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Association between Gastrointestinal Involvement and PICU Admission in Children with Human Metapneumovirus Infection in China: A Retrospective Cohort Study

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Abstract

Objectives: We aimed to explore the association between human metapneumovirus (hMPV) infection and extrapulmonary involvement risk in children admitted to the pediatric intensive care unit (PICU), and identify risk factors for severe hMPV infections. **Methods:** A retrospective cohort study was conducted on 752 hospitalized children with hMPV infection from January 2022 to June 2023. Demographic, clinical, laboratory, imaging, extrapulmonary involvement, comorbidity and co-infection data were collected. Logistic regression was used to screen factors linked to PICU admission, and the variance inflation factor (VIF) was applied to identify independent risk factors. Subgroup analyses and interaction tests were performed to verify the stability of the association between extrapulmonary involvement and PICU admission risk. **Results:** The PICU admission rate was 4.9% (37/752). Univariate analysis showed a significantly higher incidence of extrapulmonary involvement in the PICU group than in the general ward group. Variables with severe multicollinearity (VIF > 5) were excluded from the final model. After adjustment, gastrointestinal involvement was an independent risk factor for PICU admission (OR = 5.52, 95% CI: 1.33 - 22.93). Multiple diagnoses, viral co-infections, respiratory distress, congenital airway anomalies and metabolic disorders also independently increased PICU admission risk. The association between gas-

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trointestinal involvement and PICU admission was strengthened in children with severe pneumonia or without multiple diagnoses, and amplified by respiratory distress. No significant interactions were found between sex and major comorbidity subgroups (all $P > 0.05$). **Conclusion:** hMPV can cause severe infections leading to PICU admission. Gastrointestinal involvement may serve as a critical clinical indicator for PICU admission in hospitalized children with hMPV infection.

Keywords

Human Metapneumovirus, Children, Pediatric Intensive Care Unit, Gastrointestinal Involvement

1. Introduction

HMPV, first identified in 2001, belongs to the Metapneumovirus genus in the family Pneumoviridae [1]. It is considered a common respiratory virus causing mild upper respiratory infections, primarily affecting infants and children under five years of age. In China, an important cause of pediatric respiratory infections is hMPV, accounting for approximately 7.8% of cases and increasing to 12.7% among children with severe community-acquired pneumonia (CAP) [2]. Estimates suggest that hMPV causes approximately 1.42 million cases of acute lower respiratory tract infection and about 16,100 deaths annually among children under five years of age worldwide [3]. In a proportion of pediatric cases, hMPV infection can progress to severe disease characterized by respiratory distress, hypoxemia, and multisystem involvement, and may further deteriorate into critical illness requiring mechanical ventilation or multi-organ support. Although comprehensive supportive management in the PICU has substantially improved outcomes [4] [5], the high resource demands of critical care highlight the importance of establishing effective early risk stratification strategies to optimize clinical management.

Previous studies on severe hMPV infection have largely focused on respiratory involvement, pneumonia severity, or isolated laboratory markers, such as insulin values [6], oxygenation targets [7], C-reactive protein, or procalcitonin [8] [9]. Although informative, these studies often rely on single indicators or focus narrowly on respiratory parameters, which may lack the predictive power for PICU admission [10] [11]. Airin Veronese *et al.*'s found that the primary reasons for hospitalization in patients with hMPV infection were hypoxemia and dehydration [12]. Notably, extrapulmonary manifestations (gastrointestinal, neurological, circulatory) are increasingly recognized [13]. Neurological symptoms include irritability, somnolence, drowsiness, seizures, or altered mental status. Gastrointestinal symptoms include refusal to eat, severe vomiting, diarrhea, or dehydration. However, few studies have explored identifying risk factors for hMPV in children iden-

tifying risk factors of hMPV in children.

To address these gaps, we conducted a retrospective cohort study of hospitalized children with laboratory-confirmed hMPV infection in Pediatric Emergency Department of Guangzhou Women and Children's Medical Center. We compared clinical characteristics between PICU-admitted and ward-managed patients. Using multivariable logistic regression analysis, we evaluated whether extrapulmonary involvement was associated with PICU admission among children with hMPV infection. Given that extrapulmonary involvement may represent a progressive and evolving process over the course of illness rather than an acute isolated event, we further examined whether this association was consistent across subgroups, aiming to provide evidence for timely and appropriate PICU referral decisions in children with hMPV infection.

2. Methods

2.1. Participants

This study retrospectively collected clinical data from 752 hospitalized pediatric patients through the hospital's electronic medical record system. The extracted data encompassed multidimensional information including demographic characteristics, clinical details, laboratory test results, imaging features, extrapulmonary involvement, and co-infections. Severe or critical human metapneumovirus (hMPV) infection is defined as meeting diagnostic criteria for hMPV infection and presenting with at least one of the following clinical manifestations: 1) Respiratory failure necessitating mechanical ventilation; 2) Occurrence of shock; 3) Involvement of other organ failure requiring intensive care unit (ICU) admission [14] [15].

Inclusion criteria: 1) Age ≤ 14 years; 2) Confirmed hMPV infection by nucleic acid testing of respiratory specimens.

Exclusion criteria: 1) Hospital-acquired infection; 2) Incomplete case records.

The decision to transfer pediatric patients to the PICU is determined by the attending physician based on the severity of their condition and their need for advanced life support.

Respiratory secretion specimens were collected via throat swabs and used for PCR detection of respiratory pathogens, including hMPV, adenovirus, RSV, parainfluenza virus, bocavirus, influenza virus A/B, rhinovirus, enterovirus, Mycoplasma pneumoniae, and Chlamydia pneumoniae. Additionally, deep sputum or bronchoalveolar lavage fluid was collected for external testing using targeted next-generation sequencing (tNGS) to detect multiple respiratory pathogens, including 49 bacterial species (e.g., Haemophilus influenzae, Streptococcus pneumoniae), 35 viral species (e.g., hMPV, adenovirus), and 16 fungal species (e.g., Mycoplasma, Chlamydia, Rickettsia, Candida albicans).

2.2. Covariates

This study incorporated demographic data as covariates into the analysis to con-

trol for potential confounding effects. Demographic data encompass basic characteristics and pre-existing conditions. Basic characteristics include age and gender. Pre-existing conditions include prior comorbidities and multiple diagnosis status. Prior comorbidities encompass congenital cardiovascular disease, congenital airway anomalies, neurological disorders, metabolic disorders, and immunodeficiency. Multiple diagnosis status is defined as the simultaneous presence of two or more confirmed diagnoses.

2.3. Exposure

We collected various clinical, laboratory, and imaging indicators associated with PICU admission risk. Extrapulmonary involvement is a binary variable encompassing gastrointestinal, neurological, and circulatory system involvement, all diagnosed based on clinical symptoms and relevant examinations. Infection-related characteristics included viral co-infection status, pneumonia severity, fever duration, and respiratory distress status.

2.4. Statistical Analysis

All data in this study were analyzed using R-4.5.1 statistical software. Prior to formal statistical analysis, systematic quality control was conducted on the raw data. Through logical verification and missing value imputation, the integrity and accuracy of the dataset included in the analysis were ensured. For different types of research data, corresponding descriptive statistical methods were employed: Quantitative data (e.g., age, hemoglobin levels, inflammatory markers, and other laboratory indicators) were expressed as mean ± standard deviation ($\bar{x}$ ± s) after confirming normal distribution via the Shapiro-Wilk test. Independent samples t-tests were used for intergroup comparisons.

To avoid the interference of multicollinearity on regression analysis results, we first employed the Variance Inflation Factor (VIF) for collinearity diagnosis. VIF reflecting the strength of multicollinearity by quantifying the degree to which one independent variable is linearly explained by other independent variables [16] [17]. A VIF value exceeding 5 was used as the criterion for identifying significant multicollinearity, and variables meeting this criterion were subsequently excluded. Variables screened for multicollinearity were incorporated into a logistic regression model. The final results of the regression analysis are presented as odds ratios (OR) and 95% confidence intervals (95% CI).

This study conducted pre-specified subgroup analyses based on clinical characteristics. The proposed subgroups include sex subgroup (females, males), disease severity subgroups (mild-to-moderate pneumonia, severe pneumonia), and underlying disease subgroups (presence or absence of congenital disorders). By comparing the differences in OR values and 95% CIs across these subgroups, we will assess the consistency of risk factor effects across different populations, thereby providing a basis for individualized clinical risk assessment. The statistical significance level for this study is defined as a P-value < 0.05.

3. Results

3.1. Baseline Characteristics

Among 752 hospitalized children (Table 1), 37 (4.9%) required PICU admission while 715 (95.1%) were managed in the general ward. The mean age was similar between groups (2.40 ± 1.65 vs. 2.66 ± 2.57 years, P = 0.547), and sex distribution did not differ (males: 60.28% vs. 62.16%, P = 0.819). Compared with ward patients, PICU patients showed markedly lower hemoglobin levels (101.78 ± 14.38 vs. 116.08 ± 11.77 g/L, P < 0.001), higher neutrophil percentages (63.00 ± 15.04 vs. 48.90% ± 18.34%, P < 0.001), lower lymphocyte percentages (29.24 ± 12.88 vs. 40.33 ± 19.36%, P < 0.001), higher CRP (63.15 ± 89.61 vs. 29.73 ± 42.62 mg/L, P = 0.03), and higher PCT (5.78 ± 9.26 vs. 1.72 ± 3.28, P = 0.012). Co-infection was more common in the PICU (48.65% vs. 18.18%, P < 0.001), as was bronchoscopy use (24.32% vs. 2.80%, P < 0.001). Severe pneumonia predominated among PICU patients (89.19% vs. 13.01%), whereas mild-to-moderate pneumonia was rare (5.41% vs. 79.58%; both P < 0.001). Multiple diagnoses were substantially more frequent in the PICU (72.97% vs. 8.53%, P < 0.001). Five pre-existing comorbidities including congenital cardiovascular disease (8.11% vs. 1.96%, P = 0.046), congenital airway anomalies (13.51% vs. 3.08%, P = 0.004), neurological disorders (16.22% vs. 2.24%, P < 0.001), metabolic disorders (8.11% vs. 0.14%, P < 0.001), and immunodeficiency (5.41% vs. 0.28%, P = 0.013) were significantly enriched in the PICU group. PICU children had longer fever duration (8.59 ± 5.39 vs. 4.87 ± 1.91 days, P < 0.001) and markedly prolonged hospital stay (19.43 ± 16.14 vs. 6.05 ± 3.05 days, P < 0.001), as well as a higher rate of respiratory distress (83.78% vs. 12.31%, P < 0.001). Extrapulmonary involvement was also more prevalent in the PICU, including gastrointestinal (37.84% vs. 6.57%), neurological (48.65% vs. 7.27%), and circulatory involvement (8.11% vs. 0.70%; all P < 0.001). Radiologically, PICU patients more frequently exhibited patchy opacities/infiltrates (64.86% vs. 52.45%), pleural effusion (5.41% vs. 0.14%), and pneumonic/inflammatory changes (21.62% vs. 10.07%; P < 0.001). On CT, pneumonia/inflammation (40.54% vs. 5.87%) and airway disease (5.41% vs. 1.96%) were notably higher in the PICU group, whereas "normal/none" findings were much less frequent (43.24% vs. 87.27%; P < 0.001).

Table 1. Baseline characteristics of participants (N = 752).

Variables	Total (n = 752)	Ward (n = 715)	PICU (n = 37)	P
Demographics				
Age, Mean ± SD	2.41 ± 1.70	2.40 ± 1.65	2.66 ± 2.57	0.547
Sex, n (%)				0.819
Female	298 (39.63)	284 (39.72)	14 (37.84)	
Male	454 (60.37)	431 (60.28)	23 (62.16)	

Continued

Laboratory blood tests				
WBC (10^9/L), Mean ± SD	8.90 ± 4.49	8.95 ± 4.46	8.05 ± 4.89	0.238
HGB (g/L), Mean ± SD	115.38 ± 12.30	116.08 ± 11.77	101.78 ± 14.38	<0.001
PLT (10^9/L), Mean ± SD	291.16 ± 113.63	291.28 ± 110.96	289.03 ± 158.62	0.933
Neutrophil (%), Mean ± SD	49.59 ± 18.43	48.90 ± 18.34	63.00 ± 15.04	<0.001
Lymphocyte (%), Mean ± SD	39.78 ± 19.23	40.33 ± 19.36	29.24 ± 12.88	<0.001
CRP (mg/L), Mean ± SD	31.38 ± 46.52	29.73 ± 42.62	63.15 ± 89.61	0.03
ALT (U/L), Mean ± SD	22.95 ± 39.50	21.98 ± 35.98	41.68 ± 80.62	0.148
AST (U/L), Mean ± SD	52.45 ± 65.97	49.31 ± 34.82	113.19 ± 250.48	0.13
PCT, Mean ± SD	1.92 ± 3.89	1.72 ± 3.28	5.78 ± 9.26	0.012
LDH (U/L), Mean ± SD	387.06 ± 214.62	374.97 ± 127.00	620.62 ± 762.91	0.058
Albumin, Mean ± SD	42.55 ± 21.08	42.92 ± 21.52	35.39 ± 5.81	0.034
NLR, Mean ± SD	1.98 ± 2.48	1.88 ± 1.84	3.91 ± 7.55	0.111
PLR, Mean ± SD	9.87 ± 10.44	9.61 ± 9.33	15.05 ± 22.81	0.157
PNR, Mean ± SD	7.77 ± 9.99	7.91 ± 10.20	5.00 ± 3.37	0.084
SII, Mean ± SD	569.78 ± 772.53	541.82 ± 613.54	1109.99 ± 2160.72	0.119
Pathogen Detection				
Pathogen, n (%)				<0.001
hMPV	604 (80.32)	585 (81.82)	19 (51.35)	
Co-infection	148 (19.68)	130 (18.18)	18 (48.65)	
Examinations				
Bronchoscopy, n (%)				<0.001
No	723 (96.14)	695 (97.20)	28 (75.68)	
Yes	29 (3.86)	20 (2.80)	9 (24.32)	
Diagnosis				
Diagnosis, n (%)				<0.001
Mild-to-moderate pneumonia	571 (75.93)	569 (79.58)	2 (5.41)	
Severe pneumonia	126 (16.76)	93 (13.01)	33 (89.19)	
Others	55 (7.31)	53 (7.41)	2 (5.41)	
Multiple diagnoses, n (%)				<0.001
No	664 (88.30)	654 (91.47)	10 (27.03)	
Yes	88 (11.70)	61 (8.53)	27 (72.97)	
Pre-existing comorbidities				
Congenital cardiovascular disease, n (%)	17 (2.26)	14 (1.96)	3 (8.11)	0.046

Continued

Congenital airway anomalies, n (%)	27 (3.59)	22 (3.08)	5 (13.51)	0.004
History of pneumonia, n (%)	15 (1.99)	13 (1.82)	2 (5.41)	0.166
Neurological disorders, n (%)	22 (2.93)	16 (2.24)	6 (16.22)	<0.001
Metabolic disorders, n (%)	4 (0.53)	1 (0.14)	3 (8.11)	<0.001
Hematologic disorders, n (%)	21 (2.79)	20 (2.80)	1 (2.70)	1
Immunodeficiency, n (%)	4 (0.53)	2 (0.28)	2 (5.41)	0.013
Renal disease, n (%)	1 (0.13)	1 (0.14)	0 (0.00)	1
Clinical Symptoms				
Fever, n (%)	706 (93.88)	672 (93.99)	34 (91.89)	0.868
Duration of fever (days), Mean ± SD	5.06 ± 2.34	4.87 ± 1.91	8.59 ± 5.39	<0.001
Hospital stay (days), Mean ± SD	6.71 ± 5.45	6.05 ± 3.05	19.43 ± 16.14	<0.001
Cough, n (%)	738 (98.14)	703 (98.32)	35 (94.59)	0.148
Wheezing, n (%)	192 (25.53)	183 (25.59)	9 (24.32)	0.863
Hoarseness, n (%)	12 (1.60)	12 (1.68)	0 (0.00)	1
Respiratory distress, n (%)	119 (15.82)	88 (12.31)	31 (83.78)	<0.001
Extrapulmonary Involvement				
Gastrointestinal involvement, n (%)	61 (8.11)	47 (6.57)	14 (37.84)	<0.001
Renal involvement, n (%)	1 (0.13)	1 (0.14)	0 (0.00)	1
Neurological involvement, n (%)	70 (9.31)	52 (7.27)	18 (48.65)	<0.001
Circulatory involvement, n (%)	8 (1.06)	5 (0.70)	3 (8.11)	0.005
Hematologic involvement, n (%)	1 (0.13)	1 (0.14)	0 (0.00)	1
Radiology				
Xray category, n (%)				<0.001
Atelectasis/hypoventilation	3 (0.40)	1 (0.14)	2 (5.41)	
Bronchitis/bronchopneumonia	121 (16.09)	121 (16.92)	0 (0.00)	
Emphysematous changes	1 (0.13)	1 (0.14)	0 (0.00)	
Increased lung markings	104 (13.83)	103 (14.41)	1 (2.70)	
Upper-airway abnormalities	1 (0.13)	1 (0.14)	0 (0.00)	
Normal	14 (1.86)	14 (1.96)	0 (0.00)	
Patchy opacities/infiltrates	399 (53.06)	375 (52.45)	24 (64.86)	
Pleural effusion	3 (0.40)	1 (0.14)	2 (5.41)	
Pneumonic/inflammatory changes	80 (10.64)	72 (10.07)	8 (21.62)	
None	26 (3.46)	26 (3.64)	0 (0.00)	

Continued

CT category, n (%)				<0.001
Airway disease	16 (2.13)	14 (1.96)	2 (5.41)	
Atelectasis/hypoventilation	1 (0.13)	0 (0.00)	1 (2.70)	
Bronchitis/bronchopneumonia	28 (3.72)	26 (3.64)	2 (5.41)	
Consolidation	8 (1.06)	7 (0.98)	1 (2.70)	
Normal	1 (0.13)	1 (0.14)	0 (0.00)	
Pleural/pericardial effusion	1 (0.13)	1 (0.14)	0 (0.00)	
Pneumonia/inflammation	57 (7.58)	42 (5.87)	15 (40.54)	
None	640 (85.11)	624 (87.27)	16 (43.24)	

3.2. Variables Selection

In the initial VIF assessment (Table 2), Seventeen predictors demonstrated substantial multicollinearity, with HGB showing the highest VIF value (97.05), followed by cough (56.26), neutrophil percentage (49.80), SII (25.75), CT category (23.57), lymphocyte percentage (23.48), NLR (22.38), PLT (19.97), fever (18.98), LDH (10.42), PLR (8.11), duration of fever (8.06), WBC (7.33), X-ray category (6.42), AST (6.29), albumin (5.22), and hospital stay (5.11); all of these variables were removed based on the VIF > 5 threshold. After filtering, the remaining variables displayed substantially lower VIF values. For example, age decreased from 4.57 to 2.03 (−55.6%), ALT from 3.70 to 1.53 (−58.5%), PNR from 3.10 to 1.48 (−52.3%), sex from 2.69 to 2.11 (−21.5%), PICU status from 2.37 to 1.90 (−20.0%), and CRP from 2.88 to 2.50 (−13.2%). Smaller reductions were observed in respiratory distress (3.28 to 3.04), multiple diagnoses (1.67 to 1.60), pathogen detection (1.37 to 1.30), congenital airway anomalies (1.30 to 1.20), and gastrointestinal involvement (1.30 to 1.27). Three predictors had VIF values close to 1 both before and after filtering, including hematologic involvement (1.04 to 1.02), renal involvement (1.03 to 1.02), and renal disease (1.01 to 1.00).

Table 2. VIF assessment before and after variable filtering.

Variables	VIF_Before	VIF_After	Change Percent
HGB	97.04931	Delete	
Cough	56.26056	Delete	
Neutrophil	49.79567	Delete	
SII	25.74712	Delete	
CT category	23.57044	Delete	
Lymphocyte	23.47783	Delete	
NLR	22.37597	Delete	
PLT	19.96846	Delete	

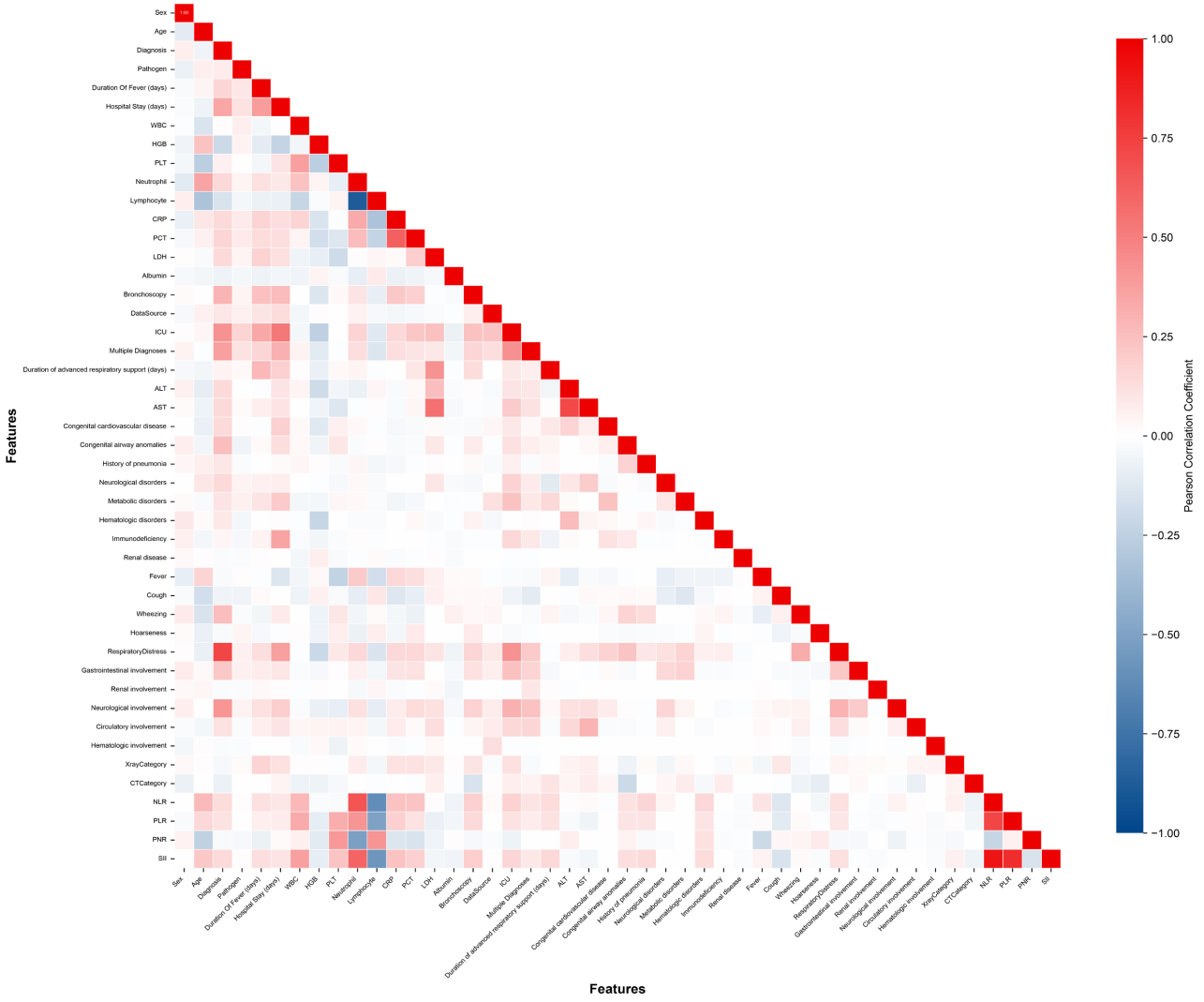
Continued

Fever	18.9777	Delete	
LDH	10.42233	Delete	
PLR	8.108574	Delete	
Duration of fever (days)	8.059895	Delete	
WBC	7.331864	Delete	
Xray category	6.424245	Delete	
AST	6.289834	Delete	
Albumin	5.215601	Delete	
Hospital stay (days)	5.106864	Delete	
Age	4.572989	2.030936	−55.5884
Diagnosis	3.789532	3.633678	−4.11277
ALT	3.696884	1.532501	−58.5462
Respiratory distress	3.276717	3.035144	−7.37242
PNR	3.100981	1.478737	−52.3139
CRP	2.876156	2.497265	−13.1735
Sex	2.685345	2.10797	−21.501
PCT	2.423989	2.200371	−9.22521
PICU	2.374642	1.899603	−20.0047
Wheezing	1.708284	1.576943	−7.68849
Multiple diagnoses	1.669259	1.597947	−4.27212
Neurological involvement	1.480863	1.443048	−2.55356
Bronchoscopy	1.422024	1.254776	−11.7613
Pathogen	1.366358	1.296927	−5.08147
Congenital airway anomalies	1.304341	1.20077	−7.94046
Gastrointestinal involvement	1.301958	1.268743	−2.55112
Hematologic disorders	1.281604	1.142925	−10.8208
Metabolic disorders	1.271241	1.187096	−6.61917
Immunodeficiency	1.270025	1.080219	−14.9451
Circulatory involvement	1.231009	1.110419	−9.79605
Congenital cardiovascular disease	1.219897	1.176744	−3.53739
Neurological disorders	1.213738	1.144633	−5.69359
History of pneumonia	1.134965	1.095267	−3.49773
Hoarseness	1.099675	1.074066	−2.32879

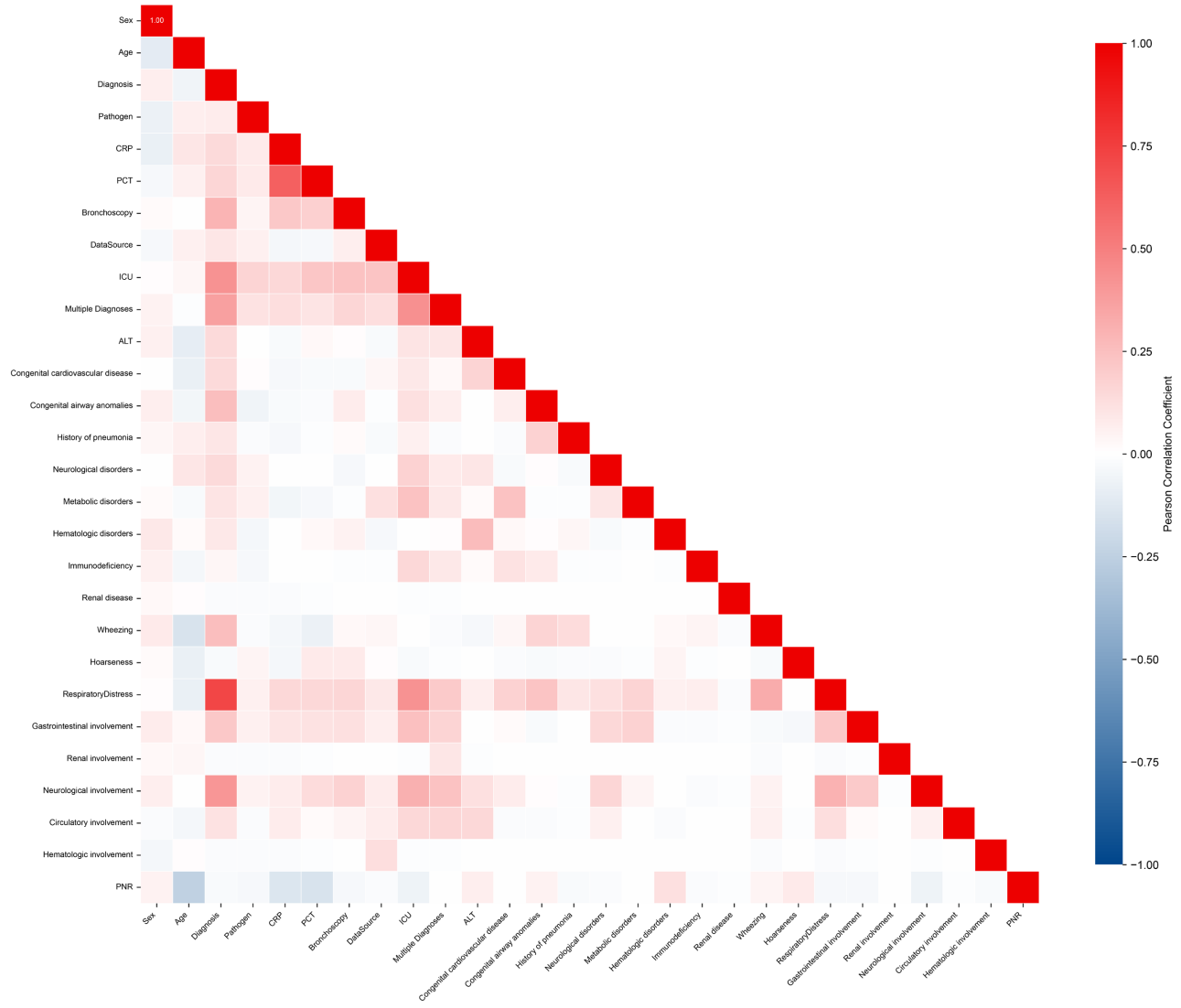
Continued

Hematologic involvement	1.036367	1.022582	−1.33009
Renal involvement	1.033801	1.022337	−1.10894
Renal disease	1.011274	1.004115	−0.70794

Figure 1 presents the correlation heatmaps of all study variables before and after VIF-based filtering. Panel (a) shows the full correlation matrix, in which many variables exhibit moderate to strong positive correlations, reflected by concentrated red blocks along the diagonal and multiple off-diagonal clusters, indicating substantial multicollinearity across hematologic markers, inflammatory indicators, clinical features, and radiological categories. Panel (b) shows the correlation structure after removing variables with VIF > 5. The reduced matrix displays markedly fewer high-correlation clusters, and the remaining variables demonstrate weaker and more sparse correlation patterns, indicating a substantial reduction in multicollinearity.



(a)



(b)

Figure 1. Comparison of heatmaps before and after VIF filtering. (a) Heatmap of all variables prior to VIF assessment; (b) Heatmap after exclusion of variables with VIF > 5.

3.3. Multivariable Logistic Regression Analysis

Table 3 shows the associations between extrapulmonary involvement and PICU admission based on univariate and multivariate logistic regression analyses. In univariate models, higher CRP (OR = 1.01; 95% CI: 1.01 - 1.01; P < 0.001), higher PCT (OR = 1.11; 95% CI: 1.06 - 1.17; P < 0.001), higher ALT (OR = 1.01; 95% CI: 1.01 - 1.01; P = 0.028), and lower PNR (OR = 0.84; 95% CI: 0.74 - 0.96; P = 0.010) were associated with PICU admission, although none of these remained significant after adjustment. Compared with mild-to-moderate pneumonia, severe pneumonia showed a strong univariate association with PICU admission (OR = 100.95; 95% CI: 23.82 - 427.79; P < 0.001), which decreased substantially in the multivariate model (OR = 11.12; 95% CI: 0.99 - 125.49; P = 0.051). The presence of multiple diagnoses was consistently associated with higher odds of PICU

admission both before (OR = 28.95; 95% CI: 13.38 - 62.62; P < 0.001) and after adjustment (OR = 36.44; 95% CI: 8.76 - 151.53; P < 0.001). Co-infection also showed significant associations in both analyses (univariate OR = 4.26; adjusted OR = 6.18; both P ≤ 0.004). Among comorbidities, congenital airway anomalies remained significant after adjustment (OR = 7.86; 95% CI: 1.23 - 50.04; P = 0.029), while metabolic disorders also retained significance (OR = 51.35; 95% CI: 1.53 - 1724.87; P = 0.028). Respiratory distress demonstrated a strong association with PICU admission (univariate OR = 36.81; 95% CI: 14.93 - 90.74; P < 0.001), and remained significant in the multivariate model (OR = 9.96; 95% CI: 1.66 - 59.95; P = 0.012). For extrapulmonary involvement, gastrointestinal involvement (adjusted OR = 5.52; 95% CI: 1.33 - 22.93; P = 0.019) maintained a significant association with PICU admission, whereas neurological and circulatory involvement lost significance after adjustment.

Table 3. Multivariable logistic regression analysis of the association between extrapulmonary involvement and PICU admission.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Demographics				
Sex				
Female	1.00 (Reference)			
Male	1.08 (0.55 - 2.14)	0.819		
Age	1.08 (0.91 - 1.29)	0.367		
Laboratory blood tests				
CRP	1.01 (1.01 - 1.01)	<0.001	1.00 (0.99 - 1.01)	0.974
PCT	1.11 (1.06 - 1.17)	<0.001	1.14 (0.99 - 1.31)	0.066
ALT	1.01 (1.01 - 1.01)	0.028	1.01 (1.00 - 1.02)	0.168
PNR	0.84 (0.74 - 0.96)	0.010	0.88 (0.72 - 1.08)	0.212
Diagnosis				
Mild-to-moderate pneumonia	1.00 (Reference)		1.00 (Reference)	
Severe Pneumonia	100.95 (23.82 - 427.79)	<0.001	11.12 (0.99 - 125.49)	0.051
Others	10.74 (1.48 - 77.76)	0.019	1.49 (0.09 - 23.57)	0.778
Multiple diagnoses				
No	1.00 (Reference)		1.00 (Reference)	
Yes	28.95 (13.38 - 62.62)	<0.001	36.44 (8.76 - 151.53)	<0.001
Pathogen Detection				
Pathogen				
hMPV	1.00 (Reference)		1.00 (Reference)	
Co-infection	4.26 (2.18 - 8.35)	<0.001	6.18 (1.77 - 21.64)	0.004

Continued

Examinations				
Bronchoscopy				
No	1.00 (Reference)		1.00 (Reference)	
Yes	11.17 (4.67 - 26.73)	<0.001	3.73 (0.76 - 18.25)	0.105
Pre-existing comorbidities				
Congenital cardiovascular disease				
No	1.00 (Reference)		1.00 (Reference)	
Yes	4.42 (1.21 - 16.11)	0.024	0.13 (0.00 - 44.73)	0.496
Congenital airway anomalies				
No	1.00 (Reference)		1.00 (Reference)	
Yes	4.92 (1.75 - 13.84)	0.003	7.86 (1.23 - 50.04)	0.029
History of pneumonia				
No	1.00 (Reference)			
Yes	3.09 (0.67 - 14.21)	0.148		
Neurological disorders				
No	1.00 (Reference)		1.00 (Reference)	
Yes	8.46 (3.10 - 23.10)	<0.001	4.57 (0.77 - 27.04)	0.094
Metabolic disorders				
No	1.00 (Reference)		1.00 (Reference)	
Yes	63.00 (6.39 - 621.60)	<0.001	51.35 (1.53 - 1724.87)	0.028
Hematologic disorders				
No	1.00 (Reference)			
Yes	0.97 (0.13 - 7.39)	0.973		
Immunodeficiency				
No	1.00 (Reference)		1.00 (Reference)	
Yes	20.37 (2.79 - 148.90)	0.003	256.62 (0.19 - 339776.93)	0.130
Renal disease				
No	1.00 (Reference)			
Yes	0.00 (0.00 - Inf)	0.990		
Clinical Symptoms				
Wheezing				
No	1.00 (Reference)			
Yes	0.93 (0.43 - 2.02)	0.863		
Hoarseness				
No	1.00 (Reference)			
Yes	0.00 (0.00 - Inf)	0.984		

Continued

Respiratory distress				
No	1.00 (Reference)		1.00 (Reference)	
Yes	36.81 (14.93 - 90.74)	<0.001	9.96 (1.66 - 59.95)	0.012
Extrapulmonary Involvement				
Gastrointestinal involvement				
No	1.00 (Reference)		1.00 (Reference)	
Yes	8.65 (4.18 - 17.90)	<0.001	5.52 (1.33 - 22.93)	0.019
Renal involvement				
No	1.00 (Reference)			
Yes	0.00 (0.00 - Inf)	0.990		
Neurological involvement				
No	1.00 (Reference)		1.00 (Reference)	
Yes	12.08 (5.98 - 24.42)	<0.001	1.29 (0.31 - 5.29)	0.728
Circulatory involvement				
No	1.00 (Reference)		1.00 (Reference)	
Yes	12.53 (2.87 - 54.61)	<0.001	1.79 (0.11 - 30.50)	0.686
Hematologic involvement				
No	1.00 (Reference)			
Yes	0.00 (0.00 - Inf)	0.990		

3.4. Subgroup Analysis

In the overall cohort of 752 children (Figure 2), gastrointestinal involvement was associated with higher odds of PICU admission (OR = 5.52; 95% CI: 1.33 - 22.93; P = 0.019). Across sex groups, the association was not statistically significant for either females (OR = 17.58; 95% CI: 0.60 - 516.15; P = 0.096) or males (OR = 4.18; 95% CI: 0.55 - 31.95; P = 0.168), with no evidence of interaction (P_interaction = 0.476). Among diagnostic categories, the association remained significant only in severe pneumonia (OR = 11.59; 95% CI: 1.63 - 82.55; P = 0.014), while P_interaction was 0.409. Similar associations were observed in children with bronchoscopy not performed (OR = 9.56; 95% CI: 1.48 - 61.76; P = 0.018). In the subgroup without multiple diagnoses, gastrointestinal involvement remained associated with PICU admission (OR = 47.08; 95% CI: 1.09 - 2040.30; P = 0.045), whereas the interaction test was not significant (P_interaction = 0.600). Significant associations were also observed in children without congenital cardiovascular disease (OR = 5.84; P = 0.016), without congenital airway anomalies (OR = 4.54; P = 0.050), without neurological disorders (OR = 4.69; P = 0.116, nonsignificant), without metabolic disorders (OR = 8.56; P = 0.007), without hematologic disorders (OR = 5.55; P = 0.018), without immunodeficiency (OR = 5.43; P = 0.020),

and without respiratory distress (OR = 0.00; P = 1.000), while the interaction P-values remained above 0.05 across all comorbidity subgroups. For clinical symptoms, wheezing (P_interaction = 0.519) and hoarseness (P_interaction = 0.216) did not modify the association. Respiratory distress showed a statistically significant interaction (P_interaction = 0.038), with strong associations in children with respiratory distress (OR = 38.63; 95% CI: 3.72 - 400.92; P = 0.002). Across extrapulmonary involvement subgroups—including renal, neurological, circulatory, and hematologic involvement—no significant effect modification was detected, with interaction P-values all above 0.20.

Subgroup	n (%)	Ward	PICU	OR (95%CI)	P	P for interaction
All patients	752 (100.00)	23/691	14/61	5.52 (1.33 ~ 22.93)	0.019	
Sex						0.476
Female	298 (39.63)	10/281	4/17	17.58 (0.60 ~ 516.15)	0.096	
Male	454 (60.37)	13/410	10/44	4.18 (0.55 ~ 31.95)	0.168	
Diagnosis						0.409
Mild-to-moderate pneumonia	571 (75.93)	1/541	1/30	19284.64 (0.00 ~ Inf)	1.000	
Others	55 (7.31)	1/51	1/4	182.80 (0.00 ~ Inf)	1.000	
Severe Pneumonia	126 (16.76)	21/99	12/27	11.59 (1.63 ~ 82.55)	0.014	
Pathogen						0.466
hMPV	604 (80.32)	12/560	7/44	7.30 (0.44 ~ 121.50)	0.166	
Co-infection	148 (19.68)	11/131	7/17	18.82 (0.89 ~ 397.43)	0.059	
Bronchoscopy						0.548
0	723 (96.14)	17/669	11/54	9.56 (1.48 ~ 61.76)	0.018	
1	29 (3.86)	6/22	3/7	0.00 (0.00 ~ Inf)	1.000	
Multiple diagnoses						0.600
No	664 (88.30)	5/621	5/43	47.08 (1.09 ~ 2040.30)	0.045	
Yes	88 (11.70)	18/70	9/18	0.00 (0.00 ~ Inf)	0.997	
Congenital cardiovascular disease						0.954
No	735 (97.74)	21/676	13/59	5.84 (1.39 ~ 24.59)	0.016	
Yes	17 (2.26)	2/15	1/2	1.00 (0.00 ~ Inf)	1.000	
Congenital airway anomalies						0.991
No	725 (96.41)	19/665	13/60	4.54 (1.00 ~ 20.64)	0.050	
Yes	27 (3.59)	4/26	1/1	0.00 (0.00 ~ Inf)	1.000	
History of pneumonia						0.990
No	737 (98.01)	22/677	13/60	4.79 (1.07 ~ 21.56)	0.041	
Yes	15 (1.99)	1/14	1/1	0.00 (0.00 ~ Inf)	1.000	
Neurological disorders						0.104
No	730 (97.07)	21/676	10/54	4.69 (0.68 ~ 32.21)	0.116	
Yes	22 (2.93)	2/15	4/7	0.00 (0.00 ~ Inf)	1.000	
Metabolic disorders						0.991
No	748 (99.47)	22/690	12/58	8.56 (1.80 ~ 40.86)	0.007	
Yes	4 (0.53)	1/1	2/3	1.00 (0.00 ~ Inf)	1.000	
Hematologic disorders						0.994
No	731 (97.21)	22/671	14/60	5.55 (1.34 ~ 23.06)	0.018	
Yes	21 (2.79)	1/20	0/1	1.00 (0.00 ~ Inf)	1.000	
Immunodeficiency						0.212
No	748 (99.47)	21/687	14/61	5.43 (1.31 ~ 22.48)	0.020	
Yes	4 (0.53)	2/4	0/0	0.00 (0.00 ~ Inf)		
Renal disease						0.212
No	751 (99.87)	23/690	14/61	5.52 (1.33 ~ 22.93)	0.019	
Yes	1 (0.13)	0/1	0/0	0.00 (0.00 ~ Inf)		
Wheezing						0.519
No	560 (74.47)	17/512	11/48	6.36 (0.70 ~ 58.02)	0.101	
Yes	192 (25.53)	6/179	3/13	0.00 (0.00 ~ Inf)	0.999	
Hoarseness						0.216
No	740 (98.40)	23/679	14/61	5.45 (1.31 ~ 22.58)	0.020	
Yes	12 (1.60)	0/12	0/0	0.00 (0.00 ~ Inf)		
Respiratory distress						0.038
No	633 (84.18)	5/598	1/35	0.00 (0.00 ~ Inf)	1.000	
Yes	119 (15.82)	18/93	13/26	38.63 (3.72 ~ 400.92)	0.002	
Renal involvement						0.212
No	751 (99.87)	23/690	14/61	5.52 (1.33 ~ 22.92)	0.019	
Yes	1 (0.13)	0/1	0/0	0.00 (0.00 ~ Inf)		
Neurological involvement						0.222
No	682 (90.69)	15/639	4/43	1.93 (0.15 ~ 24.97)	0.614	
Yes	70 (9.31)	8/52	10/18	0.00 (0.00 ~ Inf)	0.998	
Circulatory involvement						0.993
No	744 (98.94)	21/684	13/60	5.58 (1.33 ~ 23.51)	0.019	
Yes	8 (1.06)	2/7	1/1	0.00 (0.00 ~ Inf)	1.000	
Hematologic involvement						0.212
No	751 (99.87)	23/690	14/61	5.52 (1.33 ~ 22.93)	0.019	
Yes	1 (0.13)	0/1	0/0	0.00 (0.00 ~ Inf)		

Figure 2. Subgroup analysis of the association between extrapulmonary involvement and PICU admission.

4. Discussion

This study demonstrates that gastrointestinal involvement is an independent risk factor for PICU admission in children hospitalized with hMPV infection (OR = 5.52; 95% CI: 1.33 - 22.93; P = 0.019), even after adjusting for key confounders. Subgroup analysis indicated that the association between gastrointestinal involvement and PICU admission was more pronounced in the severe pneumonia subgroup (OR = 11.59, 95% CI: 1.63 - 82.55, P = 0.014) and the subgroup without multiple diagnoses (OR = 47.08, 95% CI: 1.09 - 2040.30, P = 0.045). Leveraging a large cohort, our analysis provides robust insights into the role of gastrointestinal involvement in severe hMPV outcomes.

Gastrointestinal involvement serves as an independent risk factor for admission to the PICU with hMPV, reinforcing the notion that hMPV may exert systemic effects. This is further supported by reports of its neurological complication [18]. Furthermore, this aligns with a broader pattern in pediatric respiratory virology, in which extrapulmonary involvement is a critical determinant of disease severity [19]. This pattern is well illustrated by the association of gastrointestinal symptoms with more severe illness in children with RSV infection [20]. Additionally, the key predictors of PICU admission identified in this study are corroborated by prior research: Heneghan *et al.* confirmed that children with multiple underlying conditions exhibit significantly increased intensive care requirements [21]. In contrast, our finding that co-infection was a significant risk factor diverges from the conclusions of Li *et al.*'s meta-analysis [22]. This discrepancy may stem from differences in outcome definitions or adjustments for confounding factors across studies. Collectively, while these comparisons provide external validation for several of our predictors, our core contribution lies in establishing GI involvement as a novel, independent risk factor within the systemic spectrum of severe hMPV disease.

Previous studies on extrapulmonary manifestations of hMPV infection have primarily focused on neurological and cardiovascular involvement, with limited attention given to gastrointestinal involvement. Furthermore, there is a lack of validation from large-scale cohort studies. This study is the first to confirm, through univariate and multivariate logistic regression analyses, that gastrointestinal involvement is an independent risk factor for PICU admission in children with hMPV infection. It also found that respiratory distress significantly amplifies this association effect. This finding lends clinical support to the "gut-lung axis" hypothesis in respiratory viral infections [23], providing new avenues for investigating the molecular mechanisms by which extrapulmonary involvement may drive progression to severe disease. Our study identified an independent risk factor for predicting the risk of pediatric patients with hMPV infection requiring admission to the PICU. Gastrointestinal involvement provides key indicators for establishing a clinical early warning system. Future efforts may focus on implementing early gastrointestinal interventions for pediatric patients

at moderate to high risk, while systematically documenting details of gastrointestinal symptoms in children with hMPV infection (onset time, duration, severity), intervention measures, and prognostic data. Further optimize the risk prediction model for severe disease based on gastrointestinal involvement (incorporating factors such as age, underlying conditions, and co-infections), ultimately developing a practical clinical alert score to enhance the accuracy of risk assessment.

There are some limitations. At first, this study is a single-center retrospective cohort study. Data were derived from the hospital's electronic medical record system, inevitably introducing selection bias and information bias. Moreover, the study scope was limited to hospitalized children with acute respiratory infections in southern China, excluding children with acute respiratory infections in northern China and outpatient patients. Therefore, these findings may not be generalizable to the entire Chinese population. Although this study excluded variables with severe multicollinearity through VIF analysis, the variable selection process relied solely on a threshold of VIF > 5 for exclusion. The absence of more precise variable screening methods, such as stepwise regression or LASSO regression, may have resulted in the omission of certain indicators with potential influence on PICU admission. This study focused solely on the risk of PICU admission among children infected with hMPV and did not track long-term outcomes such as length of hospitalization, complication rates, or readmission rates after discharge. Finally, it cannot assess the impact of factors like gastrointestinal involvement on the children's long-term health.

5. Conclusion

hMPV can cause severe infections that lead to PICU admission. Gastrointestinal involvement may serve as an important clinical indicator of PICU admission among hospitalized children with hMPV infection.

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Authors' Contributions

Huarong Deng contributed to drafting of the manuscript. Tiefu Fang and Wanqi Li contributed to data collection.

Daojiu Jiang and Xiaodan Li carried out statistical analysis. Guangming Liu and Qiang Wang contributed to editing of the manuscript, study design and review of the manuscript.

Data Availability Statement

We declare that data can be shared and used.

Conflicts of Interest

All authors declare that they have no competing interests.

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