学位論文の関連論文の研究背景及び要旨

古田　貴士

〔研究背景〕

human metapneumovirus (hMPV) は2001年に発見されたパラミクソウイルス科に属するウイルスである．マイナス一本鎖RNAウイルスであり，小児の気道感染症の主要なウイルスであるrespiratory syncytial virus (RSV) の属するニューモウイルス亜科に分類される．遺伝子解析の結果から，hMPVはAとBのサブグループに分けられ，それぞれのサブグループがさらに2つに分けられる (A1とA2, B1とB2). hMPVは乳幼児において上気道, 下気道感染を引き起こすとされる. 臨床症状は発熱, 咳嗽, 鼻汁，呼吸困難などである．理学所見としては，咽頭発赤，呼吸音のラ音聴取，喘鳴，陥没呼吸などを認める．胸部レントゲン写真では，気管支肺胞浸潤影，肺気腫，無気肺などを認める．血清疫学的な研究から，5歳までに90%以上が感染するとされ，その多くは入院する必要はないと考えられている．入院を必要とするhMPV感染の患者では基礎疾患を有していることが多く，早産児，染色体異常，心疾患，気管支喘息や免疫不全などが報告されている．RSVも同様に乳児において，気管支炎．細気管支炎、肺炎など急性気道感染を引き起こす主要な病原体である．hMPVの感染した小児は臨床的にはRSV感染と見分けることは困難と考えられている．

hMPV感染症とRSV感染症の比較については，すでにいくつか報告がある．hMPVは冬から春にかけて流行するのに対し，RSVは冬季に流行するとされる．RSV罹患患児に比してhMPV罹患患児の方が，年齢が高く，血清CRP値がより高いとする報告もある．また，hMPV感染症とその他のウイルス感染を比較した文献では，hMPVで肺炎が多かったと報告されている．

これまでに我々は，H1N1パンデミック[A(H1N1)pdm09]やエンテロウイルスD68による感染が気管支喘息の児に気管支喘息発作を引き起こすことを報告した．また，A(H1N1)pdm09が喘息モデルマウスで季節性インフルエンザと比較して，肺に高度な炎症を来すことを報告した．hMPVやRSV感染は気管支喘息発作の契機となりうると報告されているものの，気管支喘息が重症度にどの程度の影響を与えるかは未だ不明である．

今回我々は，　hMPVまたはRSV感染が気管支喘息児における影響を評価することを目的とし，山口県全県を対象とした後方視的研究を行った．

〔要旨〕

本研究で我々はhMPVおよびRSVの季節性の流行が小児喘息患者に与える影響について明らかにすることを目的とした.

2011年から2014年に山口県内の小児入院施設で入院したhMPVとRSV感染患者を対象とした. 感染症の診断は, 鼻腔から採取した検体によるイムノクロマト法またはpolymerase chain reaction (PCR) 法を用いて行った. 年齢, 臨床所見, 胸部レントゲン所見や血液検査結果などのカルテ情報を後方視的に収集し, hMPV群とRSV群で比較した. 気管支喘息は小児気管支喘息治療・管理ガイドライン2012に基づき, 1歳以上の児で, 3回以上の喘鳴のエピソードを認めることと定義した. 同ガイドラインにて, 入院加療を検討する気管支喘息中発作の経皮的酸素飽和度 (SpO_2) は92-95%と定義されるため, この研究で低酸素血症の定義はSpO_2<95%とした. 胸部レントゲン写真での異常所見は浸潤影と定義した. 気管支喘息の低酸素血症への影響を評価するため, 早産児, 先天性心疾患, 神経疾患, 染色体異常やその他の基礎疾患を有する児を除外した. 両群間の比較にはカイ二乗検定とMann-Whitney U検定を用いた. 低酸素血症に影響する因子を評価するためにロジスティック回帰分析を実施した.

期間中にhMPVおよびRSV感染症により1,934名が入院した. 20歳以上の症例, 重複例, データに欠損がある症例などを除外し, を解析対象とした. hMPV群は114名, RSV群は1,103名であった. hMPV感染児の月齢は12-15か月がピークで, RSV感染症のピークは生後0-3か月であった. 低酸素血症をきたした症例の割合を両群間の各年齢間で比較したが, それぞれ40-50%であり, 差は認めなかった. 1歳以上で低酸素血症をきたした症例を対象に検討したところ, hMPV群の方がRSV群よりも年齢が高く(p=0.036), 喘息と診断されている割合が多く(p=0.015), 胸部レントゲン検査で浸潤影を認めた割合が多かった (p<0.001). 低酸素血症をきたすリスク因子を評価するため, 両群間で多変量解析を実施した. hMPV, RSV群共に気管支喘息があることは, 低酸素血症のリスクであった (hMPV; Odds ratio [OR]: 15.8, p<0.001, RSV; OR 2.2, p=0.005). hMPV群では体温が高いこと (OR: 2.2, p=0.009), RSVでは月齢が低いこと(OR: 1.4, p=0.004) が低酸素血症のリスクと考えられた.

RSV群に比較してhMPV群において年齢が高い要因として, 母体からの移行抗体が影響していると推測された. 過去の報告でRSVの消失はhMPVの母体移行抗体よりも速いとされ, この差が両群間で入院児の年齢に差が出た要因と考えられた. マウスを用いた報告ではhMPVに感染したマウスはRSVに比して炎症性サイトカインの反応が強かったと報告されている. また, この研究では, hMPV感染したマウスで気道の閉塞性病変が多かったと報告している. 我々の研究ではhMPV群でRSV群よりも肺炎をきたしている割合が多く, 気管支喘息が増悪している割合が多かった. このことに両ウイルスの免疫応答の差が影響していることが推測された. 多変量解析の結果から, 気管支喘息はhMPV感染, RSV感染において独立した低酸素血症のリスク因子であると考えられた. また, ORからはRSVよりもhMPVにおいては気管支喘息の影響がより大きい可能性が示唆された.

気管支喘息のある小児において, hMPVおよびRSV感染症は低酸素血症を引き起こす重要な要因であると考えられた.

Burden of human metapneumovirus and respiratory syncytial virus infections in asthmatic children

Takashi Furuta[1], MD, Shunji Hasegawa[1], MD, PhD, Makoto Mizutani[1], MD, Takashi Iwai[2], MD, Noriko Ohbuchi[3], MD, Shoji Kawano[4], MD, PhD, Norimichi Tashiro[5], MD, PhD, Masashi Uchida[6], MD, PhD, Masanari Hasegawa[7], MD, PhD, Masashi Motoyama[8], MD, PhD, Takaomi Sekino[9], MD, PhD, Kenji Nakatsuka[10], MD, PhD, Kiyoshi Ichihara[11], MD, PhD, Komei Shirabe[12], MD, PhD, and Shouichi Ohga[1, 13], MD, PhD

Affiliations:

[1]Department of Pediatrics, Yamaguchi University Graduate School of Medicine

1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan

[2]Division of Pediatrics, Yamaguchi-ken Saiseikai Shimonoseki General Hospital

8-5-1 Yasuoka-cho, Shimonoseki, Yamaguchi 759-6603, Japan

[3]Division of Pediatrics, Japan Red Cross Yamaguchi Hospital

53-1 Yawatanobaba, Yamaguchi 753-0092, Japan

[4]Division of Pediatrics, Shimonoseki City Hospital

1-13-1 Koyo-cho, Shimonoseki, Yamaguchi 750-8520, Japan

[5]Division of Pediatrics, Yamaguchi Rosai Hospital

1315-4 Onoda, Sanyo-Onoda, Yamaguchi 756-0095, Japan

[6]Division of Pediatrics, JCHO Tokuyama Central Hospital

1-1 Koda-cho, Shunan, Yamaguchi 745-8522, Japan

[7]Division of Pediatrics, Yamaguchi Grand Medical Center

77 Osaki, Hofu, Yamaguchi 747-8511, Japan

[8]Division of Pediatrics, Shuto General Hospital

1000-1 Kogaisaku, Yanai, Yamaguchi 742-0032, Japan

[9]Division of Pediatrics, Ogori Daiichi General Hospital

862-3 Ogori Shimogo, Yamaguchi 754-0002, Japan

[10]Division of Pediatrics, Yamaguchi-ken Saiseikai Toyoura Hospital

7-3 Toyoura-cho Kogushi, Shimonoseki, Yamaguchi 759-6302, Japan

[11]Department of Laboratory Sciences, Faculty of Health Sciences, Yamaguchi University Graduate School of Medicine

1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan

[12] Yamaguchi Prefectural Institute of Public Health and Environment

2-5-67 Aoi, Yamaguchi, 753-0821, Japan

[13]Department of Pediatrics, Kyushu University Graduate School of Medical Science

3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Corresponding author: Shunji Hasegawa, Department of Pediatrics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan

E-mail: shunji@yamaguchi-u.ac.jp

Tel: 81-836-22-2258

Fax: 81-836-22-2257

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Running Title: virus infections in asthmatic children (38<44 characters)

Abstract

Background: Human metapneumovirus (hMPV) and respiratory syncytial virus (RSV) are the leading causes of acute respiratory illness in children. Clinical burden of each infection on the respiratory distress in asthmatic patients remains unclear. The purpose of the study is to clarify the effect of these infections on the severity of asthmatic children in the seasonal outbreaks. ***Methods:*** A total of 1,217 pediatric inpatients with hMPV (n=114) or RSV (n=1,103) infection in Yamaguchi prefecture, Japan between 2011 and 2014 were enrolled. Bronchial asthma was defined as having more than three episodes of wheezing illness over one year of age. Infection was determined by the positive antigen test for each virus in the nasal specimens. ***Results:*** The number of patients peaked at age 12-15 months in hMPV infection and at age 0-3 months in RSV infection. The proportion of hypoxic patients (40-50%) did not differ at any age between hMPV-infected and RSV-infected children. In the analysis of date from >1 year old patients with hypoxia, hMPV-infection group was older (p=0.036), and more frequently had history of asthma (p=0.015) or abnormal chest roentgenogram (p<0.001) than RSV-infection group. Multivariate analysis indicated that the hypoxia-associated factors were history of asthma in both hMPV (Odds ratio [OR]: 15.8, p<0.001) and RSV infections (OR: 2.2, p=0.005), higher body temperature in hMPV infection (OR:

2.2, p=0.009), and younger age in RSV infection (OR: 1.4, p=0.004). ***Conclusions:*** Outbreaks of hMPV, rather than, RSV infection may have a greater impact on the development of hypoxic respiratory illness in asthmatic children.

Introduction

Human metapneumovirus (hMPV) is a member of the paramyxovirus family that was discovered in 2001.[1] It is a non-segmented, negative-sense, and single-stranded enveloped RNA virus in the same Pneumovirinae family as respiratory syncytial virus (RSV). According to the genomic sequencing and phylogenetic analysis, there is a single hMPV serotype with two subgroups, A and B. Each genotype appears to have at least two distinct subgroups (A1 and A2, and B1 and B2).[2] hMPV infection is associated with upper and lower respiratory illness in infants and children worldwide.[1-4]. A seroepidemiological study reported that more than 90% of children experience hMPV infection by 5 years of age and most do not require inpatient care.[5] However, children hospitalized for severe hMPV infection often have underlying disorders including premature birth, chromosome aberration, congenital heart disease, bronchial asthma, or immunosuppressive conditions.[6-8]

RSV is also a major pathogen of acute respiratory illness in infants presenting with bronchitis, bronchiolitis, and pneumonia. The clinical manifestations of hMPV-infected children are indistinguishable from those of RSV-infected ones[3,4], although acute respiratory failure in infancy suggests RSV rather than hMPV infection.[9] Previous studies suggested that both viruses trigger the exacerbation of bronchial asthma in

children.[10,11] However, the age-dependent severity of patients with hMPV and RSV infections has not been fully explained.

We hypothesized that there are differences in the clinical characteristics of asthmatic children infected with RSV or hMPV. The present study aimed to determine the clinical impact of hMPV and RSV infections on the severity of asthma in children during a period of seasonal outbreaks in an area with over one million population.

Patients and Methods

The present study included all patients who were hospitalized for the treatment of hMPV or RSV infection in the divisions of pediatrics of 13 hospitals in Yamaguchi prefecture, Japan, between April 2011 and June 2014. More than 85% of pediatric inpatients with each virus infection was estimated to be covered during the period, because only 14 institutions offer pediatric inpatient care in this prefecture, located at the western edge of the main island of Japan, covering 6110.9 km^2, and with a population of 1,445,702. The diagnosis of each virus infection was determined using immunochromatographic assay (Check hMPV, Meiji Seika Pharma Co. Ltd., Tokyo, Japan) or polymerase chain reaction (performed at Yamaguchi Prefectural Institute of Public Health and Environment) using nasal epithelial cells obtained with cotton swabs.

These tests were performed to determine the pathogens in hospitalized patients with respiratory infection for the official report to infection surveillance in the prefecture. The decision for hospitalization was determined by each pediatrician based on the children's conditions. Clinical data of these patients were retrospectively collected from the medical records including age, sex, previous and family histories, clinical and laboratory findings at diagnosis and during the treatment course, and outcomes. The laboratory and chest radiographic findings on admission were included in the analyses, in addition to the highest body temperature and lowest percutaneous oxygen saturation during hospitalization. These variables were compared between hMPV and RSV infections, with a focus on asthmatic patients. The history of bronchial asthma was defined as having more than three episodes of wheezing illness according to Japanese Pediatric Guidelines for the Treatment and Management of Asthma 2012.[12] This guideline recommends that patients with moderate asthma attack (92-95% of percutaneous oxygen saturation: SpO_2) are hospitalized to receive oxygen therapy. Hypoxia was then defined as <95% SpO_2 in the present study. To assess the effect of each infection on hypoxia (<95%) in asthmatic patients, patients less than one year of age were excluded from the sub-analysis because the diagnosis of bronchial asthma might not be definitive in infants. To evaluate the impact of bronchial asthma on

hypoxia, patients with underlying diseases except for bronchial asthma; who were premature births; or who had congenital heart disease, neurologic disorder, chromosomal abnormalities, and others were excluded. We defined hypoxia as the lowest SpO_2 under 95% during hospitalization. Abnormal chest radiographic findings were defined as pulmonary consolidation encompassing all kind of infiltrates in the lung fields, based on the interpretation by pediatricians and/or radiologists.

This observational study was approved by the Institutional Review Board of Yamaguchi University Hospital (H24-11).

Statistical analysis

Differences between groups were analyzed using chi-square and Mann-Whitney U tests. Factors associated with the occurrence of hypoxia were evaluated using multiple logistic regression analysis. The factors examined as explanatory variables included age, body temperature, history of asthma, and abnormal chest radiographic findings. P values less than 0.05 were considered significant. The analyses and calculations were performed using JMP Pro version 11.2.0 (SAS Institute Inc., Tokyo, Japan).

Results

Epidemiology of hMPV and RSV infections

Data were obtained from 1,934 hospitalized patients infected with hMPV or RSV in Yamaguchi prefecture, Japan between April 2011 and June 2014 (**SDC1**). After excluding 717 patients (over 20 years of age, duplicate cases, and lack of analyzable data), 114 and 1,103 hospitalized children with hMPV and RSV infection were included, respectively.

The seasonal changes in the numbers of hMPV and RSV-infected children were as follows (**SDC2**). The number of pediatric inpatients with hMPV infection started to increase in February, peaked in April, and then rapidly decreased in June. In contrast, the number of those with RSV infections increased in July, peaked in September and December, and then gradually decreased. The age distributions of the patients with hMPV (n = 114) and RSV infections (n = 1,103) are shown in **Figure 1**. The number of pediatric inpatients with hMPV-infection peaked at 12-15 months of age and was widely distributed among those over 24 months of age. In contrast, 919 of the 1,103 pediatric inpatients with RSV-infections (83.3%) were under 24 months of age.

Clinical profiles of pediatric inpatients with hMPV or RSV infections

The demographics and clinical findings were compared between the hMPV and

RSV groups (**Table 1**). Pediatric inpatients with hMPV infections were older than those with RSV infections (median age, 22 months vs. 9 months; p <0.001). The body temperature of children in the hMPV group was higher than that in the RSV group (median, 39.0°C vs. 38.4°C; p <0.001). The serum levels of C-reactive protein in the hMPV group was higher than that in the RSV group (median, 1.5 mg/dL vs. 0.69 mg/dL; p <0.001). In contrast, the median SpO_2 and leukocyte counts did not differ between the hMPV and RSV groups. Approximately half of the patients with either infection developed hypoxia, regardless of age group (**Figure 1**). The proportion of hypoxic patients tended to be higher at one year and over 5 years of age in hMPV-infected patients compared to the RSV-infected patients; however, the difference was not statistically significant (**Figure 2**).

The frequency of hMPV-infected patients with abnormal chest radiographic findings was higher than that of RSV-infected patients (85.1% vs. 46.4%; p <0.001). The frequency of hMPV-infected patients having a history of bronchial asthma was higher than that of RSV-infected patients (18.4% vs. 6.0%; p <0.001). There were no differences in the prevalence of other underlying diseases affecting respiratory conditions between hMPV-infected and RSV-infected infants and children.

Patients 1 year and older with hypoxia and hMPV or RSV infections

To assess the clinical burden in asthmatic patients with these infections, we performed subgroup analysis of the demographics and clinical features of children 1 ≥ year of age who developed hypoxia during the treatment course for hMPV or RSV infection (**Table 2**). The hMPV-hypoxic children were older than the RSV-hypoxic children (median age, 23 months vs. 20 months; $p = 0.036$). The frequency of hMPV-hypoxic children with abnormal chest radiographic findings was higher than that of RSV-hypoxic children (91.1% vs. 62.1%; $p < 0.001$). The frequency of hMPV-hypoxic children with a history of bronchial asthma was higher than that of RSV-hypoxic children (35.6% vs. 17.7%; $p = 0.015$). The prevalence of other underlying diseases did not differ between hMPV-hypoxic and RSV-hypoxic children. When the clinical findings of hypoxic infants were compared between hMPV and RSV infection, the frequency of abnormal radiographs was higher in hMPV-infected patients (**SDC3**).

To confirm the impact of hMPV and RSV infection on the severity of asthmatic children alone, multiple logistic regression analyses were performed for the factors associated with hypoxia separately in 84 hMPV-infected patients and 425 RSV-infected patients (**SDC1, Table 3**). In the analysis of hMPV infection, body temperature (odds ratio [OR] 2.23 for each °C increase, $p = 0.009$) and history of bronchial asthma (OR

15.8, p <0.001) were selected as the contributory parameters for hypoxia. In the analysis of RSV infection, increasing age reduced the risk of hypoxia (OR 0.735 for each one-year increase in age, p =0.004) and history of bronchial asthma (OR 2.22, p =0.005) was selected as the contributory parameter for hypoxia. In asthmatic children with either virus infection, asthma controller therapy was not a contributory factor for the occurrence of hypoxia (**SDC4**).

Discussion

The notable finding in the present study was that hMPV-infected children who required inpatient care more frequently had a history of asthma and chest x-ray infiltrations than RSV-infected ones, while nearly half had hypoxia regardless of the causative virus. A history of asthma was identified as a hypoxia-associated factor in children with hMPV or RSV infections, particularly in the former with an OR of >15. These results suggested that hMPV could induce more severe inflammation in the lungs of asthmatic children compared to those with RSV. Thus, outbreaks of hMPV rather than RSV infection might place a greater burden of hypoxia on patients with bronchial asthma.

In this epidemiological study, hospitalized children with hMPV infection had a

higher age at onset, body temperature, C-reactive protein levels, and proportions of abnormal chest x-ray findings and bronchial asthma history than seen in those with RSV infection. The disease severity did not differ between the two infections based on the equivocal rate of desaturation and duration of hospitalization. hMPV often causes severe respiratory illness in young infants, which is indistinguishable from RSV bronchiolitis.[3,4] In this setting, the different impact of each virus on the disease course in pediatric patients has not been clarified. Several studies reported the effect of hMPV infection on the progression to bronchial asthma, as well as the opposite effect of bronchial asthma on the exacerbation of hMPV disease.[10,13,14] Two studies compared exacerbating factors between hMPV- and RSV-infected children over one year of age, reporting that prematurity and chronic lung disease were risk factors for severe hMPV infection.[15,16] However, these studies did not determine the impact of bronchial asthma on the disease severity in children. In the present study, asthma history was the factor most related to hypoxia in either hMPV- or RSV-infected children after the exclusion of known underlying diseases, as shown in **Table 3**. It posed a seven-fold increased risk of hypoxia in hMPV-infected children (15.8, p <0.001) than that in RSV-infected children (2.22, p = 0.005), although the value and accuracy of the ORs might not be directly comparable. This prefecture-wide survey over three years might be the first to report a

greater impact of hMPV than RSV in asthmatic children.

Distinct seasonal changes (**SDC2**) and age distributions (**Figure 1**) of RSV-infected patients from hMPV-infected ones were as reported previously.[4,17] Maternal antibodies against hMPV protect young infants against the infection or lessen the severity of illness.[2] The age-dependent susceptibility to hMPV and RSV infections might thus be explained by sequential changes in virus-specific antibody titers after birth.[17] A large cohort in Kenya showed that 97% of infants had detectable titers of RSV-specific maternal antibody. The seroprevalence gradually declined with age according to the half-life the maternal antibody (2.6 months).[18] In contrast, a study in the United States of America showed that 90% of infants less than six months of age had hMPV-specific maternal antibodies.[5] The seroprevalence declined to 35% 12-23 months after birth, which corresponded to the minimum value. However, antibody responses do not always explain severe hMPV disease.

Serum C-reactive protein levels in hMPV patients were reportedly higher than those in RSV patients.[19] These may account for the pathophysiology of hMPV-induced pneumonia in children in contrast to RSV-induced bronchiolitis in young infants.[19] Compared to mice infected with RSV, hMPV infection induced a stronger inflammatory cytokine response.[20] Mice infected with hMPV had significantly higher levels of tumor

necrosis factor-α, interleukin-6, and monocyte chemotactic protein-1 than those of RSV-infected mice. In addition, hMPV induced considerable airway obstruction and histopathology, while only minimal changes occurred in mice infected with RSV. These discrepancies between hMPV and RSV in immune response might cause increased frequencies of asthma attack and pneumonia in the hMPV group than in the RSV group.

The present study assessed hMPV or RSV infection-induced hypoxia in hospitalized children irrespective of the requirement for long-term management of bronchial asthma (*data not shown*). Further studies are necessary to shed light on the pathophysiology that predisposes asthmatic children to excessive pulmonary inflammation in hMPV infection.

This clinical and epidemiological study had some limitations. First, there might have been a potential bias when pediatricians decided to perform tests or hospitalization. This problem is inevitable due to the study design. A prospective study is necessary to confirm the impact of virus infection in asthmatic children. Second, virus-induced wheezing was not completely excluded in asthmatic children for the clinical definition, although additional data such as atopy, family history of asthma, and allergy testing might effectively rule out any wheezing disease. Third, Japanese medical insurance requires the completion of chest x-ray to perform the rapid hMPV detection

kit. The institutional constraint might have affected the frequency of chest x-ray and its abnormality in the hMPV group. Fourth, not all patients received culture-based bacteriological examinations for respiratory illness. The potential effects of bacterial co-infection on respiratory conditions and laboratory data were not considered. Finally, host immune responses including cytokine levels were not assessed in the analysis of the pathophysiology of hMPV or RSV infection, although any underlying diseases other than bronchial asthma affecting respiratory conditions were excluded.

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Figure legends

Figure 1

Age distributions of patients hospitalized with hMPV or RSV infections.

The peak of hospitalization with hMPV infection was 12-15 months of age. In comparison, the peak of hospitalization with RSV infection was under 24 months of age.

Figure 2

Percentages of hypoxic patients with hMPV and RSV infections.

In each age group, certain patients experienced hypoxia. At one year and more than five years of age, more patients with hMPV tended to experience hypoxia compared to those with RSV.

Supplementary Figure 1

Flowchart of enrolled patients with human metapneumovirus (hMPV) or respiratory syncytial virus (RSV) infections.

We obtained data from 1,934 inpatients infected with hMPV or RSV in Yamaguchi prefecture between April 2011 and June 2014. We included data from 84 and 425 patients infected with hMPV and RSV, respectively, in the multivariate analysis.

Supplementary Figure 2

Monthly cumulative numbers of hospitalized patients with hMPV or RSV infections. The number of inpatients with hMPV increased in March and peaked in April. The number of inpatients with RSV increased from August, with were bimodal peaks in September and December.

List of Supplemental Digital Content

Supplemental Digital Content 1. Supplementary Figure 1

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Table 1. Clinical profiles of the patients with hMPV infection or RSV infection

median (range)	total (n=1,217)	hMPV (n=114)	RSV (n=1,103)	*p*-value
Age, years	0.83 (0m-18y)	1.83 (1m-12y)	0.75 (0m-18y)	<0.001
Body temperature,°C	38.5 (36.0-41.7)	39.0 (36.6-41.7)	38.4 (36.0-41.5)	<0.001
SpO_2, %	95.0 (30-99)	95 (70-98)	95 (30-99)	1.00
WBC, $\times 10^9$/L	9.50 (2.50-34.1)	9.22 (2.50-27.0)	9.56 (3.28-34.1)	0.239
CRP, mg/dL	0.73 (0-19.4)	1.5 (0.03-19.4)	0.69 (0-17.8)	<0.001
Abnormal findings of chest x-ray	609, 50.0%	97, 85.1%	512, 46.4%	<0.001
Duration of hospitalization, days	6 (0-45)	6 (3-33)	6 (0-45)	0.109
Underlying diseases				
History of bronchial asthma†	87, 7.1%	21, 18.4%	66, 6.0%	<0.001
Premature infants	25, 2.1%	1, 0.9%	24, 2.2%	0.299
Congenital heart diseases	25, 2.1%	2, 1.8%	23, 2.1%	0.808
Neurological disorders	10, 0.8%	1, 0.9%	9, 0.8%	0.946
Chromosomal abnormality	16, 1.3%	4, 3.5%	12, 1.1%	0.066
Others‡	4, 0.3%	0	4, 0.4%	-

† Bronchial asthma was defined as having more than 3 times of wheezing illness in patients of one year and over.

‡ Others included laryngomalacia, obliterating bronchiolitis, fetal pleural effusion, and thoracic hypoplasia.

Table 2. Clinical findings of one year and over patients with hypoxia† after hMPV or RSV infection

median (range)	hMPV (n=45)	RSV (n=232)	*p*-value
Age, years	1.92 (1-12)	1.67 (1-18)	0.036
Body temperature,°C	39.2 (37.0-41.7)	39.0 (37.0-40.7)	0.069
WBC, $\times 10^9$/L	8.36 (2.50-22.3)	9.20 (3.65-33.5)	0.052
CRP, mg/dL	1.47 (0.06-9.45)	1.28 (0-16.0)	0.372
Abnormal findings of chest x-ray	41, 91.1%	144, 62.1%	<0.001
Duration of hospitalization, days	8 (4-33)	7 (2-45)	0.047
Underlying diseases			
History of bronchial asthma‡	16, 35.6%	41, 17.7%	0.015
Premature infants	1, 2.2%	12, 5.2%	0.885
Congenital heart diseases	2, 4.4%	9, 3.9%	0.407
Neurological disorders	1, 2.2%	8, 3.4%	0.823
Chromosomal abnormality	4, 8.9%	7, 3.0%	0.098
Obliterating bronchiolitis	0	1, 0.4%	0.551

† Hypoxia was defined as having less than 95% of SpO_2.

‡ Bronchial asthma was defined as having more than 3 times of wheezing illness in patients of one year and over.

Table 3. Multivariate analysis for the association variables affecting hypoxia† after hMPV or RSV infection

Study population	Variables	Odds ratio	95% CI lower-upper limit	*p*-value
a) One year and over patients with hMPV infection				
n=84	Age (1-year gain)	0.868	0.640-1.14	0.316
	Body temperature (1 °C elevate)	2.23	1.22-4.42	0.009
	History of bronchial asthma‡	15.8	4.13-82.2	<0.001
	Abnormal findings of chest x-ray	2.24	0.521-11.2	0.284
b) One year and over patients with RSV infection				
n=425	Age (1-year gain)	0.735	0.590-0.907	0.004
	Body temperature (1 °C elevate)	0.912	0.724-1.15	0.430
	History of bronchial asthma	2.22	1.26-3.99	0.005
	Abnormal findings of chest x-ray	1.00	0.670-1.49	0.998

† Hypoxia was defined as having less than 95% of SpO_2.

‡ Bronchial asthma was defined as having more than 3 times of wheezing illness in patients of one year and over.

Figure 1

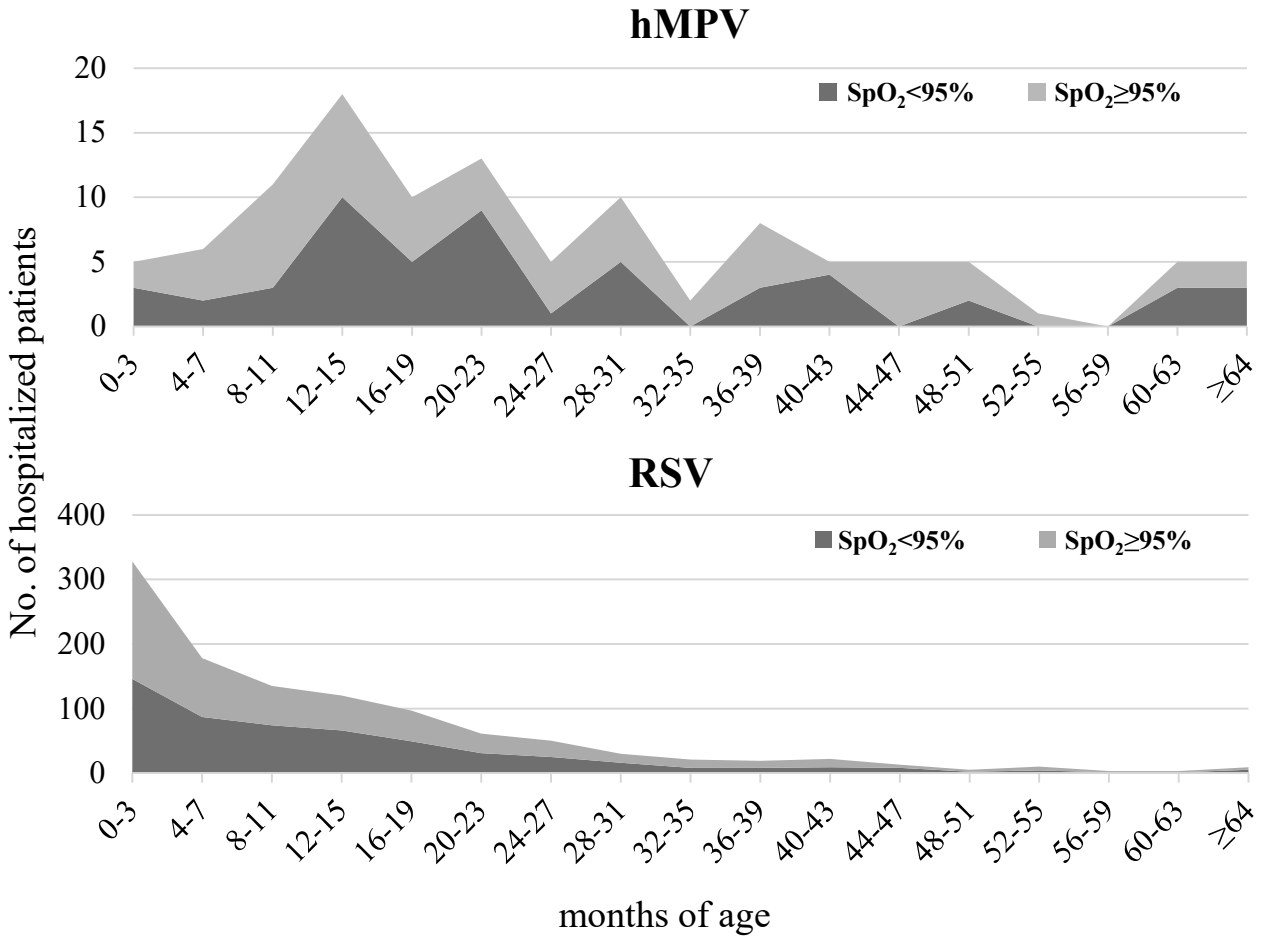
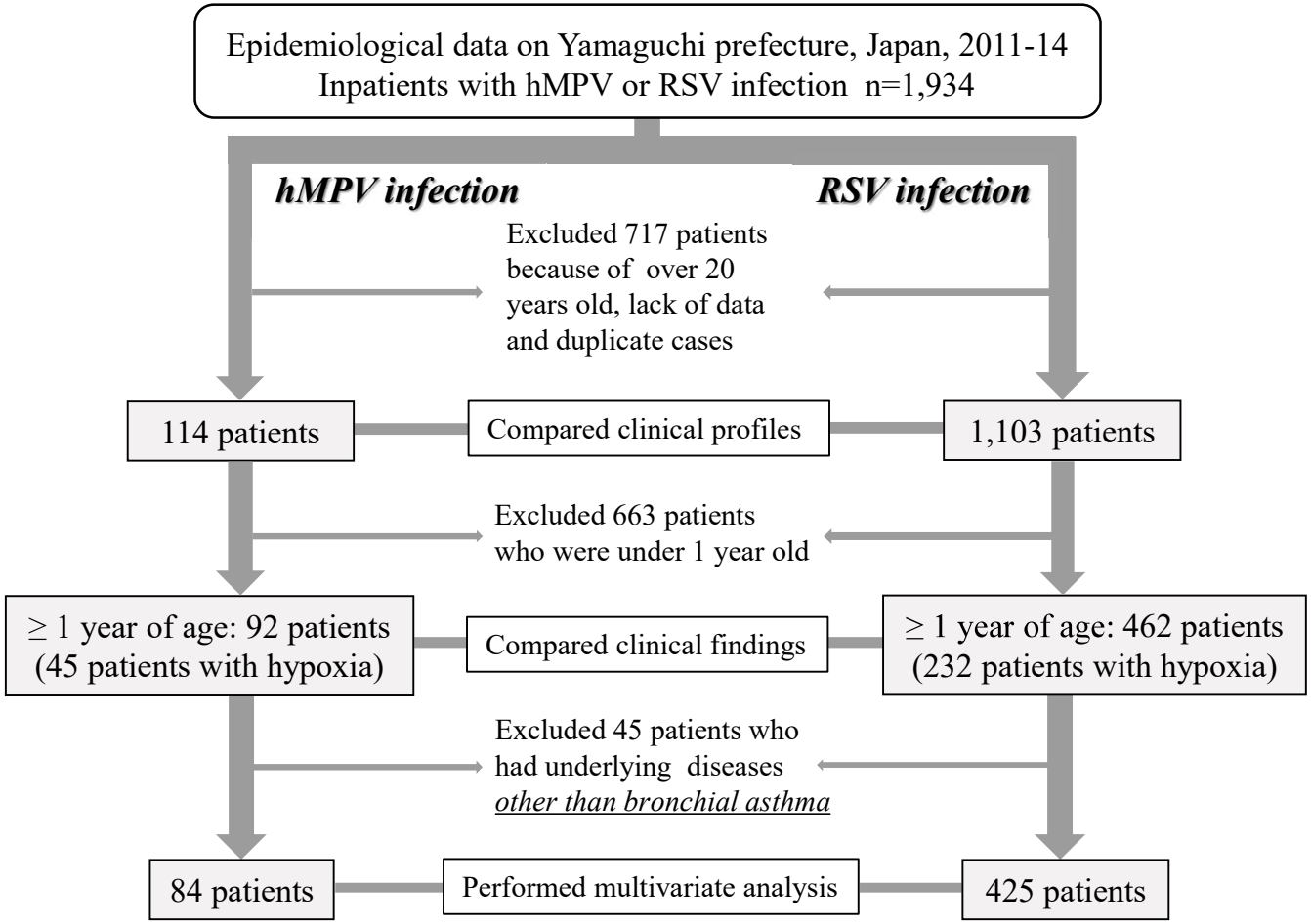
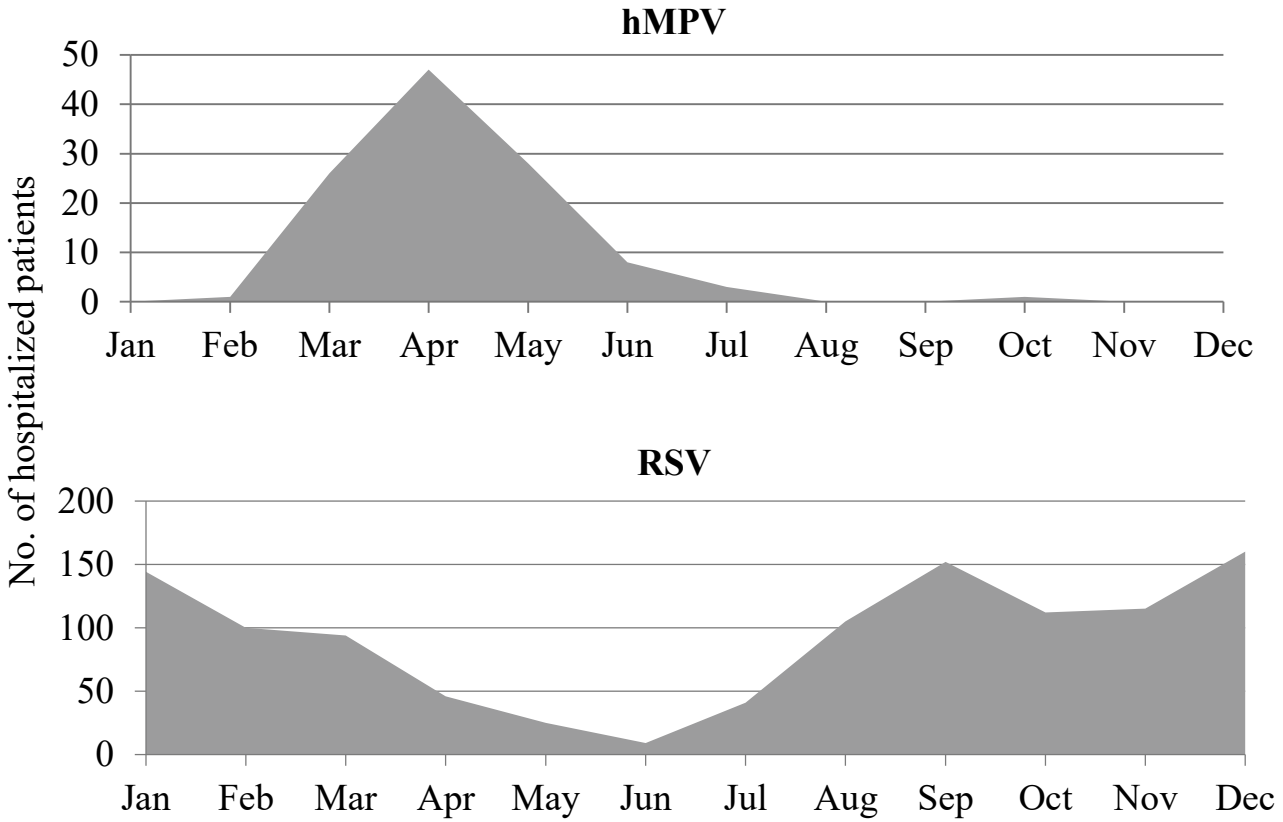

hMPV
SpO2<95%
SpO2≥95%
20
15
10
5
0
RSV
SpO2<95%
SpO2≥95%
400
300
200
100
0
No. of hospitalized patients
0-3
4-7
8-11
12-15
16-19
20-23
24-27
28-31
32-35
36-39
40-43
44-47
48-51
52-55
56-59
60-63
≥64
months of age

Figure 2

Supplemental Digital Content 1



Supplemental Digital Content 2



Supplemental Digital Content 3

Clinical findings of less than one-year-old infants with hypoxia† after hMPV or RSV infection

median (range)	hMPV (n=8)	RSV (n=307)	*p*-value
Age, months	6, (1-11)	4, (0-11)	0.219
Body temperature,°C	38.4, (36.6-40.0)	38.0, (34.6-40.3)	0.377
SpO_2, %	93, (70-94)	92, (30-94)	0.435
WBC, $\times 10^9$/L	10.9, (6.3-21.2)	9.80, (3.46-23.0)	0.344
CRP, mg/dL	0.56, (0.03-7.00)	0.51, (0-12.9)	0.575
Abnormal findings of chest x-ray	6, 75.0%	121, 39.4%	0.044
Duration of hospitalization, days	8, (3-20)	7, (1-36)	0.116
Underlying diseases			
Premature infants	0	12, 1.62%	0.611
Congenital heart diseases	0	9, 2.93%	0.493
Neurological disorders	0	1, 0.33%	0.820
Chromosomal abnormality	0	5, 1.62%	0.611
Others‡	0	2, 0.65%	-

† Hypoxia was defined as having less than 95% of SpO_2.

‡ Others included fetal pleural effusion and thoracic hypoplasia

Supplemental Digital Content 4

Multivariate analysis for the association variables affecting hypoxia† after hMPV or RSV infection in asthmatic children

Study population	Variables	Odds ratio	95% CI lower-upper limit	*p*-value
a) One year and over asthmatic patients with hMPV infection				
n=21	Age (1-year gain)	1.13	0.693-2.28	0.639
	Body temperature (1 °C elevate)	1.79	0.159-24.5	0.626
	Asthma controller therapy‡	0.937	0.046-13.6	0.962
	Abnormal findings of chest x-ray	0.520	0.008-15.3	0.716
b) One year and over asthmatic patients with RSV infection				
n=66	Age (1-year gain)	0.727	0.471-1.10	0.129
	Body temperature (1 °C elevate)	0.845	0.440-1.59	0.602
	Asthma controller therapy	1.44	0.460-4.53	0.531
	Abnormal findings of chest x-ray	1.33	0.435-4.09	0.615

† Hypoxia was defined as having less than 95% of SpO_2.

‡ Asthma controller therapy included leukotriene receptor antagonist and/or inhaled glucocorticoids.