Original Article

Pediatric intensive care unit admission due to respiratory syncytial virus: Retrospective multicenter study

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Abstract   **Background**: We investigated the characteristics and clinical outcomes of respiratory syncytial virus (RSV)-related pediatric intensive care unit (PICU) hospitalization and assessed the palivizumab (PZ) prophylaxis eligibility according to different guidelines from Korea, EU, and USA.

Methods: In this multicenter study, children <18 years of age hospitalized in six PICU from different hospitals due to severe RSV infection between September 2008 and March 2013 were included. A retrospective chart review was performed.

Results: A total of 92 patients were identified. The median length of PICU stay was 6 days (range, 1–154 days) and median PICU care cost was USD2,741 (range, USD556–98 243). Of 62 patients who were <2 years old at the beginning of the RSV season, 33 (53.2%) were high-risk patients for severe RSV infection. Hemodynamically significant congenital heart disease (22.6%) was the most common risk factor, followed by chronic lung disease (11.3%), neuromuscular disease or congenital abnormality of the airway (NMD/CAA) (11.3%), and prematurity (8.1%). The percentage of patients eligible for PZ prophylaxis ranged from 38.7% to 48.4% based on the guidelines, but only two (2.2%) received PZ ≤30 days prior to PICU admission. The median duration of mechanical ventilation was longer in children with NDM/CAA than in those without risk factors (26 days; range, 24–139 days vs 6 days, range, 2–68 days, P = 0.033). RSV-attributable mortality was 5.4%.

Conclusions: Children <2 years old with already well-known high risks represent a significant proportion of RSV-related PICU admissions. Increasing of the compliance for PZ prophylaxis practice among physicians is needed. Further studies are needed to investigate the burden of RSV infection in patients hospitalized in PICU, including children with NMD/CAA.

Key words   eligibility, guideline, neuromuscular disorder or congenital abnormality of the airway, pediatric intensive care unit, respiratory syncytial virus.

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in infants and young children and causes a significant socioeconomic burden.[1–4] Prematurity, chronic lung disease (CLD) or hemodynamically significant congenital heart disease (HS-CHD) are well-known high-risk factors for severe RSV infection, and these high-risk children comprise approximately 10% of RSV-related hospitalizations and 20–30% of pediatric intensive care unit (PICU)

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admissions.[5] Palivizumab (PZ), a humanized monoclonal antibody against the RSV F protein, was licensed for the prevention of RSV-related hospitalization and/or PICU admission in these high-risk children.[6,7]

Admission to a PICU is expensive in terms of medical resources, personnel, and treatment, yet there is a need for updated information on patient risk factors and PZ usage in PICU hospitalization. Despite the effectiveness of PZ prophylaxis, the eligibility for PZ varies widely between countries, with guidelines updated based on new evidence but also based on the changing health-care policies and economic status of each country.[6–8] In the American Academy of Pediatrics (AAP) guidelines, one new risk factor for PZ prophylaxis since 2009 is neuromuscular disorder and/or congenital

abnormality of the airway (NMD/CAA), which is not included in the South Korean or EU guidelines.[9–14] In addition, the eligibility for PZ prophylaxis in premature infants also differs in these countries, with different age restrictions used to define prematurity (gestational age at birth or chronological age at the beginning of RSV season).[11,13,15–17]

In this study, we investigated the characteristics of children admitted to PICU due to RSV infection. We analyzed clinical outcomes, medical costs for PICU care and the eligibility for PZ prophylaxis according to different guidelines.

Methods

Patient selection

Children aged <18 years who were hospitalized in six PICU with RSV infection between 1 September 2008 and 31 March 2013 were included. All of these PICU are in tertiary care hospitals in South Korea: Samsung Medical Center (SMC) in Seoul; Asan Medical Center in Seoul; Korea University Ansan Hospital in Ansan; Gachon University Gill Hospital in Incheon; Pusan National University Children's Hospital in Yangsan; and Ewha Woman's University in Seoul. Diagnosis of RSV infection was confined to RSV detection ≤48 h after PICU admission on rapid RSV antigen test, multiplex respiratory virus real-time polymerase chain reaction (PCR), and/or viral culture from a respiratory specimen such as a nasopharyngeal or endotracheal aspirate. Patients with underlying hematology–oncology disease and with RSV infection detected >48 h after PICU admission were excluded. The study was approved by the institutional review boards of Samsung Medical Center (IRB no. 2015-01-120) and all other participating hospitals. Requirement for informed consent and assent were waived. All patient-identifiable data were deleted or modified prior to analysis.

Data collection and analysis

We retrospectively reviewed medical records including age, gender, underlying disease, RSV subtype, method of RSV detection, presence of co-infection, and severity of RSV infection. LRTI was defined as clinical tachypnea with hypoxia ($SpO_2 < 93\%$) requiring oxygen supplementation and chest radiology confirmation of pneumonic infiltration or hyperinflation. Upper respiratory tract infection (URTI) was defined as respiratory symptoms without hypoxia and normal chest radiology. We analyzed the clinical outcomes of RSV-related PICU hospitalizations according to risk factors. Clinical outcome parameters were length of PICU stay, prevalence and duration of mechanical ventilator support, rate of tracheostomy, and 30 day mortality. In patients who received a tracheostomy, we assumed that the date of discontinuation of ventilator support was the date of transfer to a general ward. High risk for severe RSV infection was defined based on previous studies or guidelines as the presence of one of the following risk factors:[8,18] prematurity (gestational age <35 weeks), CLD, HS-CHD, CAA, NMD, Down syndrome,

or profound immunocompromision. We also analyzed the medical cost of PICU hospitalization at SMC.

RSV seasonality and introduction of PZ in South Korea

In South Korea, the RSV season spans autumn through early spring (XX–XX) and is monitored by Korea Influenza and Respiratory Surveillance System (KINRESS) at the Centers for Disease Control and Prevention of South Korea.[18] Typically, PZ prophylaxis could be initiated on 1 September and is given monthly until 31 March 2ith the limitation of a maximum number of five doses. PZ was introduced first in 2005 and has been covered by the National Healthcare Insurance Service in South Korea (K-NHIS) for infants and young children with CLD since January 2006, for infants with HS-CHD since 2009, and for infants born premature (gestational age <32 weeks) since 2012. Infants born at a gestational age 32–36 weeks with additional circumstances and children aged 12–24 months with HS-CHD have been covered since September 2016, but these indications are not included in this study.

Guideline eligibility for PZ prophylaxis

We compared eligibility for PZ prophylaxis for patients <2 years of age between the guidelines of three different countries/regions: South Korea's K-NHIS "Coverage Indications for Palivizumab" guidelines, updated 27 December 2012; the European Medicines Agency (EMA) guidelines, "Synagis: European Public Assessment Report–Product Information," updated 18 December 2013; and the US AAP guidelines, "Modified Recommendations for Use of Palivizumab for Prevention of RSV infection in 2014".[12,13] Detailed PZ prophylaxis eligibility criteria are listed in Table 1.

Statistical analysis

Depending on the purpose of the analysis, the patients were classified according to different age criteria. We used age at RSV infection for the analysis of clinical outcomes. In addition, age at the beginning of the RSV season (<2 years) was used for the analysis of PZ prophylaxis. Continuous variables and categorical variables are summarized as median (range) and frequency (percentage), respectively. Clinical outcomes according to risk factors were compared using Mann–Whitney test or Kruskal–Wallis test for continuous variables, and Fisher's exact test or chi-squared test for univariable analysis. Multiple linear regression analysis and multiple logistic regression analysis were performed to adjust for age at diagnosis, gender, and RSV infection clinical disease status for multivariable analysis. Non-normal continuous outcome was log-transformed and Dunnett's test was applied for multiple comparisons of each risk group with non-risk group in multiple linear regression. $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA) and GraphPad Prism version 6.04 (GraphPad Software, La Jolla, CA, USA).

Table 1 Indications for PZ prophylaxis according to guidelines

Risk factor as an indication for PZ prophylaxis	2012 K-NHIS (South Korea)	2013 EMA (EU)	2014 AAP (USA)
Premature			
<29 weeks' GA	6 months	6 months	12 months
29–31 weeks' GA	6 months	6 months	NI
32–35 weeks' GA	NI	6 months	NI
CLD	24 months	24 months	24 months
HS-CHD	12 months	24 months	12 months
NMD	NI	NI	12 months[†]
CAA	NI	NI	12 months[†]
Profoundly immunocompromised	NI	NI	24 months[†]
Other risk factors	NI	NI	NI

[†]Children with these risk factors may be considered for prophylaxis. AAP, American Academy of Pediatrics; CAA, congenital abnormality of airway; CLD, chronic lung disease; EMA, European Medicines Agency; GA, gestational age; HS-CHD, hemodynamically significant congenital heart disease; K-NHIS, National Healthcare Insurance Service in South Korea; NI, not indicated; NMD, neuromuscular disease; PZ, palivizumab.

Results

Patient characteristics

A total of 98 pediatric patients were admitted between September 2008 and March 2013 to the six PICU with RSV detection ≤48 h after admission. Of these admissions, 92 (93.8%) were identified as RSV-related PICU admissions. Six were excluded for other reasons (Fig. 1). These six PICU admissions were not due to RSV infection itself but were due to severe or progressing status of underlying disease. Two patients with encephalitis were admitted to PICU with decreased mental status, not for respiratory tract infection itself. Three patients with congenital heart disease were admitted to PICU for planned open heart surgery, and RSV infection was found on routine active surveillance or evaluation. Median age at PICU admission was 6.6 months (range, 0.5–210.4 months; IQR, 2.1–23.9 months; Table 2). Sixty-nine of 92 patients (75.0%) were <2 years of age at the time of RSV infection, and almost half (48.9%) were <6 months of age. Fifty-five of 92 patients (59.8%) were male, and 59 of 92 (64.1%) had underlying disease. Six of 92 patients (6.5%) had received PZ prior to RSV infection, and only two (2.2%) received PZ ≤30 days prior to PICU admission. Eighty-two patients (89.1%) presented with LRTI, and 10 (10.9%) presented with URTI. The median length of PICU stay was 6 days (range, 1–154 days; IQR, 4–12 days). Half of the patients required mechanical ventilation, with a median duration of mechanical ventilation of 7.5 days (range, 1–139 days; IQR, 5–19 days). Three patients (3.3%) required tracheostomy. The overall 30 day mortality was 7.6% (n= 7), and in five cases
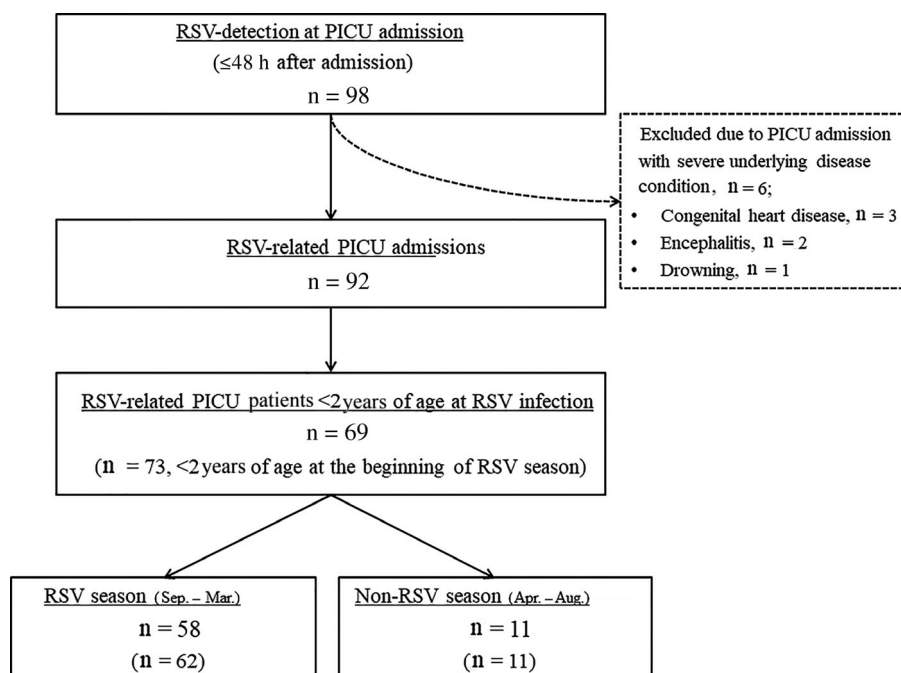

Fig. 1 Flow of case selection. Of the two excluded cases of encephalitis, one was *Listeria* meningoencephalitis, and the other was of unknown origin in a 40-month-old boy. In the latter case, the patient had no respiratory symptom except fever, and follow-up test was negative. PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

Table 2 Patient characteristics and demographics (n = 92)

Characteristics	n (%) or median (range)
Male	55 (59.8)
Age at diagnosis (months)	6.6 (0.5–210.4)
<6 months	45 (48.9)
6–11 months	14 (15.2)
12–23 months	10 (10.9)
24–59 months	12 (13.0)
≥60 months	11 (12.0)
Presence of underlying disease[†]	59 (64.1)
Diagnostic tool for RSV detection	
PCR	77 (83.7)
Culture	15 (16.3)
RSV subtype	
A	49 (53.3)
B	21 (22.8)
Unknown	22 (23.9)
Co-viral infection[‡]	16 (17.4)
PZ prophylaxis prior to RSV season (at least 1 dose)	6 (6.5)
Status of RSV infection	
LRTI	82 (89.1)
URTI	10 (10.9)
Length of PICU stay (days)	6 (1–154)
Ventilator support	
Requirement	46 (50)
Duration (days)	7.5 (1–139)
Tracheostomy	3 (3.3)
Overall 30 day mortality	7 (7.6)[§]
RSV-attributable 30 day mortality	5 (5.4)

[†]Prematurity, n = 7; chronic lung disease including bronchopulmonary dysplasia, interstitial lung disease and chronic aspiration, n = 11; congenital heart disease, n = 20; neuromuscular disorder due to mitochondrial disease and spinal muscular atrophy type 1, n = 2; airway malformation including tracheoesophageal fistula, lung sequestration, tracheomalacia and tracheal stenosis, n = 7; chromosomal anomaly including Down syndrome, n = 3; primary immunodeficiency, n = 1; acute kidney injury, n = 1; asthma, n = 1; arteriovenous malformation, n = 1; unknown severe developmental delay, n = 1; mediastinal lymphangiomatosis, n = 1; nephrotic syndrome, n = 1; renal tubular acidosis type 3, n = 1; and megacystic microcolon syndrome, n = 1. [‡]Influenza A, n = 5; rhinovirus infection, n = 4; adenovirus infection, n = 4; coronavirus infection, n = 1; both parainfluenza and rhinovirus infection, n = 1; both adenovirus and rhinovirus infection, n = 1. [§]Two died from bacterial sepsis. LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PZ, palivizumab; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.

(5.4%) death was related to severe RSV infection (Table 2). All five patients who died had a high risk of severe RSV infection. Two had HS-CHD, two had CLD, and one was a premature infant with a gestational age <29 weeks.

Seasonal distribution of RSV-related PICU hospitalization

Monthly distribution of RSV-related PICU admissions follows the seasonal pattern of RSV circulation in South Korea: increasing in September, peaking between October and December, and ending in April (Fig. 2a). During the RSV
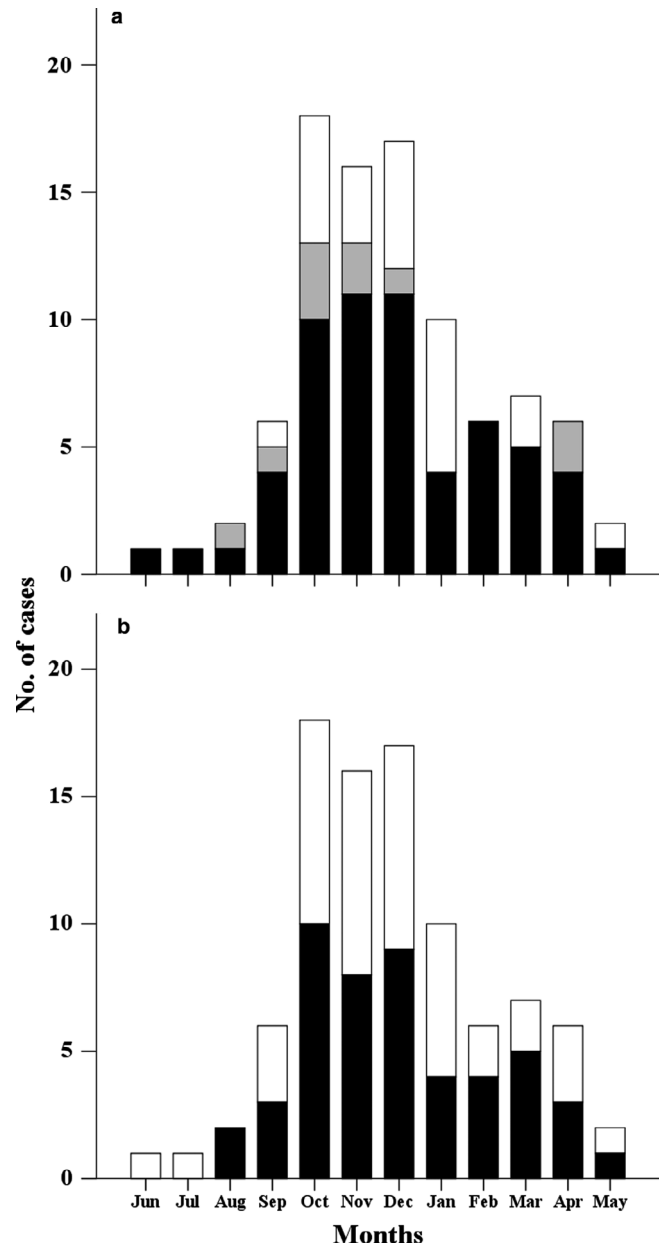

Fig. 2 Seasonal distribution of respiratory syncytial virus (RSV)-related pediatric intensive care unit (PICU) admissions according to (a) age at the time of RSV detection (■, <12 months; ▨, 12–24 months; □, >24 months); and (b) presence of risk factors (■, risk; □, no risk). (a) Sixty-nine of 92 cases (75.0%) occurred in children <2 years of age at the time of RSV detection; 59 of 92 (64.1%) occurred in children <1 year of age. (b) Forty-nine of 92 patients (53.3%) had at least one of risk factor for severe RSV infection. Risk factors for severe RSV infection include prematurity (gestational age <35 weeks), chronic lung disease, hemodynamically significant congenital heart disease, congenital abnormality of the airway or neuromuscular disorder, Down syndrome or profound immunocompromisation.

season from September to March, 80 of 92 RSV-related PICU hospitalizations (87.0%) occurred. Of these 80 patients, 58 (72.5%) were <2 years of age at the time of RSV infection, and 62 (77.5%) were <2 years of age at the beginning of the

RSV season (Fig. 1). Forty-nine of 92 patients (53.3%) had at least one risk factor for severe RSV infection regardless of age (Fig. 2b).

High-risk children in the PICU and clinical outcomes according to risk factor

There were 62 RSV-related PICU admissions in children <2 years of age at the beginning of the RSV season. HS-CHD (22.6%) was the most common risk factor, followed by CLD (11.3%), CAA (9.7%), prematurity (8.1%), and NMD (1.6%). Six patients (9.7%) had an underlying disease that did not increase the risk of severe RSV infection; 23 patients (37.1%) had no underlying disease.

There were 69 RSV-related PICU admissions in children <2 years of age at the time of RSV infection. Of these, the prevalence of mechanical ventilation was significantly higher in the high-risk group than in the no-risk group on multivariable analysis (64.9% vs 31.3%, $P = 0.006$). There was no significant difference, however, in other outcome parameters, such as length of PICU stay, duration of mechanical ventilation, requirement for tracheostomy, and RSV-related 30 day mortality. The NMD/CAA group had a longer median duration of mechanical ventilation compared with the no-risk group (26 days; range, 24–139 days vs 6 days, range, 2–68 days, $P = 0.033$; Fig. S1; Table 3).

Eligibility for PZ prophylaxis

We estimated eligibility for PZ prophylaxis according to the three different guidelines. Twenty-four of the 62 high-risk children (38.7%) were eligible for PZ prophylaxis based on the 2013 K-NHIS guidelines, 26 (41.9%) based on the 2015 EMA guidelines, and 30 (48.4%) based on the 2014 AAP guidelines (Table 4). The 2013 K-NHIS guidelines appeared more restrictive than the 2014 AAP guidelines with regard to PZ eligibility, but the difference was not significant (38.7% vs 48.4%, $P = 0.07$; Fig. 3).

Economic burden according to risk factor

Medical cost was analyzed in 37 patients who were hospitalized at SMC. For the 28 children <2 years old at the time of RSV infection, the median cost of health care in the high-risk group appeared to be higher than that of the no-risk group, although the difference was not significant ($2,284; range, $705–$98 243 vs $1,899, range, $556–$30 449; $P = 0.38$). With regard to patients who received ventilator support, although patients with risk appeared to have higher median medical costs than patients with no risk, this was not statistically significant ($15 346; range, $2,575–$91 546 vs $4,634, range, $2,312–$30 449; $P = 0.47$; Table 5).

Discussion

This study shows that high-risk children account for a high proportion of RSV-related PICU admissions. In clinical

Table 3 Clinical outcome vs presence of risk (n = 69)

Clinical outcome	No risk (n = 32) Median (range) or n (%)	All risk[†] (n = 37) Median (range) or n (%)	Risk subgroup				P-value	
			Prematurity (n = 6) Median (range) or n (%)	CLD (n = 7) Median (range) or n (%)	HS-CHD (n = 16) Median (range) or n (%)	NMD/CAA (n = 7) Median (range) or n (%)	All risk vs non-risk	Risk subgroup vs non-risk
PICU length of stay (days)	6 (1–68)	7 (1–154)	6 (4–12)	5 (1–53)	10.5 (1–37)	7 (3–154)	0.07	0.053
Mechanical ventilation								
Requirement	10 (31.3)	24 (64.9)	5 (83.3)	4 (57.1)	11 (68.8)	3 (42.9)	0.006	0.087
Duration (days)	6 (2–68)	11.5 (1–139)	5 (3–11)	27 (1–53)	12 (1–24)	26 (24–139)	0.16	0.031[‡]
Tracheostomy	0 (0)	2 (8.3)	0 (0)	1 (25.0)	0 (0)	1 (33.3)	NA	NA
RSV-related 30 day mortality	0 (0)	4 (10.8)	1 (16.7)	1 (14.3)	2 (12.5)	0 (0)	NA	NA

[†]All risk groups includes prematurity, CLD, HS-CHD, and NMD/CAA. Two cases of Down syndrome and one case of profoundly immunocompromised condition and were excluded in the analysis. [‡]Significant difference in clinical outcome of ventilation duration ($P = 0.031$). In the subsequent subgroup analysis, the NMD/CAA group had a significantly prolonged duration of mechanical ventilation compared with the no-risk group (NMD/CAA vs non-risk, $P = 0.033$; Fig. S1). Multiple linear regression and multiple logistic regression analyses were performed to adjust for age at diagnosis, gender, and clinical disease status of RSV infection. Non-normal continuous outcome was log-transformed and Dunnett's test was applied for multiple comparisons of each risk group with non-risk group in multiple linear regression. CAA, congenital abnormality of the airway; CLD, chronic lung disease; HS-CHD, hemodynamically significant congenital heart disease; NA, not applicable; NMD, neuromuscular disorder; PICU, pediatric intensive care unit.

Table 4   Risk factors for severe RSV infection and eligibility for PZ prophylaxis (*n* = 62)

Risk factor	<2 years of age at the beginning of RSV season *n* (%)	2013 K-NHIS (South Korea) *n* (%)	2015 EMA (EU) *n* (%)	2014 AAP (USA) *n* (%)
PM (weeks' GA)	5 (8.1)	3 (12.5)	5 (19.2)	2 (6.7)
<29	2 (3.2)	2 (8.3)	2 (7.7)	2 (6.7)
29–31	1 (1.6)	1 (4.2)	1 (3.8)	0 (0.0)
32–35	2 (3.2)	0 (0.0)	2 (7.7)	0 (0.0)
CLD	7 (11.3)	7 (29.2)	7 (26.9)	7 (23.3)
PM related	6 (9.7)	6 (25.0)	6 (23.1)	6 (20.0)
Non-PM related	1 (1.6)	1 (4.2)	1 (3.8)	1 (3.3)
HS-CHD[†]	14 (22.6)	14 (58.3)	14 (53.8)	14 (46.7)
Other	9 (14.5)	0 (0.0)	0 (0.0)	7 (23.3)
NMD[‡]	1 (1.6)	0 (0.0)	0 (0.0)	1 (3.2)
CAA	6 (9.7)	0 (0.0)	0 (0.0)	6 (20.0)
Profoundly immunocompromised	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Down syndrome[§]	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Underlying disease without risk factor[¶]	4 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
No underlying disease (no risk factor)	23 (37.1)	0 (0.0)	0 (0.0)	0 (0.0)
Total	62 (100.0)	24 (38.7)	26 (41.9)	30 (48.4)

[†]One patient had two risk factors: pulmonary hypertension and congenital mitral regurgitation with laryngomalacia. [‡]One patient had two risk factors: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) with hypertrophic cardiomyopathy. [§]Without congenital heart disease. [¶]Prematurity at 36 weeks and 0 days of gestation, *n* = 1; simple ventricular septal defect, *n* = 1; nephrotic syndrome, *n* = 1; and renal tubular acidosis type 3, *n* = 1. AAP, American Academy of Pediatrics; CAA, congenital abnormalities of the airway; CLD, chronic lung disease; EMA, European Medicines Agency; GA, gestational age; HS-CHD, hemodynamically significant congenital heart disease; K-NHIS, National Healthcare Insurance Service in South Korea; NMD, neuromuscular disorders; PM, prematurity; PZ, palivizumab; RSV, respiratory syncytial virus.
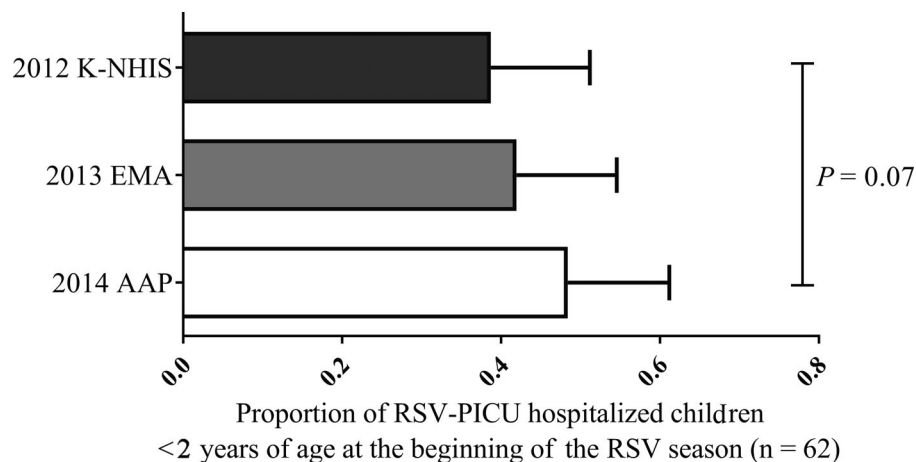

Fig. 3   Palivizumab prophylaxis eligibility. 2013 K-NHIS guidelines vs 2014 AAP guidelines, 38.7% vs 48.4% (*P* = 0.07, Mann–Whitney test). AAP, American Academy of Pediatrics; EMA, European Medicines Agency; K-NHIS, National Healthcare Insurance Service in South Korea.

outcome analysis, NMD/CAA was associated with a prolonged duration of mechanical ventilation. Eligibility for PZ prophylaxis varied according to the guidelines of different countries.

The proportion of high-risk patients in PICU was 53.3%, which was higher than that in other studies, at 20–30%.[5,19] Berger *et al.* reported that 23% of RSV-related intermediate care unit (IMU) or ICU admissions for children <3 years of age in Switzerland were high risk, with at least one risk factor such as prematurity (gestational age <32 weeks), CLD, or HS-CHD.[19] In a retrospective study of 181 children admitted to

the PICU with RSV infection in Canada from 2003 to 2009, Butt *et al.* found that 29.8% had an underlying disease.[5] These studies, however, did not include NMD/CAA as an underlying disease; and NMD/CAA was present in 11.3% of the present RSV PICU cases.

The prevalence of HS-CHD (22.6%) and of NMA/CAA (11.3%) were high in the present study compared with previous studies, while that of prematurity (gestational age <35 weeks, 8.1%) and of CLD (11.3%) were relatively low.[5,6,19–22] These observations might be due to differences in

Table 5 Economic cost according to risk factor (*n* = 28)

| Characteristics | Cost (USD)‡ | | | | | |
| | All (*n* = 28) | | | Mechanical ventilation (*n* = 13) | | |
	Median	Range	*P*-value†	Median	Range	*P*-value†
No risk	1,898.8	556.1–30 448.9		4,634.3	2,311.9–30 448.9	
Risk	2,284.0	705.4–98 243.1	0.38	15 346.3	2,575.5–91 545.9	0.47
Subgroup analysis			0.74			0.65
CLD	1,865.9	824.6–38 340.4		20 457.9	2,575.5–38 340.4	
HS-CHD	3,729.9	705.4–35 040.7		9,836.1	4,071.0–32 198.8	
NMD/CAA	9,928.8	1,125.1–98 243.1		20 226.3	10 466.2–91 545.9	

†Mann–Whitney test using exact method. ‡Exchange rate on 15 March 2016: 1 USD = 1212.5 KRW. CAA, congenital abnormality of the airway; CLD, chronic lung disease; HS-CHD, hemodynamically significant congenital heart disease; NMD, neuromuscular disorder.

PZ prophylaxis according to risk factors in different countries.[23–25] In a retrospective study of RSV-related re-admissions of preterm infants (gestational age <34 weeks) in South Korea, Lee *et al.* reported that 47.5% of 1,140 preterm infants received PZ prophylaxis, including 89.3% of those with CLD.[24] The high PZ prophylaxis rates for CLD and premature infants might have reduced the RSV-related PICU admissions for these groups in the present study. Infants with NMD/CAA are not eligible for PZ prophylaxis in South Korea, and no studies have reported PZ prophylaxis rates for children with HS-CHD. A recent study of 466 infants with HS-CHD in South Korea reported that 39% did not receive PZ prophylaxis on time.[25] In addition, the present study period includes the 2008–2009 RSV season, during which HS-CHD patients were not eligible for PZ prophylaxis. As a result, PZ prophylaxis for many children with HS-CHD might have been delayed. Furthermore, as shown in the present study, even according to restrictive 2013 K-NHIS guidelines, 24 patients (38.7%) were already eligible for PZ prophylaxis and should have received it. Only six patients (6.5%), however, had received PZ at least once before PICU admission due to RSV infection. Therefore, it is also important to promote adherence to PZ prophylaxis for high-risk children among physicians in daily clinical practice.

Currently, PZ prophylaxis guidelines vary greatly between countries. The eligibility for PZ prophylaxis for the present patients ranged from 39% to 48% based on guidelines from South Korea, EU, and the USA. The main differences were inclusion or exclusion of children with NMD/CAA and differences in the age restrictions used to define prematurity and HS-CHD.[12,13] The age restrictions used to identify high-risk children are based on many studies on prophylactic effects and cost–benefit analyses.[11,13,14] In contrast, children with NMD/CAA or profound immunocompromisation might not be included in the current guidelines due to insufficient data on the effectiveness of PZ prophylaxis. Therefore, large-scale investigations to prove the effectiveness of PZ prophylaxis for these high-risk groups are needed. In addition, although there is no doubt that Down syndrome is a risk factor for severe RSV infection, it remains controversial as to whether PZ prophylaxis is efficacious, including the cost–benefit aspects.[26–28] Therefore, further studies are needed.

Notably, although the number of patients was small (*n* = 3), the median duration of mechanical ventilation was significantly longer in children with NMD/CAA (*n* = 3) than in those with no risk (26 days; range, 24–139 days vs 6 days, range, 2–68 days; *P* = 0.033; Table 4). Children with NMD/CAA were also more likely to receive tracheostomy than children in the no-risk group, with borderline significance (40%, 2/5 vs 0%, 0/45; *P* = 0.053). Defects in respiratory defense mechanisms such as impaired ability to clear secretions and/or insufficient coughing due to weakness of the respiratory muscles are barriers to weaning children off mechanical ventilation. Although there were insufficient patients with NMD/CAA to show a cost difference, prolonged ventilator support means longer PICU care, which requires additional medical resources, thereby generating a larger socioeconomic burden (Table 5).

Given that this retrospective study was focused on tertiary-care hospitals, it is likely that more children with severe RSV infection or other severe underlying disease were included than in studies that include intermediate-care hospitals. In addition, despite the multicenter study design, the number of cases was insufficient for subgroup analysis due to the rarity of some diseases.

Nevertheless, this study provides needed data on the proportion of high-risk children with severe RSV infection in PICU in the PZ era. We wanted to express the clinical outcomes of PICU admissions due to severe RSV infection including high mortality rate of 5%, as well as the economic burden of PICU admission due to RSV. We also assessed the eligibility for PZ prophylaxis based on different guidelines. Finally, we observed that children with NMD/CAA represent a significant portion of PICU admissions in South Korea, where these children are not eligible for PZ prophylaxis. Moreover, children with NMD/CAA appear to require a prolonged duration of mechanical ventilation than those with no risk. Therefore, it is worth noting that the children with NMD/CAA might have comprised a larger portion of the RSV-related PICU admissions, if the PZ prophylaxis had been appropriately given to children with already well-known high risks according to the K-NHIS guidelines.

In conclusion, in South Korea, high-risk children represented a higher proportion of RSV-related PICU admissions

than previously reported. Further studies are needed to investigate the burden of RSV infection in PICU hospitalizations, including that associated with children with NMD/CAA.

Disclosure

Author contributions

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Duration of mechanical ventilation according to risk factor. In subgroup analysis, children with NMD/CAA had a longer duration of mechanical ventilation than children with no risk factor (median, 26 days [range, 24-139] vs. 6 days [range, 2-68], P = .033).