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Original article

Human metapneumovirus-associated community-acquired pneumonia in adults during the first wave of COVID-19

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Abstract

Objective: The clinical course of human metapneumovirus (hMPV) infection is similar to that of coronavirus 2019 disease (COVID-19). However, community-acquired hMPV infections in adults have not yet been sufficiently investigated. We examined the detection status of hMPV antigens and the clinical features of positive patients during the first wave of COVID-19, which coincided with the epidemic season of hMPV infection in Japan.

Methods: In this cross-sectional, observational, and single-center study, we recruited consecutive individuals who visited the Japan Agricultural Cooperatives Kochi Hospital due to fever, respiratory symptoms, or close contact with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected persons during the period from January to May 2020.

Results: The positive rate of immunochromatography for hMPV antigens from nasopharyngeal swabs was 9.5% (4/42), and four positive cases were community-acquired pneumonia (CAP) (5.3% of all CAP). The positive rate of hMPV antigens in the CAP group (30.8%, 4/13) was higher than that in the non-pneumonia group (0.0%, 0/19) ($p < 0.05$). The average age of the four adult patients with CAP was 69.8 years (range 35–93). Mean white blood cell counts and C-reactive protein blood levels were 6,250 cells/μL (3,500–12,180) and 4.30 mg/dL (4.05–7.04), respectively. Chest computed tomography images were diverse and two patients showed dense consolidation. No multi-organ disorder was noted during the clinical course in any of the four cases, and their prognoses were good.

Conclusion: hMPV infection may be considered in the differential diagnosis of COVID-19 and CAP in Japan under the preventive measures for SARS-CoV-2 infection, at least during the epidemic season of hMPV infection.

Key words: human metapneumovirus, community-acquired pneumonia, COVID-19, SARS-CoV-2, differential diagnosis

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Introduction

Human metapneumovirus (hMPV) is an enveloped negative-sense RNA virus that targets the respiratory tract epithelium. hMPV was newly identified in 2001 and is thought to cause upper or lower respiratory tract diseases, mainly in children[1–4]. However, it has become clear that hMPV also causes outbreaks in elderly individuals in long-term care facilities (attack rate 34–72%) and inpatients with severe motor and intellectual disabilities (attack rate 41%)[5–7]. In such cases, some infected patients present with pneumonia and severe respiratory failure. In addition, hMPV was detected in approximately 4% of adult patients with community-acquired

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pneumonia (CAP) requiring hospitalization[8, 9], and the frequency of hMPV infection in patients with severe pneumonia in intensive care units was 6.6%[10]. However, in Japan, the hMPV antigen test has not been actively performed for adult patients because the test is only covered by health insurance for children. Therefore, intrafamily or nosocomial infections due to hMPV may occur or may have already occurred without detection. Moreover, the actual hMPV detection status in daily practice and the clinical presentation of positive patients, including radiological manifestations, have not been sufficiently investigated in adults in communities.

Currently, coronavirus 2019 disease (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is expanding worldwide. Moreover, the number of active COVID-19 cases will continue to fluctuate over the long term. Adults with COVID-19 have a wide range of disease presentations from asymptomatic infection to a flu-like illness, pneumonia, and severe respiratory failure, after an incubation period of 6.4 days (95% credible interval: 5.6–7.7)[11, 12]. Therefore, differentiation from other respiratory diseases, especially infections caused by known microorganisms that can induce atypical pneumonia, is important for disease control[13].

In the typical clinical course of hMPV infection, upper respiratory tract symptoms appear after an asymptomatic period of about four to six days and resolve spontaneously in about one week; however, some patients present with lower respiratory tract involvement with persistent wheezing, including asthma and COPD exacerbations, or pneumonia[14–21]. Therefore, it is not always easy to distinguish hMPV infections from COVID-19 based solely on the clinical course. In addition, the typical computed tomography (CT) appearance of COVID-19, that is, bilateral subpleural ground-glass opacities (GGOs) with or without consolidation, overlap with those of other viral pneumonias, including hMPV[22]. In fact, hMPVs have been identified by a comprehensive search of clinical specimens of patients with suspected COVID-19 in which SARS-CoV-2 was not detected, although details of the clinical presentations of hMPV-positive cases are unknown[23, 24].

In this study, we examined the detection status of hMPV antigens from adult nasopharyngeal swabs and the clinical features of positive patients in the first wave of COVID-19, which coincided with the epidemic season of hMPV infection in Japan (around January–May 2020)[25]. Our data indicated that the positive rate of all tests was 9.5% (4/42) and four positive cases were CAP (5.3% of all CAP), suggesting that hMPV infection may be considered in the differential diagnosis of COVID-19 and CAP in Japan, at least during the epidemic season of hMPV infection.

Materials and Methods

Study design

In this cross-sectional, observational, and single-center study, we recruited consecutive individuals who visited Japan Agricultural Cooperatives (JA) Kochi Hospital due to fever, respiratory symptoms, or close contact with SARS-CoV-2 infected persons during the period from January to May 2020.

This study was approved by the Ethical Committee of JA Kochi Hospital (approval no. R2-003).

Patients

A total of 111 patients with pneumonia and 489 individuals who did not present with pneumonia but had undergone any rapid diagnostic tests for respiratory tract infections were enrolled. The tests included polymerase chain reaction (PCR) for SARS-CoV-2, immunochromatography (IC) for hMPV, influenza and respiratory syncytial virus (RSV) antigens using nasopharyngeal swabs, IC for urinary *Legionella* and *Streptococcus pneumoniae* antigens, and an enzyme immunoassay for serum anti-*Mycoplasma pneumoniae* IgM antibodies. We also investigated 34 pediatric patients who underwent hMPV antigen testing during the same period.

The adult subjects were divided into the following five groups: CAP (75 cases including 21 patients who required hospitalization), nursing and healthcare-associated pneumonia (NHCAP; according to the Japanese Respiratory Society guidelines) and/or aspiration pneumonia (31 cases including 27 patients requiring hospitalization), non-infectious pneumonia (five cases; cryptogenic organizing pneumonia [two cases], hypersensitivity pneumonia, eosinophilic pneumonia, and nonspecific interstitial pneumonia), patients without pneumonia (473 cases), and no clinical symptoms (16 cases; all were individuals who had close contact with SARS-CoV-2 infected people). Pediatric subjects included 27 cases of CAP and seven cases of acute bronchitis.

Data collection

Clinical and laboratory data and radiological findings of all subjects enrolled in this study were reviewed from the electronic medical records. PCR tests for SARS-CoV-2 were performed at the Kochi Prefectural Institute for Hygiene and Environment, and other tests were performed at our laboratory, including the use of ImunoAce Flu, RSV Neo and hMPV (TAUNS, Izunokuni, Shizuoka, Japan), BinaxNOW *Legionella* and *Streptococcus pneumoniae* (Abbott Laboratories, Chicago, IL, USA), and ImmunoCard Mycoplasma (Meridian Bioscience, Cincinnati, OH, USA).

We investigated the differences in the positive rates of the rapid diagnostic tests among the five groups and extracted clinical data regarding the positive adult cases for the

hMPV antigen test. Next, the CT findings of the hMPV-positive adult cases were evaluated with reference to a report by a radiologist at our institute.

Statistical analyses

Fisher's exact test was used for comparisons between groups. All tests were two-tailed, and P values <0.05 were considered statistically significant.

Results

The positive rates of rapid diagnostic tests for respiratory tract infections in the study subjects are shown in Table 1. The positive rate for all hMPV antigen tests was 9.5% (4/42), and the four positive cases were CAP (5.3% of all CAP). The positive rate in the CAP group (30.8%, 4/13) was higher than that in the non-pneumonia group (0.0%, 0/19) (P<0.05). The influenza antigen test positive rate in the non-pneumonia group (25.1%, 102/407) was higher than that in the NHCAP/aspiration pneumonia group (0.0%, 0/16) (P<0.05). In the CAP group, the positive rate for hMPV antigen tests (30.8%, 4/13) was higher than that for *Legionella* antigen tests (0%, 0/31) (P<0.01) and *Streptococcus pneumoniae* antigen tests (4.3%, 2/47) (P<0.05). In the non-pneumonia group, the positive rate for influenza antigen tests (25.1%, 102/407) was higher than that for hMPV (0.0%, 0/19) and RSV (0.0%, 0/16) antigen tests ($p < 0.05$) and *Legionella* (0.0%, 0/28) and *Streptococcus pneumoniae* (0.0%, 0/57) antigen tests (P<0.01). The positivity rate for anti-*Mycoplasma pneumoniae* IgM antibodies (20.4%, 20/98) was also higher than that for hMPV (0.0%, 0/19) antigen tests (P<0.05) and *Legionella* (0.0%, 0/28) and *Streptococcus pneumoniae* (0.0%, 0/57) antigen tests (P<0.01).

The clinical features of the four adult patients with community-acquired hMPV infection are shown in Table 2. The average age was 69.8 years (range 35–93), and two patients were male. Two patients had underlying vascular disease, and one had bronchial asthma. Fever (>37.0°C) was observed in all patients, with an average duration of 4.3 days (1–11). Three patients presented with fatigue or loss of appetite. Cough was observed in three patients, one of whom had sputum production (normal flora in culture). Wheezing was observed in one patient. Mean white blood cell counts and C-reactive protein blood levels were 6,250 cells/μL (3,500–12,180) and 4.30 mg/dL (1.16–7.04), respectively. Biochemical tests revealed a slight increase in creatine and a decrease in Alb in one patient, but no abnormalities in lactic dehydrogenase, aspartate aminotransferase (AST), alanine transferase (ALT), and creatinine kinase (CPK) levels. The results of the other rapid diagnostic tests for respiratory tract infections were all negative, suggesting no mixed infections. The main CT findings were bronchial wall thickening, lobular opacity, and dense consolidation, and these findings were observed in both lungs of all four patients. Representative CT images of the four cases are shown in Figure 1. Antibiotics were empirically administered to these patients without evidence of bacterial co-infection, and all patients recovered from pneumonia.

Discussion

hMPV can cause respiratory tract infections in patients

Table 1 Positive rates for the rapid diagnostic tests for respiratory tract infections in the study subjects

	hMPV*		SARS-CoV-2		Influenza†		Respiratory syncytial virus		*Mycoplasma pneumoniae*		*Legionella*		*Streptococcus pneumoniae*	
	n tested	*n* positive (%)	*n* tested	*n* positive (%)	*n* tested	*n* positive (%)	*n* tested	*n* positive (%)	*n* tested	*n* positive (%)	*n* tested	*n* positive (%)	*n* tested	*n* positive (%)
Adults														
CAP (*n*=75)‡	13	4 (30.8)	17	1 (5.9)	19	1 (5.3)	8	0 (0)	34	5 (14.7)	31	0 (0)	47	2 (4.3)
NHCAP /aspiration pneumonia (*n*=31)	7	0 (0)	5	0 (0)	16	0 (0)	3	0 (0)	6	1 (16.7)	15	0 (0)	24	2 (8.3)
Non-infectious pneumonia (*n*=5)	3	0 (0)	4	0 (0)	0	NA	1	0 (0)	4	0 (0)	4	0 (0)	4	0 (0)
Non-pneumonia (*n*=473) §	19	0 (0)	7	0 (0)	407	102 (25.1)	16	0 (0)	98	20 (20.4)	28	0 (0)	57	0 (0)
No clinical symptoms (*n*=16)	0	NA	16	1 (6.3)	0	NA	0	NA	0	NA	0	NA	0	NA
Children														
CAP (*n*=27)	27	3 (11.1)	1	0 (0)	5	0 (0)	19	1 (5.3)	27	8 (30.0)	0	NA	0	NA
Acute bronchitis (*n*=7)	7	0 (0)	0	NA	1	0 (0)	0	NA	6	1 (17.0)	0	NA	0	NA

CAP: community-acquired pneumonia; NHCAP: nursing and healthcare-associated pneumonia; hMPV: human metapneumovirus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. Adults: * CAP vs. non-pneumonia: P<0.05. † Non-pneumonia vs. NHCAP/aspiration pneumonia: P<0.05. ‡ hMPV vs. *Legionella*: P<0.01. hMPV vs. *Streptococcus pneumoniae*: P<0.05. § Influenza vs. hMPV, respiratory syncytial virus: P<0.05. Influenza vs. *Legionella*, *Streptococcus pneumoniae*: P<0.01. *Mycoplasma pneumoniae* vs. hMPV: P<0.05. *Mycoplasma pneumoniae* vs. *Legionella*, *Streptococcus pneumoniae*: P<0.01.

Table 2 Clinical features of four adult patients with community-acquired hMPV infection

Patient no.	Age (years) / Sex	Comorbidities	Smoking status	Symptoms and signs	Highest body temperature (℃)	White blood cell count (cells/μL)	C-reactive protein (mg/dL)	LDH (IU/l)	AST (IU/l)	ALT (IU/l)	CPK (IU/l)
1	85/F	Old cerebral infarction, hypertension, dyslipidemia	Nonsmoker	Fever (1 days), Cough, Sputum (white or yellow), Loss of appetite	38.4	3,500	4.96	227	33	31	54
2	93/F	Nothing particular	Nonsmoker	Fever (3days), Cough, Wheeze, Fatigue	38.8	4,900	4.05	234	24	18	39
3	35/M	Nothing particular	Current	Fever (11 days), Cough	39.9	121,800	7.04	209	20	20	98
4	66/M	Bronchial asthma, hypertension	Former	Fever (2 days), Fatigue	37.4	4,430	1.16	272	33	25	162

Patient no.	Albumin (g/dl)	BUN (mg/dl)	Creatinine (mg/dl)	Rapid Test						Main CT findings	Affected lobes	Outcome
				SARS-CoV-2	Influenza	RS virus	*Mycoplasma pneumoniae*	*Legionella*	*Streptococcus pneumoniae*			
1	4.4	14.2	1.2	NT	(–)	NT	(–)	(–)	(–)	Lobular opacity Bronchial wall thickening	Right middle and lower lobe. Left lower lobe	Survived
2	3.2	17	0.73	(–)	(–)	(–)	(–)	(–)	(–)	Dense consolidation Lobular opacity Bronchial wall thickening Pleural effusion	All lobes	Survived
3	4	11.4	0.98	(–)	(–)	(–)	(–)	(–)	(–)	Dense consolidation Lobular opacity Bronchial wall thickening	Bilateral lower lobes	Survived
4	3.4	8.2	0.65	(–)	(–)	(–)	(–)	(–)	(–)	Lobular opacity Bronchial wall thickening	All lobes	Survived

RS virus: respiratory syncytial virus.

of all ages. However, symptomatic infections mostly occur in younger children or older adults. In a series of 37 cases of hMPV infection in Canada, 35% of patients were under five years of age, and 46% were over 65[26]. Three of the four adult patients with hMPV infection diagnosed at our hospital were elderly (Table 2). Since most children are infected by the age of five according to seroprevalence study data, reinfection is thought to be the cause of hMPV infection in adults[1]. Therefore, in adult hMPV infections, the main presentation is upper respiratory tract infections, and the frequency of lower respiratory tract infections is lower than that in children[14–16]. However, all four patients diagnosed with hMPV infection at our hospital were in the CAP group (13 cases), and no hMPV antigens were detected in seven patients with NHCAP/aspiration pneumonia and 19 without pneumonia (Table 1). Clinical presentations of adult hMPV infections have been investigated mainly in outbreaks in long-term care facilities and hospitals. In this study, the main target of the analysis was patients infected in the community, which may be the reason why pneumonia was the main presentation, unlike in previously reported cases.

In the analysis of outbreaks of hMPV infection in long-term care facilities, patients with pneumonia were reported to have elevated AST, ALT, CPK, and white blood cell counts[27]. In the four cases of community-acquired hMPV pneumonia, leukocytosis was observed in one case, but no increase was observed in the other biochemical tests (Table 2). The main CT finding of hMPV pneumonia in immunocompromised patients was extensive bilateral GGOs and signs of bronchitis/bronchiolitis (thickening of peribronchovascular bundles and central lobular nodules)[28]. On the other hand, in hMPV-infected patients in outbreaks in long-term care facilities, lobular opacity with bronchial wall thickening was most frequently observed, while GGO and dense consolidation were rare[27]. All four cases of community-acquired hMPV pneumonia showed lobular opacity with

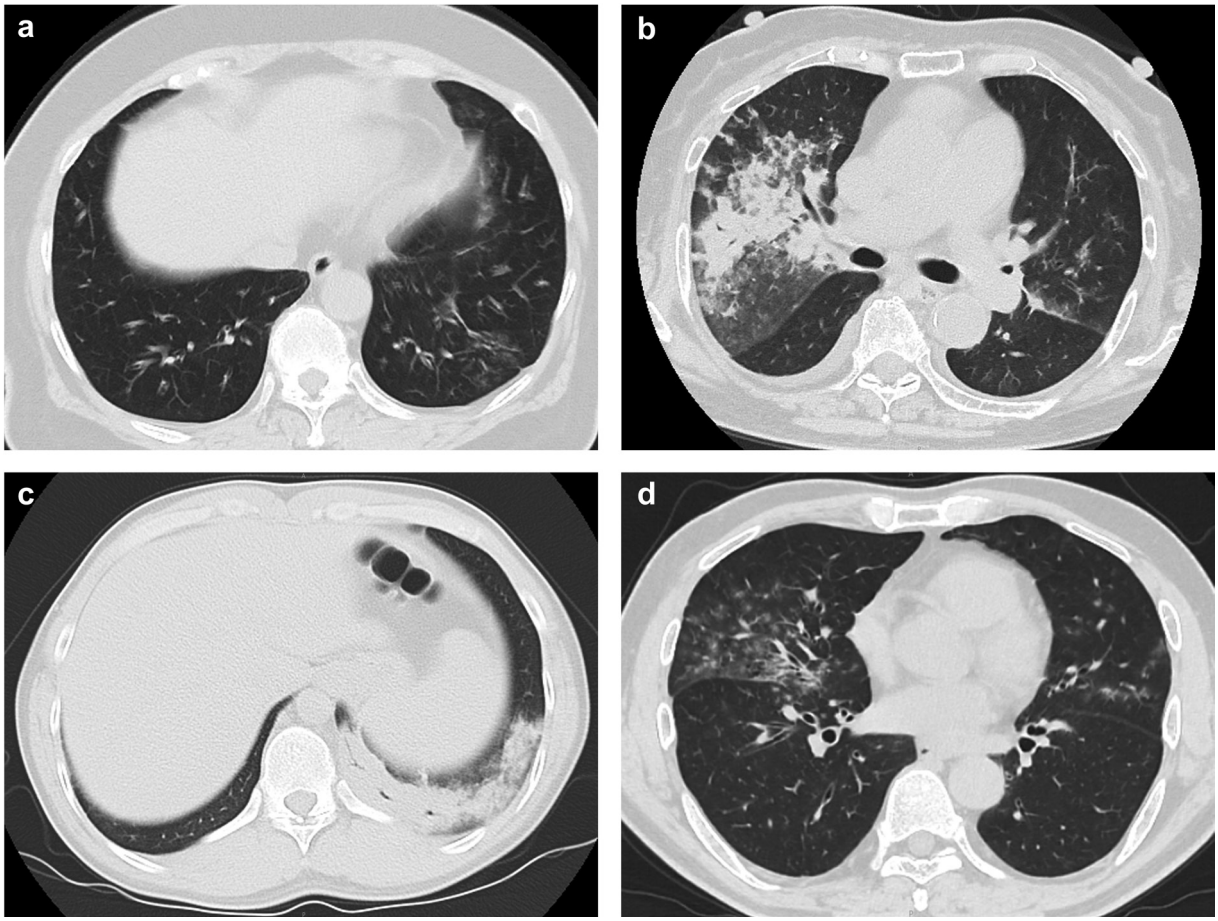

Figure 1 Representative chest CT images in community-acquired hMPV pneumonia. a: Patient no. 1. b: Patient no. 2. c: Patient no. 3. d: Patient no. 4. a, d: Lobular opacities with bronchial wall thickening. b, c: Dense consolidation.

bronchial wall thickening, consistent with previous reports, and two of them had rare dense consolidation. Both patients exhibited persistent fever (Table 2). In hMPV infections that occur in adults in the community who appear to have no immune disorders, inflammatory host responses in the lungs may be strongly induced, making them prone to dense consolidations. However, no multi-organ disorders seen in patients with hMPV infection in long-term care facilities were noted during the clinical course in any of the four cases, and their prognosis was good.

Transmission of hMPV appears to occur through direct or close contact with secretions carrying the virus involving droplets, aerosols, or medical equipment[29]. Intrafamily transmission of hMPV occurs mainly among children, but child-to-adult transmission has also been reported[19]. One patient with hMPV pneumonia (patient no. 3) had a child suspected of having MPV infection. Standard precautions were used for two patients with hMPV pneumonia requiring admission to our hospital (patient no. 1 and 2), and no nosocomial infection was confirmed.

The epidemic season of hMPV infection varies depending on the region, and in Japan, it is from winter to spring (around January to May)[25]. However, sporadic cases occur throughout the year. The number of adult patients diagnosed with influenza at our hospital from January to May 2020 was 103, which decreased compared to the same period of the previous year (281: data not shown). The influenza epidemic in 2020 may have been curbed by measures taken to prevent SARS-CoV-2 infection[30]. The decrease in patients with influenza may be related to the low positive rate of the *Streptococcus pneumoniae* antigen in the CAP group (4.3%, 2/47) in this study (Table 1), but the inoculation rate of *Streptococcus pneumoniae* vaccine has not been examined due to insufficient descriptions in electronic medical records. There were three hMPV-positive cases in children from January to May 2020 at our hospital (Table 1), a fall from the same period in the previous year (six: data not shown), as in the case of influenza. It is not clear to what extent measures for avoiding COVID-19 have contributed to the prevention of community-acquired hMPV infections in adults due to insufficient data from the previous year. However, the fact that adult MPV infections were observed in four cases,

comparable to positive cases in children under the measures for COVID-19 prevention, accounting for 5.4% of CAP suggests that hMPV infection should be considered as a differential diagnosis for COVID-19. Reverse transcription (RT)-PCR is the most sensitive method for detecting hMPV[31]. However, like shell vial centrifugation cultures, it is used mainly in research institutes and is not available in clinical practice. Serum antibody titers have also been measured in epidemiological studies. Currently, the only test available in clinical practice in Japan is the hMPV antigen test with IC using a nasopharyngeal swab. Using real-time RT-PCR as the reference standard, the sensitivity, specificity, and false positive rate of the IC assay have been reported to be 70.6%, 95.5%, and 4.5%, respectively[32]. While the IC assay is less sensitive than real-time RT-PCR, it is a simple and rapid test for diagnosing hMPV infections.

The present study has several limitations. First, the study population of this retrospective study was small, and the subjects were selected from a medium-sized hospital. Therefore, the results do not necessarily represent a nationwide situation. Second, the research period was limited to the epidemic of hMPV infections, and the significance of antigen testing in sporadic community-acquired hMPV infections in adults is unclear. Third, laboratory tests did not confirm mixed infection in patients with CAP, but bacterial co-infection and false positives for the hMPV antigen test could not be fully ruled out due to empirical antibiotic administration. Fourth, the hMPV antigen test was performed at the discretion of the attending physician to obtain a differential diagnosis from COVID-19 or atypical pneumonia, and the proportion of cases in which the test was performed was low in each group. In this regard, hMPV-infected individuals without symptoms or with only fever-free upper respiratory tract symptoms have not been sufficiently evaluated. Fifth, because this was a retrospective study, the route of infection and intrafamily transmission were not fully investigated.

Conclusion

hMPV infection may be considered in the differential diagnosis of COVID-19 and CAP in Japan under the preventive measures for SARS-CoV-2 infection, at least during the epidemic season of hMPV infection. However, the evidence we have provided is very limited, and further large-scale prospective cohort studies, especially for adults, are needed to clarify community-acquired hMPV infection status and its clinical presentations.

Because intrafamily or nosocomial infection due to hMPV may occur or may have already occurred without being detected, insurance coverage for hMPV antigen tests conducted on adults is desirable.

Author contributions: KS drafted the manuscript. TS edited and submitted the manuscript. SM and KT were involved in diagnosing and treating patients. MK, HK, and YT contributed to the data collection. All authors have read and approved the final manuscript.

Conflicts of interest: The authors declare that they have no conflict of interest.

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