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Enterovirus respiratory infection in adults: an overlooked clinical burden emerging in the post-pandemic era

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SUMMARY

Enterovirus (EV) is increasingly identified as a cause of acute respiratory infections in adults, yet its clinical burden in real-world settings remains poorly characterized. Individuals with underlying chronic respiratory conditions, such as asthma or chronic obstructive pulmonary disease, are at heightened risk of severe respiratory compromise from EV infection, as they are from many other respiratory pathogens.

Following an increase in EV circulation in our healthcare district in recent years, as reported in other countries, we performed a retrospective analysis of all adults (≥18 years) including only acute respiratory EV infection documented by multiplex RT-PCR of nasopharyngeal swabs between January and December 2024. Seventy patients were included (mean age 68.5 ± 19.2 years, balanced sex distribution) with a high prevalence of comorbidities, particularly cardiovascular disease (37%) and chronic respiratory disease (34%). The clinical presentation was dominated by cough (74%) and dyspnea (70%), whereas fever was less common. At presentation, 41% (n=29) met criteria for acute respiratory failure, defined as a partial pressure of oxygen <60 mmHg on arterial blood gas. Chest radiography was abnormal in most cases (74%), showing predominantly interstitial markings (51%), followed by consolidations (16%) and mixed patterns (7%). Inflammatory markers were frequently elevated, with C-reactive Protein >0.5 mg/dL in 93.7% and leukocytosis in 44.3%. Forty patients (57%) required hospital admission, 35 (50%) needed oxygen or ventilatory support (predominantly low-flow oxygen), and seven patients (10%) required escalation to advanced support (high-flow oxygen in four cases, non-invasive ventilation in two, and invasive mechanical ventilation in one). Two patients (2.8%) were admitted to the Intensive Care Unit, and 30-day mortality was 2.8% (n=2). In our cohort, patients with COPD (n = 14) had the most severe course (respiratory failure 57%, oxygen requirement 64%, hospitalization 71%, 1 IMV, 1 death), whereas those with asthma (n = 7) had a comparatively milder clinical course (respiratory failure 43%, no ventilatory support, no deaths).

Overall, in our real-world scenario, EV infection was associated with frequent gas-exchange impairment, radiographic abnormalities, and clinically meaningful resource utilization in adults, particularly among those with chronic respiratory disease.

Keywords: Enterovirus, respiratory infection, adult patients, epidemiological surveillance.

INTRODUCTION

Enterovirus (EV) respiratory infections have traditionally been regarded as predominantly pediatric illnesses. Historically, clinical attention has focused on children because of the higher incidence of symptomatic EV infections in this age

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group and the association with outbreaks of severe respiratory disease, such as those caused by EV-D68 [1]. However, clinically significant EV disease has been increasingly recognized also in adults since the pre-pandemic era [2]. Reports from multiple regions have documented that adults, particularly those with underlying respiratory or cardiovascular comorbidities, can experience severe or complicated respiratory presentations associated with EV infection. Despite this, the true burden of EV in the adult population is likely underestimated, as routine respiratory virus diagnostics were historically performed less frequently in this population than in pediatric patients, and systematic surveillance for EV has often been lacking [3-6].

The COVID-19 pandemic profoundly disrupted typical patterns of respiratory virus circulation, with measures such as lockdowns, social distancing, and widespread use of non-pharmaceutical interventions greatly reducing seasonal respiratory infections. Following the relaxation of these measures, a "rebound" in respiratory virus activity was seen across Europe and North America, including renewed and, in some settings, sustained circulation of EV, particularly EV-D68 [4, 7]. This post-pandemic situation has increased clinical focus on EV as a cause of acute respiratory disease in adults, especially among individuals with vulnerabilities such as asthma or Chronic Obstructive Pulmonary Disease (COPD), as well as in elderly or comorbid populations [3, 5, 6].

Respiratory viruses, particularly EVs, are recognized triggers of acute airflow obstruction and exacerbations in susceptible individuals [8, 9]. In asthma, EV infection may exacerbate pre-existing epithelial dysfunction, promote airway inflammation, and impair mucociliary clearance, thereby increasing susceptibility to bronchospasm and more severe exacerbations [10]. Epidemiologic and clinical data indicate that EV-D68 infection is often associated with wheezing and asthma exacerbations in both children and adults, and frequently involves the lower respiratory tract [6, 11, 12]. Similarly, in patients with COPD, respiratory viral infections are commonly detected during exacerbations and are associated with increased symptom burden, inflammatory activation, and healthcare utilization [9, 13, 14]. These observations underscore the importance of considering EV infections as potential contributors to acute respiratory illness in adults, particularly in those with pre-existing airway disease. In addition to respiratory comorbidities, older age and the presence of chronic cardiovascular conditions may further increase susceptibility to severe EV-associated respiratory disease. Surveillance data from Europe and North America indicate that EV-D68 outbreaks have been associated with substantial morbidity in adults, with some patients requiring hospitalization and respiratory support [3-6]. However, clinical data describing adult presentations, outcomes, and healthcare resource utilization remain relatively scarce, particularly in real-world settings.

In our healthcare area, an ongoing epidemiologic surveillance program has documented substantial changes in respiratory virus circulation before, during, and after the SARS-CoV-2 pandemic. Notably, EV detections increased from less than 1% in the pre-pandemic period to approximately 3% in 2024, coinciding with the re-emergence of multiple seasonal respiratory pathogens [7, 15]. This trend underscores the need to better characterize the clinical spectrum and impact of EV infections in adults. Against this background, the present study aimed to assess the burden of EV-associated acute respiratory infections in adults within our healthcare network. Specifically, we conducted a retrospective observational analysis to characterize the demographics, comorbidities, clinical manifestations, radiographic and laboratory findings, and outcomes of adults with PCR-confirmed EV respiratory infections. By doing so, we sought to provide insight into the real-world clinical impact of EV in adults and to highlight populations at increased risk of severe disease, informing diagnostic, therapeutic, and preventive strategies in the post-pandemic era.

METHODS

We conducted a retrospective observational study across three hospitals: Santa Maria degli Angeli Hospital in Pordenone, Santa Maria dei Battuti Hospital in San Vito al Tagliamento, and the Hospital of San Giovanni dei Battuti in Spilimbergo, all within the Azienda sanitaria Friuli Occidentale network in northern Italy.

We retrospectively included all adult patients (≥18 years) evaluated for acute respiratory symptoms between 1 January and 31 December 2024 who

had EV detected by multiplex RT-PCR on a nasopharyngeal swab. To avoid duplicate observations, only the first EV-positive specimen per episode during the study period was included.
Respiratory specimens were tested using a multiplex real-time RT-PCR assay (Allplex™ Respiratory Panel Assays, Seegene®, Seoul, Republic of Korea), which reports rhinovirus and enterovirus as distinct targets. Because the panel concurrently interrogates multiple respiratory pathogens (viral and selected bacterial targets), results for other pathogens detected by the multiplex assay were also recorded. EV subtyping (e.g., EV-D68) was not performed. As part of routine clinical assessment, patients presenting with acute respiratory symptoms underwent SARS-CoV-2 antigen testing. In patients with suspected community-acquired pneumonia, urinary antigen testing for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* and blood cultures were obtained when clinically indicated. Additional microbiological investigations (e.g., blood cultures, respiratory cultures, urine culture, and other microbiological tests) were conducted at the treating physician's discretion, in accordance with hospital protocols. Where available, microbiology results were reviewed to exclude potential co-infections.
To maximize attribution of the index episode to EV, each case was adjudicated using: (i) multiplex panel results (systematically assessed for additional viral/bacterial targets); (ii) all available routine microbiology (blood cultures, urinary antigen test and respiratory cultures when obtained); and (iii) discharge diagnoses.
Patients were excluded if they tested positive for other viral targets or had a microbiologically documented bacterial infection during the index episode, as determined by clinical data, microbiological findings, and discharge diagnosis. For episodes with radiographic consolidation, we systematically reviewed urinary antigen tests and blood and respiratory cultures when obtained; we excluded cases with findings consistent with bacterial pneumonia (including pneumococcal urinary antigen positivity in a clinically compatible syndrome). The final analytic cohort was restricted to episodes in which EV was the sole pathogen detected by the multiplex panel and no alternative microbiological diagnosis was established.
Data were extracted from electronic medical records, including demographics, comorbidities (with specific details on documented asthma and COPD), symptoms at presentation, laboratory results (such as white blood cell count and C-reactive protein - CRP), imaging findings from chest radiography or ultrasound, arterial blood gas values, need for oxygen therapy or ventilatory support, patient disposition (discharge, general ward or ICU admission), length of hospital stay, and 30-day all-cause mortality. Acute respiratory failure was defined as PaO_2 less than 60 mmHg on arterial blood gas analysis [16].

RESULTS

During the study period, 135 respiratory specimens from 135 patients tested positive for EV. Pediatric cases were excluded, leaving 93 adults. Patients with documented concomitant bacterial infection and/or SARS-CoV-2 antigen positivity were also excluded. Regarding co-detections on the multiplex panel, rhinovirus (RV) was the only additional respiratory virus detected alongside EV in 12 patients. After exclusions (n=23), the final cohort included 70 adults with acute respiratory symptoms and confirmed EV infection, who were included in the final analysis (*Figure 1*).
The cohort's mean age was 68.5 ± 19.2 years, with a balanced sex distribution (*Figure 2*). Chronic comorbidities were frequent, particularly cardiovascular and respiratory conditions (*Table 1*). Table 1 presents clinical characteristics and outcomes. Respiratory symptoms were the primary reason for medical evaluation. Cough (74%) and dyspnea (70%) were the most common manifestations and frequently co-occurred, whereas fever was reported in a minority of cases. Overall, 41% of patients met criteria for acute respiratory failure (PaO_2 <60 mmHg). An additional 41% had clinically significant hypoxemia without meeting the definition of acute respiratory failure.
Radiographic findings were nonspecific and were present in most cases, including increased interstitial markings (51%), bibasilar consolidations (16%), or mixed patterns (7%). Only 26% of patients had normal chest X-rays.
More than half of patients (57%, 40 patients) required hospital admission. Length of stay most commonly ranged from 8 to 20 days. Overall, 50% of patients required supplemental oxygen or ventilatory support. The most common modality was conventional low-flow oxygen (n=35). Escalation

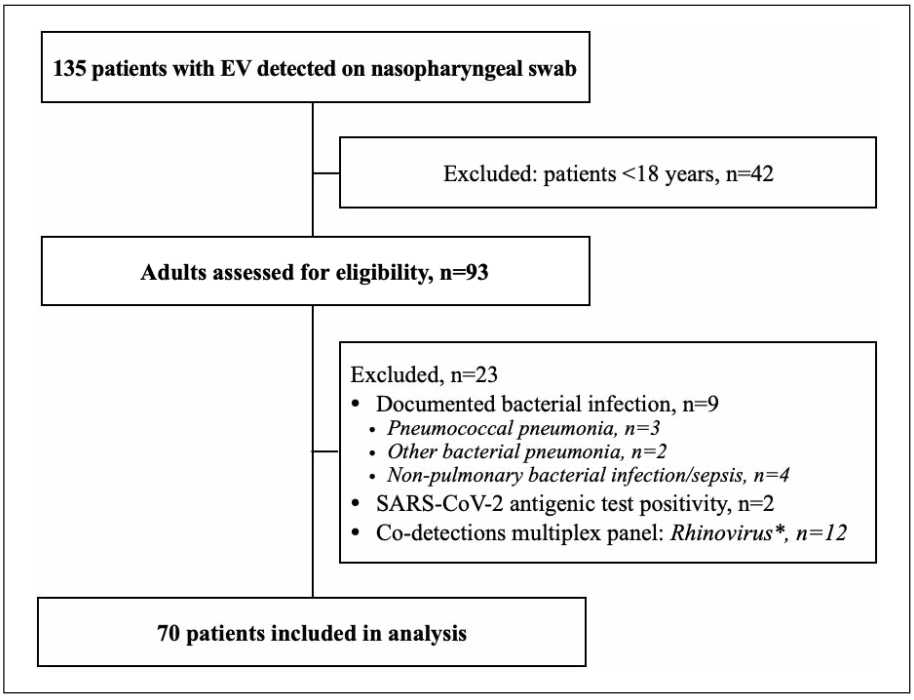

Figure 1
Flow diagram of patient selection. EV: enterovirus. *Rhinovirus was the only additional target detected with EV on the multiplex panel.

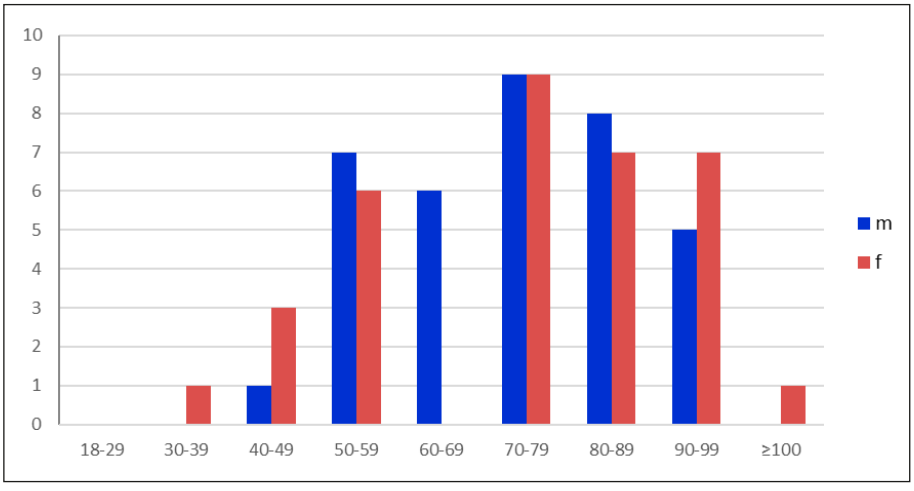

Figure 2
Distribution of patients by sex and age (years).

to advanced respiratory support occurred in 7 patients: high-flow nasal cannula (HFNC, n=4), non-invasive ventilation (NIV, n=2), and invasive mechanical ventilation (IMV, n=1). Two deaths occurred (2.8%); both were in older patients with significant comorbidities.

We conducted a focused subgroup analysis of patients with COPD and asthma (*Table 1*). Among patients with COPD (n=14), 57% developed acute respiratory failure, and 64% required oxygen or ventilatory support. Nearly two-thirds (71.4%) were hospitalized, and one patient required invasive mechanical ventilation. Patients with asthma (n=7) had a milder course: three developed acute respiratory failure and were hospitalized, but none required NIV or IMV, and there were no deaths.

Table 1 - Key clinical characteristics and outcomes of patients, overall and by respiratory comorbidity (COPD, asthma).

Patients characteristics	*Tot (n = 70)*	*COPD subgroup (n = 14) ***	*Asthma subgroup (n = 7) ***
Age (years) mean ± SD (range)	68.5 ± 19.2 (34-102)	74 (48-89)	49.3 (34-67)
Sex (female), n (%)	34 (48.6)	6 (42.9)	4 (57.1)
Comorbidities, n (%)			
- smoke (current/past)	17 (24.3)	9 (64.3)	3 (42.9)
- chronic respiratory disease	24 (34.3)	2 (14.3) ***	0 (0.0) ***
- cardiovascular disease	26 (37.1)	10 (71.4)	3 (42.9)
- cerebrovascular disease	5 (7.1)	3 (21.4)	0 (0.0)
- chronic kidney disease	2 (2.8)	2 (14.3)	0 (0.0)
- chronic liver disease	6 (8.6)	4 (28.6)	1 (14.3)
- malignancy	4 (5.7)	2 (14.3)	1 (14.3)
- diabetes	5 (7.1)	2 (14.3)	3 (43)
- obesity	12 (17.1)	6 (42.9)	3 (43)
-immune depression	6 (8.6)	3 (21.4)	1 (14.3)
*Symptoms at admission, n (%)**			
- cough	52 (74.3)	12 (85.7)	7 (100)
- dyspnea	49 (70.0)	10 (71.4)	5 (71.4)
- fever	31 (44.3)	6 (42.9)	3 (42.9)
- chest pain	5 (7.1)	3 (21.4)	1 (14.3)
- neurologic symptoms	3 (4.3)	2 (14.3)	0 (0.0)
Respiratory failure at admission	29 (41.4)	8 (57.1)	3 (42.9)
Laboratory features, n (%)			
- WBC >12 $\times 10^3/\mu L$	31 (44.3)	11 (78.6)	4 (57.1)
- CRP > 0.5 mg/dL	66 (94.3)	13 (92.9)	5 (71.4)
Blood gas analysis – room air, mean (range)			
- $paCO_2$	40.2 (25.6-56.3)	44.7 (41.0-56.5)	38.3 (28.8-45.5)
- paO_2	82.6 (42.1-95.2)	60 (42.4-78.4)	76 (53.3-88.5)
- PaO_2/FiO_2	393 (200-452)	286 (200–371)	362 (252–419)
Radiological features (chest X-ray), n (%)			
- normal	18 (26)	3 (21.4)	3 (42.9)
- interstitial markings	36 (51)	7 (50.0)	3 (42.9)
- consolidation	11 (16)	4 (28.6)	1 (14.3)
- mixed pattern	5 (7.1)	0 (0.0)	0 (0.0)
Destination, n (%)			
- discharged at home	30 (43)	4 (28.6)	4 (57.1)
- admitted – medical ward	38 (54)	9 (64.3)	3 (42.9)
- admitted - ICU	2 (2.8)	1 (7.1)	0 (0.0)
*Length of stay of hospitalized patients, n (%)***			
- ≤ 7 days	12 (30)	1 (10.0)	1 (33.3)
- 8-20 days	25 (62.5)	8 (80.0)	2 (66.7)
- ≥ 21 days	3 (7.5)	1 (10.0)	0 (0.0)
*O2 and ventilatory support, n (%)**			
- none	35 (50)	5 (35.7)	4 (57.1)
- Venturi mask/nasal cannulae	35 (50)	7 (50.0)	3 (42.9)
- HFNC	4 (6)	1 (7.1)	1 (14.3)
- CPAP/NIV	2 (3)	2 (14.3)	0 (0.0)
- IMV	1 (1)	1 (7.1)	0 (0.0)
30-day mortality, n (%)	2 (2.8)	1 (7.1)	0 (0.0)

Notes: WBC, white blood cells; CRP, C-reactive protein; ICU, intensive care unit; HFNC, high flow nasal cannulae; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; IVM, invasive mechanical ventilation. * Patients may have more than one symptom and receive more than one ventilatory support modality; therefore, percentages in these categories may exceed 100%. ** Percentages refer to the specific population. *** Other chronic respiratory conditions may be present in COPD/asthma patients (e.g. obstructive sleep apnea, interstitial lung disease).

DISCUSSION

In this real-world cohort of adults with PCR-confirmed respiratory EV infection, our findings describe the spectrum of clinical burden, with frequent lower respiratory tract involvement and substantial healthcare utilization. Acute respiratory failure (PaO_2 <60 mmHg) occurred in 41% of patients. Chest radiography was frequently abnormal, and more than half required hospitalization and some form of respiratory support. Overall mortality was low (2.8%) but occurred in older, comorbid patients, a pattern consistent with the well-recognized vulnerability of frail hosts to severe viral respiratory illness.

Our findings, although lacking EV typing, align with the renewed circulation of EV-D68 reported across Europe and North America following disruptions to typical respiratory virus patterns during the COVID-19 period and the subsequent "rebound" phase. In Northern Italy, enhanced laboratory surveillance documented a rapid increase in EV-D68 detections in 2024 and reported an increase in adult cases. Similarly, genomic surveillance from a large US health system identified increased EV-D68 circulation in 2024 and the re-establishment of a cyclical pattern after the pandemic disruption. Collectively, these data support the premise that EV is not exclusively a pediatric pathogen [2-5, 7, 15].

Although EV typing was unavailable in our study, the clinical spectrum we observed – prominent dyspnea and hypoxemia, frequent radiographic abnormalities, and occasional requirement for advanced respiratory support – is consistent with earlier reports of EV-D68-related respiratory illness. During the 2014 U.S. outbreak, severe respiratory disease was widely reported, and asthma was disproportionately represented among affected patients. In adults evaluated in emergency departments, EV-D68 has been associated with prominent dyspnea and wheezing, and adult severity has been reported to overlap with other seasonal viral lower respiratory tract infections [6, 11, 12].

A key clinical signal in our cohort was the heterogeneity of severity across obstructive airway disease phenotypes. COPD patients had the highest rates of acute respiratory failure, requirement for oxygen and respiratory support, and hospitalization, whereas asthma patients, while at risk for hypoxemic presentations, generally experienced a milder course. This heterogeneity aligns with the established pathophysiology and clinical epidemiology of viral triggers across chronic airway diseases. Viral respiratory infections are major drivers of acute airflow obstruction and exacerbations, particularly in susceptible individuals, including severe clinical presentations [8, 9, 19, 20]. In asthma, epithelial susceptibility, altered antiviral responses, and mucociliary dysfunction can amplify wheeze and symptom burden during picornavirus infections, whereas in COPD, viral infections are strongly linked to exacerbation burden and healthcare utilization – particularly in advanced airflow limitation and frequent-exacerbator phenotypes [13, 14, 17, 18]. Clinically, the highest-risk phenotypes include (i) COPD with severe airflow limitation, chronic bronchitis/bronchiectasis features, baseline hypercapnia, and/or frequent exacerbations, and (ii) asthma with severe or poor control, prior severe exacerbations, fixed obstruction, or asthma-COPD overlap (ACO) traits, groups more likely to require oxygen and ventilatory support [14, 16].

Radiographic and laboratory findings in our cohort further underscore the diagnostic challenge: radiological abnormalities were common, and inflammatory markers were frequently elevated. From a diagnostic and stewardship perspective, this combination illustrates how EV infection may mimic bacterial pneumonia and plausibly contributes to antibiotic initiation when viral diagnostics are delayed or unavailable, particularly in post-pandemic seasons marked by the asynchronous re-emergence of multiple respiratory pathogens. Timely multiplex molecular diagnostics can therefore be framed not only as a diagnostic tool but also as a lever for antimicrobial stewardship and appropriate infection control strategies, particularly during periods of increased community viral circulation [7, 15, 21].

Several implications can be inferred from our analysis. From a practical perspective, rapid multiplex molecular testing may support earlier etiologic classification of adult acute respiratory syndromes, thereby guiding proper clinical decision-making and antimicrobial stewardship [20]. In parallel, the emergence and cyclical circulation of enterovirus with an appreciable adult component in European and North American surveillance indicate that adult-focused surveillance systems should be enhanced, as current monitoring

mainly targets pediatric populations [3-6]. Finally, the potential development of EV-specific treatments (neutralizing monoclonal antibodies and vaccines), still under investigation, deserves particular attention in high-risk groups [22].

This study has limitations inherent to its retrospective design and its conduct within a single healthcare area, with small subgroup sample sizes that constrain the generalizability of the findings. Additionally, because microbiological investigations beyond the nasopharyngeal swab were performed at the treating physician's discretion, ascertainment of co-infections may be incomplete and subject to selection bias.

In our dataset, concomitant detection of rhinovirus and enterovirus (HRV–EV) accounted for approximately 17% of all virus-positive respiratory panels. Because multiplex RT-PCR detects viral nucleic acid rather than replication-competent virus, dual HRV–EV positivity may reflect co-detection, sequential infections with persistent or intermittent viral shedding, or, less commonly, assay-related cross-reactivity due to the genetic relatedness of picornaviruses. Nevertheless, picornavirus co-detections could also represent true viral coinfections [23-27]. In a retrospective study, it is not possible to ascertain their clinical impact; therefore, we elected to exclude these patients from the analysis. This exclusion, however, constitutes a notable limitation of the study.

Finally, EV subtyping was not available, limiting the ability to make clade-specific inferences about respiratory severity across enterovirus types [28]. Consequently, these findings should be interpreted as a preliminary clinical signal that warrants confirmation in future studies that incorporate molecular typing and prospective data collection.

In conclusion, in our real-world cohort of adults with EV respiratory infection, we observed a high frequency of hypoxemia, common radiographic abnormalities, and substantial healthcare utilization, particularly among COPD patients. These findings align with reports of increasing EV burden in adults, underscoring the importance of including EV in the differential diagnosis of acute respiratory illness, strengthening microbiologic surveillance, and increasing clinician awareness. Future studies should include EV typing, address the role of co-infections, evaluate risk-stratified outcomes, and inform preventive strategies.

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Conflict of interest
No conflict of interest must be declared for any of the authors.

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