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ORIGINAL ARTICLE

Human Metapneumovirus Infection is Associated with Severe Respiratory Disease in Preschool Children with History of Prematurity

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Key Words
asthma;
human metapneumovirus;
prematurity;
wheezing

Background: Human metapneumovirus (HMPV) is a recently discovered respiratory pathogen of the family Paramyxoviridae, the same family as that of respiratory syncytial virus (RSV). Premature children are at high risk of severe RSV infections, however, it is unclear whether HMPV infection is more severe in hospitalized children with a history of severe prematurity.
Methods: We conducted a retrospective analysis of the clinical respiratory presentation of all polymerase chain reaction-confirmed HMPV infections in preschool-age children (≤5 years) with and without history of severe prematurity (<32 weeks gestation). Respiratory distress scores were developed to examine the clinical severity of HMPV infections. Demographic and clinical variables were obtained from reviewing electronic medical records.
Results: A total of 571 preschool children were identified using polymerase chain reaction-confirmed viral respiratory tract infection during the study period. HMPV was identified as a causative organism in 63 cases (11%). Fifty–eight ($n = 58$) preschool-age children with HMPV

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infection were included in this study after excluding those with significant comorbidities. Our data demonstrated that 32.7% of children admitted with HMPV had a history of severe prematurity. Preschool children with a history of prematurity had more severe HMPV disease as illustrated by longer hospitalizations, new or increased need for supplemental O_2, and higher severity scores independently of age, ethnicity, and history of asthma.
Conclusion: Our study suggests that HMPV infection causes significant disease burden among preschool children with a history of prematurity leading to severe respiratory infections and increasing health care resource utilization due to prolonged hospitalizations.
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1. Introduction

Respiratory tract infections are the second leading cause of death among children who are aged < 5 years worldwide.[1] Human metapneumovirus (HMPV), a relatively new respiratory pathogen of the family Paramyxoviridae—the same family as that of respiratory syncytial virus (RSV)—was discovered only a decade ago,[2] however, it is now recognized as a frequent cause of acute lower respiratory tract infections in the pediatric population.[1,4–6] Most children who are <5 years old have already been infected with HMPV,[3] with the overall prevalence of acute HMPV infection in the pediatric population ranging from 5–25% with some variation across different regions and age groups.[5,7–12] It has been estimated that approximately 27,000 HMPV-related hospitalizations will occur per year in the future among preschool children in the US.[13] This estimation is alarming and emphasizes the need to investigate the epidemiology and pathogenesis of HMPV in children.

HMPV shares the same clinical respiratory signs and symptoms as RSV, including cough, wheezing, rales, hypoxemia, and respiratory distress in high-risk groups.[5,14–16] HMPV lower respiratory tract infections contribute to 5–15% of all hospitalizations in infants and young children.[17,18] Despite the importance of this pathogen in the pediatric population, no treatment or prevention strategies have been developed,[19,20] which may reflect the lack of understanding of the risk factors that increase the morbidity and mortality of HMPV infection in children.[19,20] Interestingly, prematurity has recently been suggested to be an important risk factor for severe HMPV infection.[20–22] Young children with a history of prematurity are at an increased risk of hospitalization and frequent outpatient visits due to HMPV bronchiolitis and pneumonia,[20–23] epidemiologies that resemble the phylogenetically and clinically related pathogen RSV.[21] Other risk factors associated with severe HMPV infection include immunosuppression, young age, and existence of underlying comorbidities, such as asthma, congenital heart diseases, neuromuscular disorders, and other chronic pulmonary conditions.[23–25]

Although the aforementioned risk factors have been reported, there are limited data about the clinical presentation of severe HMPV infection in hospitalized premature children. Moreover, the link between the severity of HMPV respiratory infections and the history of prematurity in hospitalized children still needs to be better defined. Accordingly, the aim of this cross-sectional study was to examine the clinical severity of HMPV infection in hospitalized children aged ≤ 5 years with and without a history of severe prematurity (<32 weeks gestation), using respiratory parameters derived from standardized bronchiolitis scores validated by our group,[26,27] and health care utilization (i.e, length of admission).

2. Materials and methods

2.1. Study participants

We conducted a retrospective cross-sectional analysis of a cohort of preschool children aged ≤ 5 years who were admitted with HMPV infection, which was confirmed using polymerase chain reaction (PCR) analysis, at Children's National Medical Center (CNMC) between January 2013 and February 2014. Viral PCRs were performed on patients who presented to the hospital with suspected viral respiratory tract infection at the discretion of the clinician. We only included children with positive PCR for HMPV and excluded individuals with mixed viral infections.

Patients with significant comorbidities such as cardiorespiratory conditions (other than asthma and prematurity), genetic syndromes, and immunosuppression were excluded from the study. This study was approved by the Institutional Review Board at CNMC.

2.2. Clinical and demographic variables

Clinical and demographic variables were obtained by reviewing electronic medical records (EMR) at CNMC. Demographic variables comprised gestational age in weeks, age, sex, and ethnicity. Other clinical variables included tachypnea, retractions, abnormal breath sounds (wheezing), asthma diagnosis, oxyhemoglobin saturation values by pulse oximetry (SaO_2), supplemental oxygen (O_2) requirement relative to the patient's baseline, length of hospitalization, and the need for admission to the pediatric intensive care unit (PICU). In our institution, PICU admission criteria include worsening hypoxemia or hypercapnia, worsening respiratory distress, continuing requirement for >50% O_2, hemodynamic instability, and apnea. In addition, in the setting of viral respiratory tract infection PICU admission is also required for the following: (1) initiation of

"noninvasive advanced respiratory support", which is defined as the use of high-flow nasal cannula or positive airway pressure via mask in continuous or bilevel modes; and (2) initiation of mechanical ventilator support via endotracheal intubation or tracheostomy. Patients with baseline mechanical ventilator support are not automatically admitted to PICU unless that there is a modification in baseline parameters. The variable "need for invasive mechanical support" during HMPV infection was defined as new onset of mechanical support, or increase in baseline parameters from baseline.

For the purpose of the study, clinical parameters were characterized as binary outcome for: severe prematurity defined *a priori* by a gestational age of <32 weeks to include extremely preterm and very preterm patients based on the World Health Organization definition of prematurity,[28] asthma status, and O_2 supplementation. Tachypnea was stratified and scored in groups (0–3) according to respiratory rate definitions used in bronchiolitis scores as follows: 0 for <30 breaths/min (bpm); 1 for 30–45 bpm; 2 for 46–60 bpm; and 3 for >60 bpm.[27,29] "Asthma" was defined in this pediatric population using a definition that required the presence of at least one of the following criteria: (1) ever being diagnosed with asthma by a physician on the basis of criteria recommended for children in the National Asthma Education and Prevention Program Guidelines; and (2) use of asthma therapy and/or presence of asthma symptoms in the past 12 months and previously described.[30]

2.3. Clinical evaluation of viral respiratory tract infection severity based on lower airway obstruction and respiratory distress

To retrospectively assess overall clinical severity of HMPV infection, we recorded wheezing, retractions, supplemental O_2 need (which we found retrospectively to be more consistently documented than the exact initial SaO_2 saturation), and tachypnea at the initial presentation based on EMR and combined them in a respiratory distress score (0–10). For this score, we used a stratified value for tachypnea (0–3) and combined assigned values with the binary need of O_2 (0–2), presence of wheezing (0–3), and retractions (0–2), yielding a total maximal value of 10 points (Table S1). Of note, the four clinical variables included in this respiratory distress score were selected because they represented the main phenotypical features of viral bronchiolitis in children, lower airway obstruction, and respiratory distress,[30] and they are the parameters included in the bronchiolitis scores validated by our group [Modified Wood's Clinical Asthma score (M-WCAS) and Tal severity score].[27,29]

2.4. Statistical analysis

Data were analyzed using the software SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to calculate the prevalence of HMPV. Collected demographic and clinical data were compared with the use of a Chi-square test (categorical variables) or *t* test or Wilcoxon rank-sum test, as appropriate for continuous variables. Significance was taken at the $p < 0.05$ level.

3. Results

3.1. Prevalence of prematurity in hospitalized preschool children with HMPV infection

We reviewed records of all preschool-age children (0–5 years) admitted to our institution during the 2013 season with a PCR confirmed diagnosis of viral respiratory tract infection ($n = 571$). We identified HMPV as the causative organism in 63 cases (11%). Fifty-eight ($n = 58$) preschool-age children with HMPV infection were included in this study after excluding those with significant comorbidities such as cardiorespiratory conditions (other than asthma and prematurity). In terms of age distribution, a history of severe prematurity (born at <32 weeks gestational age) was present in 42% ($n = 8/19$) in infants aged < 1 year and 24% ($n = 9/39$) of individuals aged 1–5 years. The overall prevalence of a history of severe prematurity was 32.7% in the entire population ($n = 19/58$), indicating that prematurity was highly prevalent in preschool children hospitalized due to HMPV infection. Clinical characteristics and comorbidities of premature children with HMPV infection are shown in Table 1. Comparison of demographic and

Table 1 Baseline characteristics for study patients with human metapneumovirus (HMPV). Comparison of children with and without history of severe prematurity (<32 weeks gestation) and comorbidities of premature patients. For quantitative variables, data are presented as mean ± standard deviation (SD). For categorical variables, data are presented as count number (column percentage). The *p* values are obtained using either two-sample *t* test, or Chi-square test, depending on the type of variables.

Variable	Nonpremature	Premature	*p*
N	39	19	
Gestational age (wks), mean (SD)	39 ± 1.8	26.2 ± 2.5	<0.001
Sex (Male)	23 (58)	9 (53)	0.676
Age (y)	2.1 ± 1.6	1.9 ± 1.6	0.549
Race/Ethnicity			
– Black	23 (58)	8 (42)	0.221
– White	5 (13)	7 (37)	0.051
– Hispanic,	11 (28)	4 (21)	0.545
Asthma	15 (38)	10 (58)	0.252
Prematurity comorbidities			
– Necrotizing enterocolitis		7 (37)	
– Bronchopulmonary dysplasia		13 (68)	
– Tracheostomy/ home mechanical support		3 (16)	
– Intraventricular hemorrhage		7 (37)	

Data are presented as mean ± SD or *n* (%).

Table 2 Clinical severity parameters in children with human metapneumovirus (HMPV) infection. Comparison of children with and without history of severe prematurity. For quantitative variables, data are presented as mean ± standard deviation (SD). For categorical variables, data are presented as count number (column percentage). The *p* values are obtained using either two-sample *t* test, or Chi-square test, depending on the type of variables.

	Nonpremature	Premature	*p*
N	39	19	
Initial O_2 saturation (%)	95 ± 3.4	89 ± 7.1	<0.01
Mean total respiratory distress score (0—10)	4.7 ± 3.3	7.3 ± 2.3	<0.01
— Supplemental O_2 (new or increased from baseline	15 (38.4)	16 (84)	<0.01
— Stratified tachypnea (0—3)	1.21 ± 0.9	1.73 ± 0.7	0.04
— Wheezing	22 (56.4)	15 (79)	0.09
— Subcostal retractions	20 (51.2)	15 (79)	0.04

Date are presented as mean ± SD or *n* (%).

baseline study variables of children with and without a history of severe prematurity revealed no significant differences (Table 1).

3.2. HMPV in premature children is associated with higher clinical severity

To assess HMPV severity in premature children, we first evaluated the absolute degree of hypoxemia assessed with the value of SaO_2 at presentation, which was significantly lower in children with history of severe prematurity [mean SaO_2 89%; 95% confidence interval (CI) = 85.5—94.1%] relative to children born at term (mean SaO_2 95%; 95% CI = 94.4—96.7%). We also investigated the odds of needing supplemental O_2 (new or increased from baseline) in severely premature children hospitalized with HMPV infection. After adjusting for age, sex, and history of asthma (logistic regression), we identified that severely premature children were six times more likely to need supplemental O_2 [adjusted odds ratio (OR) 5.9; 95% CI = 1.25—26.; $p = 0.02$]. We next examined the overall clinical severity using a respiratory distress score (0—10; Table S1), which includes the most characteristic phenotypical features of viral bronchiolitis: lower airway obstruction (wheezing) and respiratory distress (subcostal retractions, supplemental O_2 need, and tachypnea).[26,27] Severely premature born children with HMPV had more severe respiratory distress scores relative to nonpremature HMPV-infected children [score mean ± standard deviation (SD) in full term HMPV-infected 4.7 ± 3.3 and in severely premature HMPV-infected 7.3 ± 2.3, $p < 0.01$; Table 2]. Individual parameters of respiratory distress were also significantly increased except for wheezing that did not reach statistical significance (Table 2).

In terms of the clinical presentation of premature children infected with HMPV, we found that lung auscultation and chest radiographs were abnormal in virtually all cases. Specifically, diffuse or localized crackles were present in 95% of the cases ($n = 18/19$) and focal infiltrates were identified in 74% ($n = 14/19$) of premature born children infected with HMPV. Lung infiltrates in premature born children infected with HMPV were typically poorly defined air occupying lesions affecting different segments of both lungs (Figure 1). These focal infiltrates were not associated with ground-glass pattern, pleural effusion, or necrotizing pneumonia in any of the cases. Fever (>38 °C) was present in 68% of the cases ($n = 13/19$), however, it was typically a low degree and present only during the onset of the symptoms. In terms of laboratory abnormalities, mild—moderate leukocytosis was identified in 26% of the cases ($n = 5/19$) and mild thrombocytopenia was present in two of the premature children infected with HMPV.

3.3. Severe prematurity is associated with longer hospitalization in children with HMPV infection

Preschool children with HMPV infection had a median duration of hospitalization of 4 days (95% CI 2.6—4.7 days,

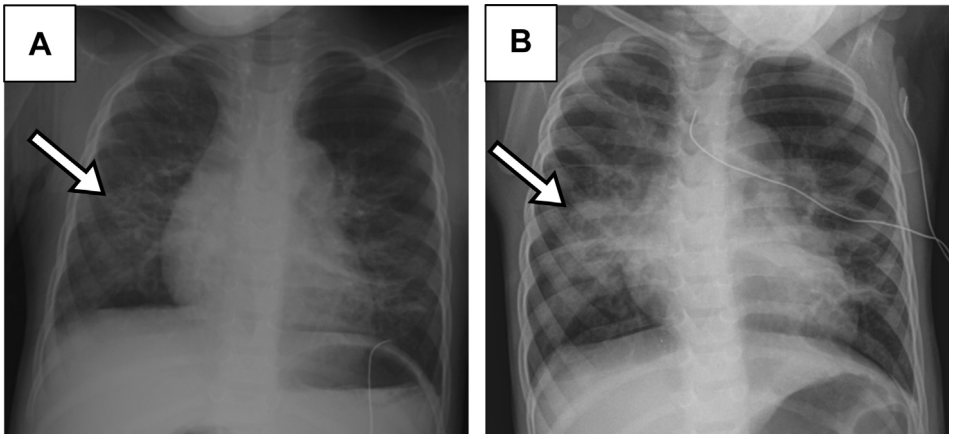

Figure 1 Comparative chest radiographs (CXRs) of a 2-year-old premature girl with human metapneumovirus (HMPV) infection. (A) Initial CXR during admission to the hospital due to HMPV infection showing a focal infiltrate in the right lower lobe (arrow); (B) 48 hours later CXR shows progression of right lower lung opacities (arrow) that correlated with worsening of crackles, poor air entry, respiratory distress, and hypoxemia.

Figure 2). By contrast, preschool children with a history of severe prematurity had a significantly longer hospitalization during HMPV infection with a median of 9 days (95% CI 6.8—12.7 days, Figure 2). Interestingly, the length of hospitalization during HMPV infection was nonsignificantly different in preschool children with the diagnosis of asthma relative to that in individuals without history of this condition (nonasthmatic children median 3.2 days, 95% CI 2.2—6.3 vs. asthmatic children median 4.7 days, 95% CI 4.1—6.4; $p > 0.05$). During the study period, 23 children with HMPV infection were admitted to PICU (39%). Thirty—three percent of nonpremature children with HMPV infection needed PICU admission ($n = 13/39$). In the group of severely premature children, 58% were admitted to PICU ($n = 11/19$). Premature born children hospitalized with HMPV infection were more likely to require noninvasive respiratory support ($n = 5/39$ nonpremature vs. $n = 7/19$ premature; $p < 0.05$). No significant differences were found in the need for invasive mechanical ventilation ($n = 5/39$ nonpremature vs. $n = 5/19$ premature; $p = 0.07$), and no mortality was present during the study period.

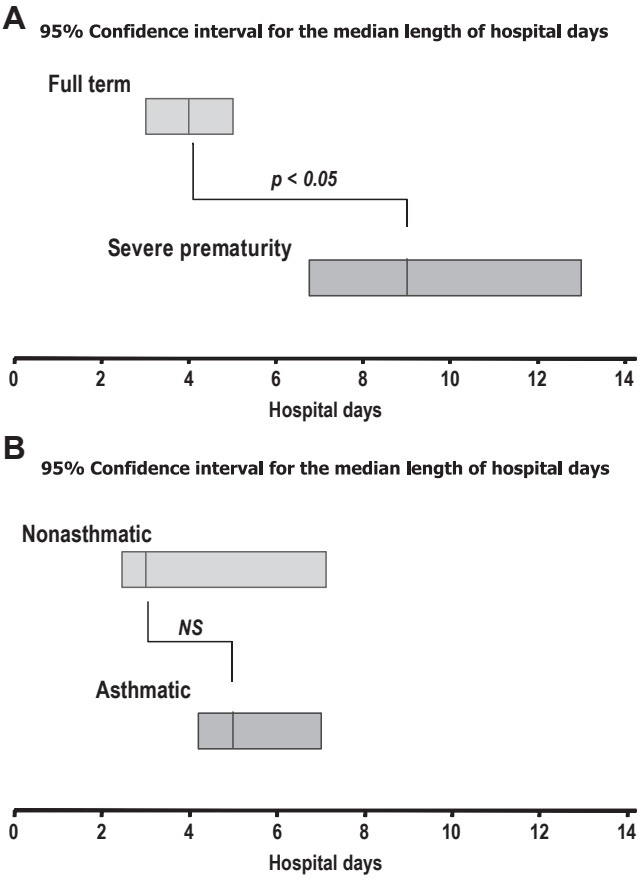

Figure 2 Mean duration of hospitalization in children with HMPV infection. Bars represent the 95% confidence interval for the median length of admission (hospital days) in children with and without history of (A) severe prematurity or (B) asthma. The *p* values were obtained using nonparametric Mann-Whitney test contrasting median hospital days in the two groups presented.

4. Discussion

Our data demonstrated that hospitalized preschool children (aged $\leq$ 5 years) with HMPV and history of severe prematurity (born $\leq$32 weeks gestational age) had severe HMPV disease, illustrated by high clinical severity scores (wheezing, retractions, need for supplemental O_2, and tachypnea) relative to children without history of prematurity. We also identified that severe prematurity was associated with a twofold increase in the duration of HMPV hospitalization in preschool-aged children. Accordingly, this study provides new evidence to support that severe prematurity is an important risk factor to be considered in the development of preventive strategies to reduce morbidity, mortality, and high costs generated by HMPV infection during the first years of life.

HMPV and RSV infection have similar clinical respiratory signs and symptoms, including cough, wheezing, rales, hypoxemia, and respiratory distress in the same high-risk groups.[5,14—16] Premature children are at increased risk of severe RSV infections that can lead to hospitalization, PICU admission, and death.[25] The clinical features of lower respiratory tract infection and the disease spectrum caused by HMPV and RSV are quite similar, with similar possible risk factors. In this study, a focus on prematurity's association with the severity of HMPV has been established. Our results revealed that premature children aged 0—5 years acquired a more clinically severe HMPV infection than children who were born nonpremature. In agreement with our observations, a study by Papenburg et al[21] identified that prematurity was more frequent among HMPV hospitalized children who were aged 0—5 months compared with nonpremature children who presented to the pediatric clinic. Similar to our present results, their severity score was based on the inclusion of at least one of the following criteria: admission to PICU, hospitalization stay $>$ 5 days, and a requirement for supplemental O_2. Moreover, prematurity was independently associated with increased severity of HMPV infection among hospitalized children of the same cohort (OR, 13.97; 95% CI, 1.5—130).[21] Population-based studies have identified that HMPV can cause severe respiratory compromise in premature infants and children with or without chronic lung disease.[32] In another investigation by Robinson et al[33] 34% of HMPV hospitalized children were born premature, suggesting that prematurity could be as important risk factor as it is for RSV, however, the severity of HMPV infection in premature children was not quantified. In our study we modified bronchiolitis severity scores validated in hospitalized children[27,29] to allow the retrospective assessment of the most characteristic phenotypical features of viral bronchiolitis: lower airway obstruction (wheezing) and respiratory distress (subcostal retractions, need for supplemental O_2, and tachypnea).[26,27] Given that EMR review did not allow us to assign mild/severe categories for wheezing and retractions accurately, we used binary variables with weighted scores and combined with hypoxemia and stratified tachypnea (0—3). Using this approach we were able to determine that children with history of severe prematurity develop more hypoxemia, stratified tachypnea, and subcostal retractions during HMPV infection. Wheezing alone was not more common in children with

history of prematurity, suggesting that rather than triggering airway reactivity, HMPV primarily exacerbates abnormal alveolar gas/exchange in the lungs of young children with history of severe prematurity. This is further supported by the presence of crackles and alveolar infiltrates in most of the premature children infected with HMPV (Figure 1).

We also investigated whether the severe HMPV infection in premature children may impact health care resource utilization in preschool children hospitalized with HMPV infection. To this end, we contrasted the length of hospitalization (days) in patients with and without a history of severe prematurity. Our results showed that the mean duration of hospitalization in infants with severe prematurity was two times higher (9 days vs. 4 days; $p < 0.05$, see Figure 2). By comparison, asthmatic children with HMPV did not have longer hospitalizations than nonasthmatic children. This indicates that additional factors (other than airway hyperreactivity/asthma) are present in children with a history of severe prematurity that make them more susceptible to respiratory viruses in early life. Based on our data reporting that hypoxemia is a common clinical presentation of HMPV in this population, it is possible that prematurity predisposes patients to more alveolar damage during HMPV infection. In parallel with longer hospitalization and frequent need for supplemental O_2, we also identified that children with a history of severe prematurity often required advanced respiratory support, which in our institution includes the use of high-flow nasal cannula or positive airway pressure via mask in continuous or bilevel modes in the PICU. Collectively, our data indicate that HMPV infection in children with history of prematurity is associated with severe respiratory disease and consequent increase in health care utilization.

Our findings add more support to the prevalent notion that the length and costs of hospitalizations in severely preterm infants are very high,[34,35] with the cost being inversely proportional to decreasing gestational age, and birth weight.[34,35] This is further aggravated by the fact that premature infants are at high-risk of recurrent hospitalization due to lower respiratory tract infections, as well as chronic pulmonary symptoms.[36] Moreover, although severely premature children have a high incidence of hospitalizations in the first few years of life,[37,38] there is also evidence than these children need more respiratory health care services later in childhood.[37,38] This may in part be due to other comorbidities associated with prematurity such as neurological impairment, artificial airways, and respiratory support that result in high care resource utilization at least during the first 5-years of life.[31] Accordingly, our current data demonstrates that there is an association between prematurity and severe HMPV infection during the first 5-years of life, and thus provides additional support for the potential use of preventive measures for HMPV infected children with a history of prematurity to ameliorate morbidity and mortality in this vulnerable population through childhood. Some future preventive strategies against HMPV may include the use of passive prophylaxis because it has been implemented with a F protein-directed monoclonal antibody (mAb)—palivizumab against RSV. However, it is important to mention that mAb prophylaxis-based approaches have pros and cons. For instance, while palivizumab was initially shown to reduce RSV-associated hospitalization by 39—78% in selected high-risk premature infants,[39] subsequent cost-economic analyses of palivizumab prophylaxis indicated that it did not represent good value for money when used unselectively in children.[40] However, subgroup analysis suggests that prophylaxis with palivizumab may be cost-effective for some subgroups, particularly those with chronic lung disease of prematurity or congential heart disease (high—risk groups).[40] In addition to risk stratification, we also believe that clinicians should consider local socioeconomic factors to determine whether mAb-based prophylaxis approaches are cost-effective in their clinical setting and geographic area.

The main limitations of the present study are its retrospective design, the small sample size, the limited number of predictor variables included in the multivariate analysis, and the fact that it was conducted in a specialized, tertiary referral hospital. With respect to the first point, because the data were taken from EMR, and the majority of variables analyzed were hard variables, it is unlikely that its retrospective design significantly compromised the validity of data collected. Secondly, although our statistical analysis included a small number of patients and limited predictor variables, we obtained an adequate signal (significant results) after including the majority of variables that have been reported in literature as validated markers of bronchiolitis severity and potential confounders.[26,27] However, as is the case in cross-sectional studies, residual confounding and type II error (due to a small sample size) cannot be excluded, therefore, interpretation of our results requires caution. It is also important to mention that important variables could not be obtained in our EMR review, including insurance information, the duration between symptom onset, and hospitalization as well as specific medical treatment(s) provided. Our study patients underwent viral PCR analysis at the discretion of the clinician, which can result in selection bias. Lastly, it is important to emphasize the fact that the study was conducted in a specialized, tertiary referral hospital makes it likely that the patients included represent the extreme of the spectrum of severity of all patients with HMPV infection, which could limit the generalization of results to other contexts (external validity). However, the similarity of the results to previous studies linking prematurity with HMPV,[20—22] as well as with the phylogenetically and clinically related pathogen RSV,[2] suggests that the results of this study could be extrapolated to other contexts.

In summary, our data demonstrated that preschool children with a history of prematurity had the more severe cases of HMPV disease, according to clinical scoring of wheezing, retractions, need for supplemental O_2, and tachypnea. Importantly, greater clinical severity also translated into increased health care resource utilization with a twofold increase in the duration of hospitalization relative to individuals with HMPV infection and no history of prematurity.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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References

1. World Health Statistics 2013. World Health Organization 2013. Available at http://www.who.int/gho/publications/world_health_statistics/EN_WHS2013_Full.pdf Accessed November 13, 2014.
2. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001;**7**:719—24.
3. Freymuth F, Vabret A, Lebon P, Legrand L, Bach N, Brouard J, et al. Le métapneumovirus humain. *Virologie* 2004;**8**:413—23 [Article in French].
4. Edwards KM, Zhu Y, Griffin MR, Weinberg GA, Hall CB, Szilagyi PG, et al. Burden of human metapneumovirus infection in young children. *N Engl J Med* 2013;**368**:633—43.
5. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004;**350**:443—50.
6. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis* 2012;**206**:56—62.
7. Mullins JA, Erdman DD, Weinberg GA, Edwards K, Hall CB, Walker FJ, et al. Human metapneumovirus infection among children hospitalized with acute respiratory illness. *Emerg Infect Dis* 2004;**10**:700—5.
8. McAdam AJ, Hasenbein ME, Feldman HA, Cole SA, Offermann JT, Riley AM, et al. Human metapneumovirus in children tested at a tertiary-care hospital. *J Infect Dis* 2004;**190**:20—6.
9. Boivin G, De Serres G, Côté S, Gilca R, Abed Y, Rochette L, et al. Human metapneumovirus infections in hospitalized children. *Emerg Infect Dis* 2003;**9**:634—40.
10. Esper F, Martinello RA, Boucher D, Weibel C, Ferguson D, Landry ML, et al. A 1-year experience with human metapneumovirus in children aged < 5 years. *J Infect Dis* 2004;**189**:1388—96.
11. Sloots TP, Mackay IM, Bialasiewicz S, Jacob KC, McQueen E, Harnett GB, et al. Human metapneumovirus, Australia, 2001—2004. *Emerg Infect Dis* 2006;**12**:1263—6.
12. van den Hoogen BG, van Doornum GJ, Fockens JC, Cornelissen JJ, Beyer WE, de Groot R, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. *J Infect Dis* 2003;**188**:1571—7.
13. Williams JV, Edwards KM, Weinberg GA, Griffin MR, Hall CB, Zhu Y, et al. Population-based incidence of human metapneumovirus infection among hospitalized children. *J Infect Dis* 2010;**201**:1890—8.
14. Jartti T, van den Hoogen B, Garofalo RP, Osterhaus AD, Ruuskanen O. Metapneumovirus and acute wheezing in children. *Lancet* 2002;**360**:1393—4.
15. Madhi SA, Ludewick H, Kuwanda L, Niekerk Nv, Cutland C, Little T, et al. Pneumococcal coinfection with human metapneumovirus. *J Infect Dis* 2006;**193**:1236—43.
16. Williams JV, Tollefson SJ, Heymann PW, Carper HT, Patrie J, Crowe JE. Human metapneumovirus infection in children hospitalized for wheezing. *J Allergy Clin Immunol* 2005;**115**:1311—2.
17. Tecu C, Mihai ME, Alexandrescu VI, Orăşeanu D, Zapucioiu C, Ivanciuc AE, et al. Single and multipathogen viral infections in hospitalized children with acute respiratory infections. *Roum Arch Microbiol Immunol* 2013;**72**:242—9.
18. Papenburg J, Boivin G. The distinguishing features of human metapneumovirus and respiratory syncytial virus. *Rev Med Virol* 2010;**20**:245—60.
19. Feuillet F, Lina B, Rosa-Calatrava M, Boivin G. Ten years of human metapneumovirus research. *J Clin Virol* 2012;**53**:97—105.
20. Schuster JE, Williams JV. Human metapneumovirus. *Pediatr Rev* 2013;**34**:558—65.
21. Papenburg J, Hamelin MÈ, Ouhoummane N, Carbonneau J, Ouakki M, Raymond F, et al. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. *J Infect Dis* 2012;**206**:178—89.
22. Schildgen V, van den Hoogen B, Fouchier R, Tripp RA, Alvarez R, Manoha C, et al. Human Metapneumovirus: lessons learned over the first decade. *Clin Microbiol Rev* 2011;**24**:734—54.
23. Spaeder MC, Custer JW, Bembea MM, Aganga DO, Song X, Scafidi S. A multicenter outcomes analysis of children with severe viral respiratory infection due to human metapneumovirus. *Pediatr Crit Care Med* 2013;**14**:268—72.
24. Englund JA, Boeckh M, Kuypers J, Nichols WG, Hackman RC, Morrow RA, et al. Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. *Ann Intern Med* 2006;**144**:344—9.
25. Pelletier G, Déry P, Abed Y, Boivin G. Respiratory tract reinfections by the new human metapneumovirus in an immunocompromised child. *Emerg Infect Dis* 2002;**8**:976—8.
26. Rodríguez DA, Rodríguez-Martínez CE, Cárdenas AC, Quilaguy IE, Mayorga LY, Falla LM, et al. Predictors of severity and mortality in children hospitalized with respiratory syncytial virus infection in a tropical region. *Pediatr Pulmonol* 2014;**49**:269—76.
27. Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. *J Asthma* 2013;**50**:1056—61.
28. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;**379**:2162—72.
29. Tal A, Bavilski C, Yohai D, Bearman JE, Gorodischer R, Moses SW. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;**71**:13—8.
30. Gutierrez MJ, Zhu J, Rodriguez-Martinez CE, Nino CL, Nino G. Nocturnal phenotypical features of obstructive sleep apnea (OSA) in asthmatic children. *Pediatr Pulmonol* 2013;**48**:592—600.
31. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. *Pediatrics* 2003;**112**:1290—7.
32. Klein MI, Coviello S, Bauer G, Benitez A, Serra ME, Schiatti MP, et al. The impact of infection with human metapneumovirus and other respiratory viruses in young infants and children at high risk for severe pulmonary disease. *J Infect Dis* 2006;**193**:1544—51.
33. Robinson JL, Lee BE, Bastien N, Li Y. Seasonality and clinical features of human metapneumovirus infection in children in Northern Alberta. *J Med Virol* 2005;**76**:98—105.

34. Rogowski J. Measuring the cost of neonatal and perinatal care. *Pediatrics* 1999;**103**:329—35.
35. Marbella AM, Chetty VK, Layde PM. Neonatal hospital lengths of stay, readmissions, and charges. *Pediatrics* 1998;**101**:32—6.
36. Renard ME, Truffert P, Groupe EPIPAGE. Clinical respiratory outcome of very preterm newborn at 5 years. The EPIPAGE cohort. *Arch Pediatr* 2008;**15**:592—4 [Article in French].
37. Gray D, Woodward LJ, Spencer C, Inder TE, Austin NC. Health service utilisation of a regional cohort of very preterm infants over the first 2 years of life. *J Pediatr Child Health* 2006;**42**: 377—83.
38. Rautava L, Häkkinen U, Korvenranta E, Andersson S, Gissler M, Hallman M, et al. Health and the use of health care services in 5-year-old very-low-birth-weight infants. *Acta Paediatr* 2010; **99**:1073—9.
39. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics* 1998;**102**:531—7.
40. Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. *Health Technol Assess* 2011;**15**:iii—iv, 1—124.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.pedneo.2015.03.008