCC who received 1 or 2 molecular-targeted agents, followed by the introduction of nivolumab as second- or third-line therapy at Hamamatsu University School of Medicine (n=23), Fujita Health University School of Medicine (n=23), Nagoya City University Graduate School of Medical (n=17) and Gifu University Graduate School of Medicine (n=14).

All procedures performed in the present study were done in accordance with the ethical standards of all the institutional and/or national research committees (approval no. 19-101), and the guidelines described in the 1964 Helsinki declaration and its later amendments or comparable ethical standards (17). The need to obtain informed consent for the publication of any associated data and accompanying images from all patients included in this study was waived due to its retrospective design after approval by the ethics committees of all four institutions.

Treatment. In the recruited patients, prior to the introduction of nivolumab, all patients were treated using either 1 or 2 molecular-targeted agents approved in Japan, and as a rule, each agent was administered under a standard dosing schedule. After the failure of molecular-targeted agents, nivolumab (3 mg/kg or a flat dose of 240 mg) was generally administered intravenously every 2 weeks until the patients exhibited unacceptable toxicity, the disease progressed or the patient declined. It was possible to alter the dosage or postpone nivolumab treatment considering the degree of treatment-associated adverse events. Depending on the general condition and preference of each patient, a molecular-targeted agent was further introduced after the discontinuation of nivolumab.

Evaluation. Clinicopathological data, including the treatment profiles, were retrospectively obtained from the medical records of each patient. Prior to the administration of nivolumab, standard laboratory data were obtained, and radiological examinations by computed tomography (CT) of the brain, chest and abdomen, and/or radionuclide bone scintigraphy were performed as routine procedures on all patients. In addition, immune inflammation-related markers, including NLR, the platelet-lymphocyte ratio (PLR) and systemic immune inflammation index (SII), were evaluated based on previously described calculations (13,18). As a rule, tumor measurements were performed by CT every 2-3 courses after the introduction of nivolumab and disease progression was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.1 (19). Progression-free survival (PFS) was defined as the time from the start of nivolumab to disease progression or death, whereas OS was defined as the time from the start of nivolumab therapy to death from any cause or the last follow-up.

Statistical analysis. All statistical analyses were performed using R version 4.0.0 (r-project.org) (20) and $P<0.05$ was considered to indicate a statistically significant difference. PFS and OS rates were calculated using the Kaplan-Meier method, and the prognostic significance of factors were analyzed employing univariate and multivariate Cox proportional hazards models. The factors with P-values <0.15 in the univariate analysis were included in the multivariate analysis using backward stepwise selection, as previously reported (8). In the assessment of prognostic factors, reference values at each institution were used as cut-off values for laboratory data, whereas for those without reference values, cut-off values were set according to the Youden index obtained from receiver operating characteristic curves plotted for the value of each parameter to predict OS. Patients were then categorized according to the positive number of independent risk factors for OS identified by multivariate analysis as follows: Group A, no risk factors; group B, single risk factor; and group C, multiple risk factors.

Results

The clinicopathological characteristics of the 77 patients included in this study at the initiation of nivolumab treatment are summarized in Table I. Of the 77 patients, 60 patients were males (77.9%) and 17 were females (22.1%), with a median age of 72 years (range, 44-83 years). The median number of cycles of nivolumab therapy was 12 (range, 1-67) and the median duration of treatment was 6 months (range, 1-35 months). The best responses to nivolumab were as follows: Complete response in 3 patients, partial response in 27, stable disease in 33 and progressive disease in 14; therefore, the objective response rate (ORR) in the 77 patients was 39.0%. During the follow-up period after the introduction of nivolumab (median, 11 months; range, 1-38 months), 14 (18.2%) patients exhibited disease progression and 21 (27.3%) died. As shown in Fig. 1, the median PFS and OS were 7 months and not reached, respectively; there were no significant differences in PFS or OS amongst the four institutions (data not shown). As shown in Table II, the univariate analysis revealed that OS was significantly associated with age, KPS, neutrophil count, albumin levels and NLR. Of these significant factors, only three of them, age (≥71 years), KPS (<80%) and neutrophil count (≥ upper limit of normal detection), independently affected OS based on the multivariate analysis. To further clarify the effects of these three factors on OS, the 77 patients were stratified into 3 groups based as follows: Group A (n=20), no risk factors; group B (n=48), single risk factor; and group C (n=9), multiple risk factors. The median OS in groups A, B and C was not reached; 25 and 8 months, respectively, and there were significant differences in OS amongst these 3 risk groups (Fig. 2A). However, the IMDC system was unable to significantly stratify OS after the initiation of nivolumab in these 77 patients (Fig. 2B). Prognostic outcomes according to the 3 risk groups stratified by the IMDC and present model systems are summarized in Table III.

Table I. Patient characteristics at the initiation of nivolumab in patients with clear cell renal carcinoma (n=77).

Characteristic	Value
Age at nivolumab initiation, years[a]	72 (44-83)
Sex (male)[b]	
Female	17 (22.1)
Male	60 (77.9)
Prior immunotherapy[b]	13 (16.9)
Prior nephrectomy[b]	69 (89.6)
<1 year from diagnosis to systemic therapy[b]	49 (63.6)
Karnofsky Performance Status <80%[b]	20 (26.0)
IMDC classification at nivolumab initiation[b]	
Favorable	6 (7.8)
Intermediate	53 (68.8)
Poor	18 (23.4)
Metastatic lesion[b]	
Brain	6 (8.0)
Lung	61 (81.3)
Bone	32 (42.7)
Number of metastatic organs (≥2)[b]	45 (58.4)
Laboratory data[a]	
Hemoglobin, g/dl	11.9 (7.8-16.8)
Serum-corrected calcium, mg/dl	9.6 (8.2-11.4)
Neutrophils, x10^9/l	3.62 (0.90-24.1)
Platelets, x10^9/l	219 (28-664)
Albumin, g/dl	3.6 (1.7-4.4)
C-reactive protein, mg/dl	0.43 (0.02-27.0)
Lactate dehydrogenase, U/l	191 (123-3,490)
Neutrophil to lymphocyte ratio	3.1 (0.6-19.6)
Platelet to lymphocyte ratio	185.8 (6.8-961.0)
Systemic immune inflammation index, x10^9/l	637.7 (50.5-7,806.3)
First-line targeted agent[b]	
Sunitinib	42 (54.5)
Sorafenib	4 (5.2)
Axitinib	7 (9.1)
Pazopanib	20 (26)
Temsirolimus	3 (3.9)
Second-line targeted agent[b]	
Axitinib	36 (87.8)
Everolimus	1 (2.4)
Temsirolimus	2 (4.9)
Pazopanib	2 (4.9)
Duration from first-line therapy to nivolumab initiation, months[a]	15 (1-134)
Cycles of nivolumab administration, cycles[a]	12 (1-67)
Duration of nivolumab administration, months[a]	6 (1-35)
Follow-up period after nivolumab initiation, months[a]	11 (1-38)

[a]Median (range); [b]n (%). IMDC, International Metastatic Renal Carcinoma Database Consortium.

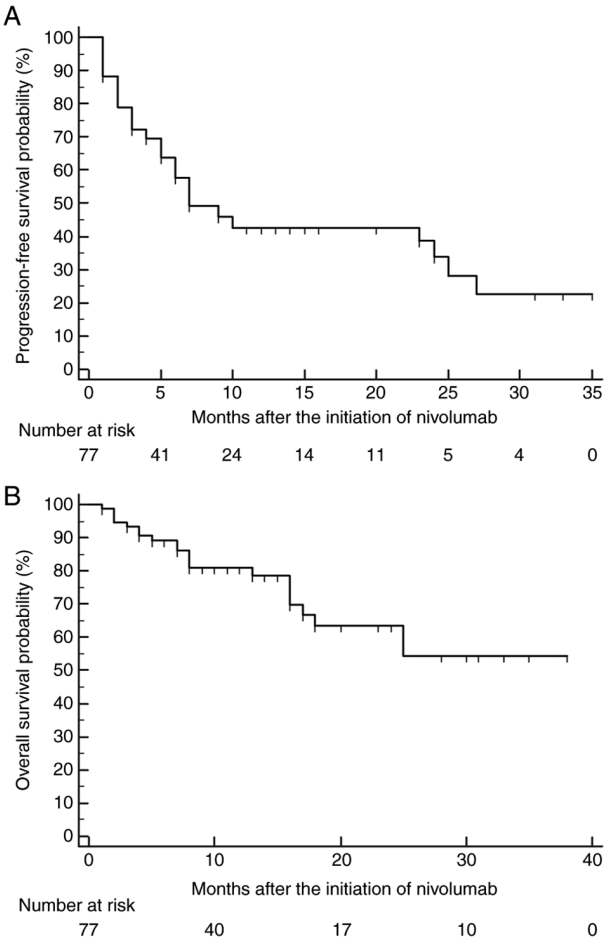

Figure 1. Kaplan-Meier plots of 77 patients with previously treated metastatic renal cell carcinoma who received nivolumab as either the second- or third-line agent: (A) Progression-free and (B) overall survival.

Discussion

Several types of ICIs, either alone or in combination with another agent, were demonstrated to significantly prolong the survival of treatment-naïve or previously treated patients with mRCC (2-6). Considering the increasing number of therapeutic options for patients with mRCC, including several regimens containing ICIs, it has become important to identify parameters that can aid in the selection of patients with mRCC who are more likely to benefit from the use of ICIs (1,2). However, data related to the outcomes of patients with mRCC treated using ICIs in routine clinical practice are limited, resulting in the lack of established prognostication tools for this cohort of patients. As such, 77 previously treated Japanese patients with clear cell mRCC who received nivolumab were recruited to analyze their clinical data in order to develop a system to stratify their prognosis.

Recently, Hinata *et al* (21) reported the real-world prognostic outcomes of a wide range of Japanese patients with mRCC receiving nivolumab, and they were shown to be slightly poorer compared with those in the present study. The present study excluded patients who were diagnosed with non-clear cell RCC and/or received >3 molecular-targeted agents prior to the introduction of nivolumab in order to minimize the risk of bias induced by the heterogeneous characteristics of the

Table II. Univariate and multivariate analyses of prognostic factors for overall survival after the initiation of nivolumab.

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Sex, male	0.62	0.25-1.53	0.30			
Age, ≥71 years	2.04	0.84-4.97	0.11[a]	3.8	1.40-10.33	0.0087[c]
<1 year from diagnosis-systemic therapy	1.04	0.42-2.58	0.93			
Karnofsky Performance Status <80%	2.56	1.08-6.08	0.03[b]	4.98	1.83-13.59	0.0017[c]
IMDC model at nivolumab initiation						
Favorable	1					
Intermediate	1.92	0.25-14.48	0.53			
Poor	2.76	0.34-22.71	0.35			
Metastatic lesion						
Brain	1.69	0.39-7.42	0.49			
Lung	2.08	0.48-9.00	0.33			
Bone	0.86	0.36-2.08	0.74			
Number of metastatic organs (≥2)	1.13	0.47-2.74	0.79			
Laboratory data						
Low hemoglobin, ≤LLN	1.32	0.51-3.38	0.57			
High calcium, ≥ULN	1.93	0.65-5.73	0.24			
High neutrophils, ≥ULN	2.69	0.90-8.05	0.07[a]	3.75	1.22-11.50	0.021[b]
High platelets, ≥ULN	0.9	0.21-3.89	0.89			
Low albumin (≤3.5 g/dl	1.9	0.79-4.67	0.15[a]	-	-	-
High C-reactive protein, ≥0.5 mg/dl	1.63	0.68-3.91	0.28			
High lactate dehydrogenase, ≥1.5xULN	1.73	0.51-5.87	0.38			
Neutrophil-lymphocyte ratio, ≥6.1	3.02	1.11-8.25	0.03[b]	-	-	-
Platelet-lymphocyte ratio, ≥249	1.84	0.76-4.43	0.18			
Systemic immune inflammation index, ≥456x10^9/l	2.52	0.75-8.51	0.14			
Duration from first-line therapy-nivolumab initiation (≥16 months)	1.86	0.75-4.60	0.18			

[a]P<0.15, [b]P<0.05, [c]P<0.01. HR, hazard ratio; CI, confidence interval; IMDC, International Metastatic Renal Carcinoma Database Consortium; LLN, lower limit of normal detection; ULN, upper limit of normal detection.

included patients. As a result, the ORR, PFS and OS in this series were 39%, 7 months and not reached, respectively, which were similar to the outcomes of a Japanese subgroup analysis from the CheckMate 025 study, reporting 43%, 5.6 months and not reached, respectively (22). Accordingly, it may be optimal to use the prognostic data from the 77 patients included in the present study for the development of a prognostication system for patients with mRCC receiving nivolumab as either a second- or third-line agent.

To date, well-accepted models predicting the prognosis of patients with mRCC, specifically the MSKCC and IMDC models, have been used to classify patients with mRCC into 3 prognostic groups (7-10); however, these models were not developed based on data from those receiving ICIs. Therefore, it remains controversial whether these models can be used in the era of ICI therapy. For example, Yip *et al* (23) performed a retrospective analysis using the IMDC database analyzing patients with mRCC who received ≥1 line of ICI, and confirmed that the IMDC criteria appropriately stratified these patients into favorable-risk, intermediate-risk and poor-risk groups for OS, whereas Martini *et al* (12) reported no significant differences in the OS of 100 patients with mRCC who were treated using ICIs classified according to the IMDC model. Both of these studies included patients receiving either ICI monotherapy or ICI combination therapy at the first-line setting; however, the conclusion is controversial, and may be explained by differences in patient backgrounds, such as the proportion of those with clear cell RCC. In the present study, 6, 53 and 18 patients were classified into favorable, intermediate and poor risk groups, respectively, based on the IMDC model, whereas 16, 58 and 3 were similarly classified by the MSKCC model. However, no significant differences in OS were noted according to the classification by either model. This suggests that a novel prognostication system applicable to patients with mRCC treated using ICIs is required.

In recent years, there have been a number of studies reporting the significant impact of inflammatory biomarkers,

Table III. Risk stratification using each prognostic model after the initiation of nivolumab.

Model	Number of patients, n (%)	Number of deaths, n (%)	Median overall survival, months (95% CI)	Hazard ratio (95% CI)
IMDC model				
Favorable	6 (7.8)	1 (16.7)	NR	1 (reference)
Intermediate	53 (68.8)	14 (26.4)	NR	1.92 (0.44-3.39)
Poor	18 (23.4)	6 (33.3)	25.0 (8.0-25.0)	2.75 (0.52-14.6)
Risk model developed in the present study				
A	20 (26.0)	2 (10.0)	NR	1 (reference)
B	48 (62.3)	13 (27.1)	25.0 (16.0-25.0)	3.43 (1.34-8.74)
C	9 (11.7)	6 (66.7)	8.0 (1.0-25.0)	12.5 (2.23-69.9)

IMDC, International Metastatic Renal Carcinoma Database Consortium; OS, overall survival; HR, hazard ratio; CI, confidence interval; NR, not reached.

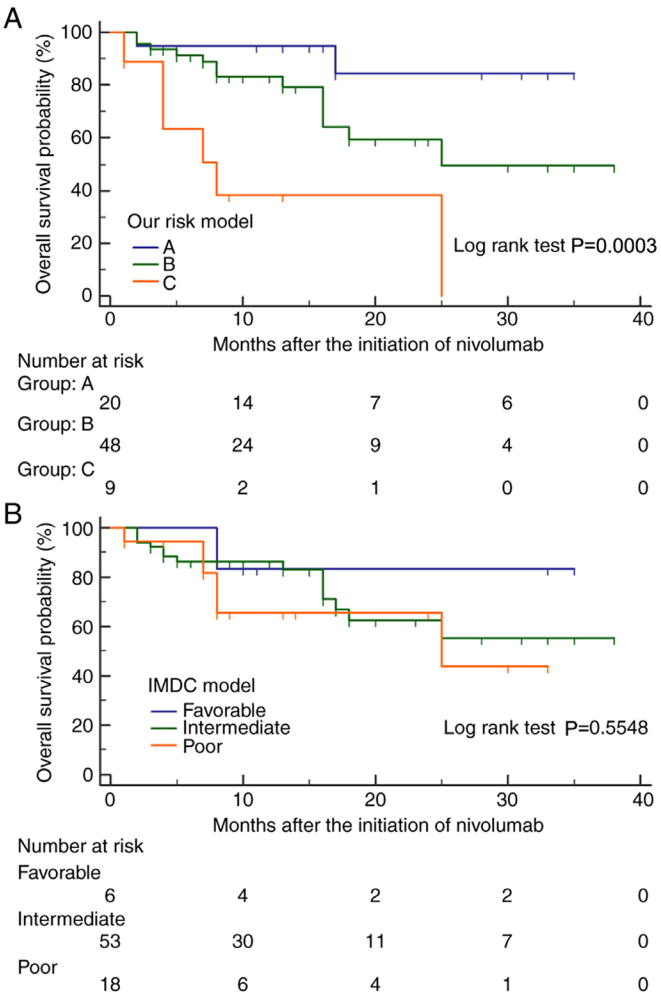

Figure 2. Kaplan-Meier plots of 77 patients with previously treated mRCC who received nivolumab as either the second- or third-line agent: (A) Overall survival according to the sum of the three risk factors (elderly age, poor Karnofsky Performance Status and high neutrophil count) as follows: Group A (n=20), patients with no risk factors; group B (n=48), those with a single risk factor; and group C (n=9), those with multiple risk factors. (B) Overall survival according to the International Metastatic Renal Cell Carcinoma Database Consortium model. mRCC, metastatic renal cell carcinoma.

such as NLR, PLR, the monocyte-to-lymphocyte ratio (MLR) and SII, on the prognosis of patients with mRCC receiving ICIs (11-15). For example, De Giorgi *et al* (13) reported that patients with mRCC treated using nivolumab with a high SII and low body mass index (BMI) had a markedly poor OS, whereas Martini *et al* (12) demonstrated the value of risk scoring using MLR, BMI and the number and sites of metastases for prognostication of patients with mRCC receiving ICIs. Therefore, the associations between OS and several parameters, including inflammatory biomarkers were assessed in the present study to identify potential prognostic factors for previously treated patients with mRCC receiving nivolumab, and revealed that OS was independently affected by age, KPS and the neutrophil count, and was able to be stratified by dividing them into 3 groups according to these 3 independent risk factors. However, all laboratory data, except the neutrophil count, had no significant impact on OS, which may be explained by the following: The indispensable effects of previous systemic therapies or disease aggressiveness at the introduction of nivolumab on laboratory data, and the close association between the efficacies of ICIs and the host cell-mediated immune system. Taken together, assessing the impacts of a wide variety of parameters on the prognosis of patients with mRCC receiving ICIs may aid in the development of useful alternatives to conventional prognostication models for this patient cohort.

The present study has several limitations. First, this was a retrospective study including a small number of patients and different populations may have different responses to molecular-targeted agents or nivolumab, thus the present findings must be confirmed in a prospective study with a larger sample size, with multiple different ethnicities. Second, the present study included all patients treated using nivolumab for at least one cycle, resulting in the lack of consideration of usage cycles and dosage, which may affect the prognostic outcomes. Third, a focus was placed on only previously treated patients with mRCC receiving nivolumab; however, considering the current therapeutic trend for mRCC (4-6), prognostication of patients with treatment-naïve mRCC

should also be investigated. Fourth, although the unbalanced distribution of patients with mRCC based on the MSKCC and IMDC models is considered a disadvantage (24), the proportion of patients classified into the intermediate risk group by the model used in the present study was the highest amongst the groups. Lastly, there may be other parameters that have not been well characterized, but are closely associated with the prognosis of patients with mRCC receiving ICIs that were not taken into consideration.

In conclusion, a retrospective multi-institutional study on 77 previously treated patients with mRCC who received nivolumab as either the second- or third-line agent, and demonstrated a comparatively favorable prognosis. Moreover, unlike the IMDC model, only 3 independent risk factors, age, KPS and neutrophil count, were identified as independent risk factors of OS, making it possible to stratify the OS of these patients into 3 groups.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

TK, TY, RS and HM conceived and designed the study. TI, KM, RA and KT acquired the data. TI and HM analyzed and interpretated the data, and drafted the manuscript. TI and HM confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in this study were done so in accordance with the ethical standards of all the institutional and/or national research committees (approval no. 19-101), and the guidelines described in the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The need to obtain informed consent for the publication of any associated data and accompanying images from all patients included in this study was waived due to its retrospective design after approval by the ethics committees of all four institutions.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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