

Thrombolysis for Acute Ischemic Stroke: Experience in Dubai, and Comparison of Arab with Non-Arab Population

Abstract

Background: Intravenous alteplase is now the standard of care for treatment of acute ischemic stroke. Rashid Hospital was the first hospital in Dubai, UAE to start giving intravenous alteplase. Our objective is to present our experience with patients thrombolysed and to evaluate the differences between Arab and non-Arab patients.

Methods: In a prospective manner, all subjects presenting to Rashid Hospital emergency and receiving intravenous thrombolysis were identified. Data was collected on demographics, stroke severity, risk factors, and outcomes. Comparisons were made between Arab and non-Arab patients in terms of risk factors and outcomes. SPSS 20 was used for analysis and p-value of 0.05 was considered significant.

Results: A total of 176 patients were thrombolysed during the study period. The mean age of the patients was 50.83 (SD 14.10) and 82.8% were males. 22.2% of the patients were of Arab origin and 62.5% were of South Asian origin. Mean Door to needle time was 64.14 minutes (SD 24.02). Hypertension was the commonest risk factor (54.6%). Mean NIHSS at presentation was 11.84 (SD 4.29). Twelve patients (6.9%) developed post thrombolysis symptomatic intracerebral hemorrhage. Ten patients (5.7%) died in the hospital.

Patients of Arab origin were significantly older at stroke onset, and had higher proportions of major vascular risk factors. There were no differences in the safety and efficacy outcomes in the two ethnic groups.

Conclusion: Compared to international data, use of intravenous thrombolysis was safe and effective. Arab patients differ in age and risk factor profile from their non-Arab counterparts.

Keywords: Stroke; Thrombolysis; Hemorrhage; Arabs; Outcomes

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Maria Khan*, Husnain Hashim, Zebun Nisa, Syed Habibullah Kamran and Suhail Alrukn

Department of Neurology, Rashid Hospital, UAE

***Corresponding author:** Maria Khan, Department of Neurology, Rashid Hospital, Postal Address: Villa number 178, Esmeralda, Victory Heights, Dubai Sports City, Dubai, UAE, Tel: 00971502280297; Email: mhkhan.junaidi@gmail.com

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Abbreviations: UAE: United Arab Emirates; NINDS rtPA: Neurological Disorders and Stroke recombinant tissue plasminogen activator; tPA: tissue Plasminogen Activator; CT: Computerized Tomography; mRS: modified Rankin Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment criteria; NIHSS: National Institute of Health Stroke Scale; SPSS: Statistical Package for Social Sciences; IQR: Interquartile range; OTT: Onset to treatment time

Introduction

Stroke is a significant cause of morbidity and mortality in the developing Arab world. A systematic review from 2009 highlighted the dearth of sound epidemiological data from these countries [1]. More recently a review on temporal trends suggested a rise in stroke incidence in Asian countries, an earlier age at onset, and a relative increase in ischemic stroke subtypes [2]. There is reason to believe that since Arab countries are in a similar stage of epidemiological transition as other Asian countries, they would be sharing these trends as well. United Arab Emirates (UAE) is

no exception. Results from a population based screening program demonstrate a very high cardiovascular risk factor prevalence especially of diabetes and obesity [3]. Judging from this, it is expected that the burden of stroke would also be substantial.

Ever since the National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (NINDS rtPA) trial followed by its approval in 1996, intravenous thrombolysis has remained the standard of care for acute ischemic stroke patients [4]. The window has also since been extended from 3 hours to 4.5 hours [5]. Despite its proven benefits, the intervention remains under-utilized in most parts of the world. Reasons for this include lack of proper set-up for administration, decreased awareness regarding the intervention and hence delayed presentations, and lack of properly trained physicians to administer and take care of these patients.

Utilization of intravenous tissue plasminogen activator (tPA) is very poor in the Arab world as well. An article published in 2011 showed that even in a large country like Saudi Arabia, only seven out of 350 hospitals provide thrombolysis for acute stroke, and

the average number of patients thrombolysed per year is merely 50 [6]. Another study from six large stroke centers in the Arabian peninsula [7] showed that a mere 0.8% of the 780 ischemic stroke cases were thrombolysed during the study period, a number too small to make any meaningful conclusion regarding the efficacy and safety of the intervention in this population.

Dubai is the most populous city of UAE and Rashid Hospital is the city's largest public sector hospital with one of the busiest emergencies in the country. Despite seeing a substantial number of stroke cases every year, intravenous thrombolysis was not being utilized up until 2009. Even after that, the number of patients thrombolysed was very small. In 2011, the stroke unit at Rashid Hospital, Dubai was set up. The number of patients being thrombolysed per year has steadily gone up since then.

The objectives of our study were two fold. First, to describe the number and proportion of stroke patients treated with intravenous thrombolysis, their demographic characteristics, time to treatment, outcomes and complications; second to compare Arab with non-Arab ethnic groups in terms of stroke risk factors and outcomes of thrombolysis as measured by modified Rankin Scale.

Methods

All patients treated with intravenous thrombolysis within 4.5 hours of symptom onset, by the stroke team at Rashid hospital between September 1, 2011 and August 31, 2014 were prospectively identified. Our stroke team consists of consultants and specialist registrars who rotate on 'first call' to respond immediately to stroke code and provide this coverage round the clock, seven days a week. In addition, there is a dedicated 4 bed stroke unit with nurses trained in care of acute stroke cases, post thrombolysis. Since the establishment of the stroke service, periodic educational training sessions have been held by our stroke team, to orient the emergency staff in quick identification of acute stroke and the steps necessary to ensure timely administration of thrombolysis, including generation of stroke code and expediting Computerized Tomography (CT) scanning.

For the purpose of this study, trained personnel recruited these acute stroke patients prospectively through clinical identification. Stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin." [8]. All patients underwent Computerized Tomography (CT) imaging which supported the diagnosis of ischemic stroke and ruled out intracranial hemorrhage. In addition, the stroke unit log was checked on a biweekly basis, since all thrombolysed patients get admitted to this unit. This was done to ensure that no cases are missed.

The following information was recorded on a pre-designed questionnaire: date of birth, ethnicity, gender, baseline functional status (as per modified Rankin Scale-mRS) time of stroke onset, time of arrival to emergency, time of CT imaging, and time of tPA administration. Data was also collected on post tPA complications, in-hospital mortality and risk factors. This included, information on known diabetes, hypertension, dyslipidemia, ischemic heart disease, tobacco use and atrial fibrillation. Patients were labeled diabetic if they were known with the condition or had elevated

HbA1c on admission. Hypertension was diagnosed if patients had known history of elevated blood pressure or if they were on anti-hypertensive medications. Dyslipidemia was diagnosed if patient had a total cholesterol of >220mg/dL or was on lipid lowering medications. Atrial fibrillation was diagnosed based on ECG tracing in the hospital or if a patient was known with the condition. Strokes were sub typed using the Trial of Org 10172 in Acute Stroke Treatment criteria (TOAST) [9].

Clinical outcomes were measured by National Institute of Health Stroke Scale (NIHSS score) [10] and Modified Rankin Scale score, mRS [11] at presentation, at 72 hours and at discharge. mRS was also assessed by telephonic follow up at 3 months post stroke onset when possible. mRS measures functional dependence on a scale of 0 (completely independent) to 6 (death). NIHSS is a quantitative measure of neurological deficits based on examination. When not documented, an NIHSS score as well as mRS score were obtained by inference using the clinical data in the neurology case record.

Primary Safety outcome was symptomatic intracranial hemorrhage as per the ECASS II definition [12]. This is defined as clinical deterioration on NIHSS scale of 4 or more associated with intracranial hemorrhage on repeat CT scan within 24 hours of receiving thrombolysis. Other safety outcomes included serious systemic hemorrhage defined as extracranial bleeding considered to be life-threatening by the treating physician.

We took permission from the Ethical Review committee at Rashid hospital for this data collection. To maintain confidentiality, all patient data was coded and de-identified before analysis.

Statistical analysis

Data was analyzed using SPSS (Statistical Package for the Social Sciences) version 20. Mean±Standard deviation, and medians with interquartile range (IQR) are reported for continuous variables, and proportions for categorical variables. Comparisons were made between Arabs and non Arabs with respect to basic demographic characteristics, stroke severity and type, and safety and efficacy outcomes. Independent sample t-test was used to compare various continuous variables and chi square test for comparing categorical variables between groups. We also analyzed the various time components across the three years, using one-way ANOVA. p-value of 0.05 or less was considered significant.

Results

Section 1: Demographics and outcomes of thrombolysed patients

A total of 176 patients received intravenous thrombolysis between September 1, 2011 and August 31, 2014. Of these only one patient was wrongly thrombolysed and he was eventually diagnosed as having brainstem encephalitis. Mean age of our patients was 50.84 (SD 14.17, range 22-84 years) years and 83.5% were men. Almost two thirds of the patients (62.1%) were of South Asian origin, followed by Arabs (17.5%) and Far East Asians (10.2%). 145 patients (82.4%) presented via Emergency Medical Services and the median onset to door time was 80 minutes (IQR 60-115 minutes). Median door to needle time for all patients was

60 minutes (IQR 55-77). Small vessel strokes were the commonest subtype (31.1%), followed by cardioembolic (20.9%) and large artery strokes (17.5%). Forty eight (27.4%) patients had strokes of undetermined etiology. Hypertension was the most common risk factor reported by 95 of the thrombolysed patients (54.2%) followed by dyslipidemia and smoking. A quarter of the patients were diabetic and ten percent had history of prior stroke. Table 1 demonstrates the demographic and risk factor profiles of the thrombolysed patients.

Pre-treatment mean NIHSS was 11.9 points (SD 4.33, Median 12, IQR 9-15). Seven patients had intra-arterial thrombolysis and six of these also required mechanical thrombectomy. At discharge, 71.2% of the thrombolysed patients had a good functional outcome defined as an mRS of 2 or less. The median NIHSS had also improved to 4 (IQR 2-8) at discharge. When safety outcomes were analyzed, 12(6.8%) of the 176 subjects had symptomatic intracranial hemorrhage of which four died in hospital and another three required decompressive surgery. None of the subjects had life threatening extracranial bleeds. Nineteen subjects had malignant Middle Cerebral artery infarctions, of which 10 required decompressive surgery. Twelve patients died during a hospital stay (6.8%). The efficacy and safety outcomes are shown in Table 2.

Section 2: Comparison of Arabs with Non-Arabs

We compared the demographic and risk factor profiles of Arabs with non-Arabs and found significant differences between the two groups. Patients of Arab origin were older at stroke onset (56.3±14.65 years versus 49.7±13.8 years, p=0.02) and a significantly higher proportion had hypertension (77.4% versus 50%, p-value 0.005), dyslipidemia (54.8% versus 35.2%, p-value 0.04) and diabetes (45.2% versus 20.4%, p-value 0.004), compared to their non-Arab counterparts. Stroke severity, time to treatment and its components, safety and efficacy outcomes were comparable between the two groups.

Section 3: Performance of Stroke Service over 3 years

We also analyzed the performance of our stroke service over the three years after introduction of intravenous thrombolysis. Table 3 demonstrates the various time components across the three years. There was a statistically significant improvement in all time components, with the mean door to needle time improving from 78.9 minutes in the first year to 57.4 minutes in the third year of our thrombolysis service (p<0.001). Also the proportion of subjects receiving intravenous thrombolysis within 60 minutes of hospital arrival improved from 21.9% in the first year of service to 70.8% in the third year. Graph 1 and 2 depict this improvement in timely administration of intravenous thrombolysis.

Discussion

Our study demonstrates that the outcomes of intravenous thrombolysis from our newly established stroke service are comparable to internationally reported data. We thrombolysed patients with moderate to severe strokes (median NIHSS 12) and the outcomes at discharge were excellent (median NIHSS 4). A total of twelve patients (6.8%) developed symptomatic intracranial hemorrhage defined as a deterioration in NIHSS scale of four or more points associated with a bleed on repeat CT scan. Of these four died in hospital.

Table 1: Demographic and Risk Factor Profile of Thrombolysed patients (n=176).

Age (years) Mean (SD)	50.84 (14.17) Range 22-84
Male (%)	147 (83.5)
Ethnicity (%)	
UAE Arab	6 (3.4)
Non UAE Arab	25 (14.3)
South Asian	110 (62.5)
Caucasian	15 (8.5)
Far East Asian	18 (10.2)
African	2 (1.1)
Income (%)	
Less than 25,000 AED	132 (75.0)
25-50,000 AED	34 (19.3)
Greater than 50,000 AED	10 (5.7)
Education level (%)	
Illiterate	57 (32.4)
High School	81 (46.0)
University	38 (21.6)
Mode of Admission (%)	
Via EMS	144 (81.8)
Via Non-EMS	31 (17.6)
In-hospital stroke	1 (0.6)
Baseline Functional status (%)	
Independent at home	175 (99.4)
Special care at home	1 (0.6)
Time lapse (Minutes) Median (IQR)	
Onset to door	80.00 (60.00-115.00)
Door to Emergency physician	3.00 (2.00-7.00)
Door to CT	20.00 (13.00-30.00)
Door to Neurologist	30.00 (22.50-48.50)
Door to Needle	60.00 (50.00-77.00)
TOAST (%)	
Cardioembolic	37 (21.0)
Large Artery Atherothrombotic	31 (17.6)
Small Vessel	55 (31.3)
Other determined	6 (2.8)
Undetermined	48 (27.4)
Vascular Risk Factors (%)	
Hypertension	96 (54.5)
Diabetes	43 (24.4)
Dyslipidemia	68 (38.6)
Smoker	57 (32.4)
Coronary Artery Disease	28 (15.9)
Prior Stroke	18 (10.4)
Atrial fibrillation	22 (12.5)
Peripheral arterial disease	2 (1.1)

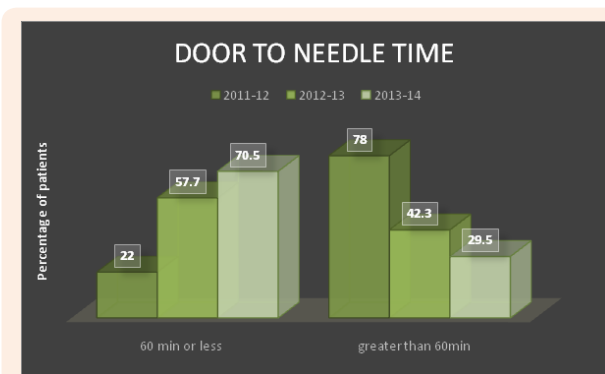
Table 2: Efficacy and Safety outcomes.

Outcome	
mRS 2 or less n (%)	
Day 0	26 (14.8)
Day 3	102 (58.0)
Discharge	126 (71.6)
3 months (71)	61 (85.9)
NIHSS (Median (IQR))	
Day 0	12 (9-15)
Day 3	7 (3-13)
Discharge	4 (2-8)
Post tpa Symptomatic Intracranial hemorrhage n(%)	12 (6.8)
In-hospital death (%)	12 (6.8)

Table 3: Improvement in Time components across three years.

Year	2011-12 (47)	2012-13 (60)	2013-14 (69)	p-value
Door to Emergency Physician	10.12 (14.19)	5.90 (7.99)	3.80 (3.17)	0.002
Door to CT	33.00 (21.91)	25.42 (16.23)	17.34 (9.57)	<0.001
Door to NMP	56.19 (23.55)	36.58 (18.47)	26.57 (13.58)	<0.001
Door to needle	78.88 (29.50)	61.41 (22.95)	57.22 (15.94)	<0.001

were analyzed separately, the median age of thrombolysed Arab patients was slightly higher (56 years) but still lower than that reported internationally. This is consistent with the emerging data suggesting a much younger age at stroke onset in Asian population.



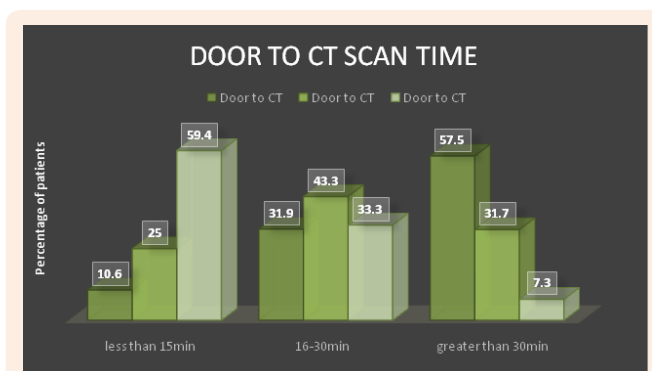
Graph 2: Improvement in Door to Needle time over three years of service.

When risk factor profiles for the thrombolysed patients were compared, we found that the proportion of hypertensive patients was almost the same as that seen in some of the Western cohorts. However, the proportion of diabetics was higher compared to reports from other countries (15% in the Canadian [13] and Belgian [15] cohorts and 18.8% from China [19]). When comparing Arabs to non-Arabs within our cohort, this proportion was much higher, with 45.2% Arabs reporting diabetes, 77% reporting hypertension and more than 50% reporting dyslipidemia. This is consistent with high prevalence of vascular risk factors reported from a population based study from Abu Dhabi. Atrial fibrillation was much less common in our cohort compared to international data which may be because our patient population was much younger.

The severity of stroke for our thrombolysed patients is comparable to patients from other thrombolysis registries. In the recent Asian cohort [22] the median NIHSS at presentation was 12, similar to our patients. The European and North American cohorts [13-17] report a slightly higher median NIHSS.

We used the standard dose of 0.9mg/kg alteplase for our patients. This is the dose used in the NINDS rtPA trial and all Western countries. However, as pointed out by a recent review [23], the doses used in Asia are more diverse. After the Japanese Acute Stroke Trial [24] which demonstrated the efficacy of 0.6mg/kg alteplase with fewer hemorrhagic complications, various Asian countries have adopted lower doses of alteplase for their patients. This precludes effective comparisons between various Asian cohorts. In our patients, we used the standard 0.9mg/kg dose, and found our symptomatic ICH rates to be slightly higher than those reported from USA and UK [16,17].

The median onset to treatment time (OTT) was 145 minutes (IQR 116-190 minutes) for our thrombolysed patients. This compares very favorably with available international data on initial experiences with thrombolysis. From developed countries



Graph1: Improvement in Door to CT time over three years of service.

When comparing our results with the initial thrombolysis experience from around the world, several interesting observations can be made. Firstly, the age of stroke onset for our patients is almost two decades younger when compared to Western countries [13-16], and almost one decade younger than that reported from other Asian countries [17-21]. When Arabs

[13-17] median OTT is reported between 140 and 155 minutes whereas much higher values are reported from Asian countries like China [19] and Singapore [21]. The median door to needle time for our patients was 60 minutes. When initial experiences are compared with developed Western nations as well as developing Asian countries, this figure is much lower indicating the excellent performance of our stroke service. Furthermore,

we have demonstrated that since the establishment of our stroke service three years ago, each year the performance in terms of timely administration of intravenous thrombolysis is consistently getting better.

Table 4 summarizes how our results compare with thrombolysis outcomes from other developed as well as developing countries.

Table 4: Comparing Thrombolysis experience between countries

Country	Number of patients	Window Dose	Onset to needle time	Stroke Severity	Outcome	Primary safety outcome
Dubai (UAE) 2011-2014	176 Median Age 49 (40-62)	4.5 0.9mg/kg	OTT 145 (116-190) DNT 60 (IQR 50-77.5)	NIHSS 12 at onset discharge 4		SICH 6.8%
Canada[13] 1999-2001	1135 Median age 73	3 0.9mg/kg	OTT 155 (130-175) DNT 85 (60-109.5)	NIHSS 14 (9-19)	mRS 0-1 31.8% 90 day mortality 22.3%	SICH 4.6% Any clinical decline within 24 hours associated with hemorrhage on follow up CT
SITS MOST 2002-2006[14] 14 EU countries	6483 Median age 68	3 0.9mg/kg	OTT 140 (115-165) DNT 68 (30)	NIHSS 12 (8-17)	mRS 0-2 at 3 months 54.8%	SICH 4.6% ECASS
Belgium[15] 2002-2007	743 Median age 71	3 0.9mg/kg	Median OTT 140 DNT 75	NIHSS 14 (9-19)	mRS 0-2 43.5%, Mortality 23% at 3 months	SICH 6.9% ECASS
USA[16] 1996-2000	269 Mean age 68	3 0.9mg/kg	OTT 137 DNT Mean 70 (28)	NIHSS at onset mean 14.4 (6.1) At discharge 6.6 (6.9) Median 3	3 month outcomes not reported	SICH 5.6% ECASS
UK[17] 2002-2006	327 SITS MOST Median age 68 287 SITS ISTR Median age 72	3 0.9mg/kg	OTT Median 155 OTT Median 165	NIHSS at onset median 14.5	Outcome at 3m 48% mRS 0-2	SICH 4.8% ECASS 3.2% SITS-MOST
Poland[18] 2003-2007	481	3 0.9mg/kg	OTT Median 160 DNT 82(mean)	NIHSS Mean 11	Outcome at 3m 54% mRS 0-2	SICH 1.2% (SITS MOST)
China[19] 2007-2008	181	3 56% received 0.9mg/kg	OTT 180 (150-228) DNT 116 (IQR 70-150)	NIHSS 4-14 (56.4%) NIHSS ≥15 (29.8%)	Not reported	Not reported
Iran[20] 2010-2012	37 Mean age 70.2	4.5 0.9mg/kg	Onset to needle mean 186 (61)	NIHSS at onset 15.4 (4.6) 7day 12.8 (2.5)	Not reported	SICH 5.4% Any hemorrhage with clinical deterioration
Singapore[21] 2000-2008	130 Mean age 60	3 Low dose + standard dose	OTT 160 median	NIHSS at onset 14 median	mRS 0-1 at 3 months 35% low dose 59% standard dose	SICH 6.2% (ECASS) Any hemorrhage with clinical deterioration of NIHSS 4 or more
Asia[22] (South Korea, China, India, Singapore) 2006-2008	591 Median age 64	3 0.9mg/kg	OTT 130	NIHSS at onset 12	mRS 0-2 at 3 m 62.5%	SICH 1.9% (SITS MOST) SICH 5.6% (ECASS)
Australia[25] 2002-2008	581 Median age 73	3 0.9mg/kg	OTT 145 (123-166) DNT 75 (IQR 57-98)	NIHSS 13 at onset	Outcome reported as odds 18.6% mortality at 3 months	6.6% ECASS 1.3% SITS MOST

To the best of our knowledge, this is the first comprehensive report on thrombolysis experience and outcomes from an Arab country. We have shown that a dedicated stroke service with individuals committed to improving stroke care can achieve results comparable to any developed nation. Additionally, our data demonstrates how there is room for improvement in timely administration of rtPA if continuous reinforcement is done for the individuals involved in acute stroke care. The strength of our study also lies in the multi-ethnic origin of our patients, giving a unique comparison between various groups in terms of stroke characteristics and risk factors. Also, Thrombolysis at our center is covered by the government, so non affordability did not serve as a limitation to treatment as is the case with many developing countries.

Our study had several limitations as well. Firstly, the representation of Arabs in this cohort of thrombolysed patients was low, only 18% with the rest being expatriates working in the country. This represents the structure of the UAE population as well. Due to their relatively small numbers, conclusions from the study cannot be generalized to people of Arab origin only. Secondly, our follow-up data was also limited, with only 71 of the 162 discharged patients being accessible at 3 months. This was because following stroke, most expatriates return to their home countries. As a result, the follow-up results are biased since only those who were functionally independent and able to work stayed back in the country and those with poorer outcomes had most likely left and could not be contacted. For this reason we were unable to effectively compare our 3 month outcomes with reports from other thrombolysis registries. Yet another limitation of the study is that we have not been able to effectively evaluate the protocol violations that happened at our center and the impact that had on patient outcomes.

Conclusions and Recommendations

This is the first comprehensive thrombolysis registry from an Arab country. We have reported the safety and efficacy of intravenous thrombolysis in an ethnically diverse group and have shown that our results are comparable to any developed country. We have also shown that strokes are occurring at a younger age in our population, and the prevalence of certain risk factors like diabetes needs special attention.

We feel that the Rashid hospital experience can be duplicated in other parts of the country. Keeping in view the rising incidence of cardiovascular risk factors and stroke, there is a need to set up stroke services in other hospitals across UAE, and staff needs to be trained in appropriate administration of intravenous thrombolysis.

Competing Interests

The authors declare that they have no competing interests.

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