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Clinical Burden of Respiratory Syncytial Virus in Hospitalized Children Aged ≤5 Years (INSPIRE Study)

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Background. Respiratory syncytial virus (RSV) is a leading cause of hospitalizations in children (≤5 years of age); limited data compare burden by age.

Methods. This single-center retrospective study included children (≤5 years of age) hospitalized for >24 hours with reverse-transcription polymerase chain reaction (RT-PCR)–confirmed RSV infection (2015–2018). Hospital length of stay (LOS), intensive care unit (ICU) admissions, ICU LOS, supplemental oxygen, and medication use were assessed. Multivariate logistic regression analyses identified predictors of hospital LOS >5 days.

Results. Three hundred twelve patients had RSV infection (ages 0 to <6 months [35%], 6 to <12 months [15%], 1 to <2 years [25%], and 2–5 years [25%]); 16.3% had predefined comorbidities (excludes preterm infants). Median hospital LOS was 5.0 days and similar across age; 5.1% (16/312) were admitted to ICU (ICU LOS, 5.0 days), with those aged 0 to <6 months admitted most frequently (10/108 [9.3%]). Supplemental oxygen was administered in 57.7% of patients, with similar need across ages. Antibiotics were administered frequently during hospitalization (43.6%). Predictors of prolonged LOS included pneumonia (odds ratio [OR], 2.33), supplemental oxygen need (OR, 5.09), and preterm births (OR, 3.37). High viral load (RT-PCR RSV cycle threshold value <25) was associated with greater need for supplemental oxygen.

Conclusions. RSV causes substantial burden in hospitalized children (≤5 years), particularly preterm infants and those aged <6 months.

Keywords. infant; children; hospitalization; burden of disease; predictors.

By the age of 2 years, nearly all children have been infected with the common respiratory tract infection respiratory syncytial virus (RSV). RSV infection is typically mild and self-limiting [1]. However, in certain populations, such as children aged <5 years, older adults (aged ≥60 years), immunocompromised patients, and patients with chronic cardiac or pulmonary disease, infections can be more severe [1, 2].

RSV is the most common cause of respiratory-related hospitalizations in children aged <5 years worldwide. A recently published modeling study estimated that 575 000 medically attended acute respiratory infections were attributable to RSV in Germany in 2017–2018 [3]. In 2015 and 2016, an estimated 33.1–68.0 million episodes of RSV-associated lower respiratory tract infections resulted in approximately 3.2–5.1 million hospital admissions and 59 600 in-hospital deaths [4, 5]. The morbidity and mortality associated with RSV infection in infants places a substantial burden on healthcare systems [6, 7]. Compared with influenza, retrospective analysis has shown that RSV causes up to 16 times more hospitalizations and emergency department (ED) admissions in children aged <5 years [6, 8–10]. Hospitalizations can be lengthy and, in severe cases, result in intensive care unit (ICU) admissions, which contribute to significant medical resource utilization (MRU) [5, 11]. Aerosolized ribavirin is the only drug approved for RSV treatment in pediatric patients in selected countries; however, its recommended use is limited to severe RSV infections in immunocompromised infants [12, 13], due largely to its high cost, inconclusive efficacy overall, potential toxicity issues, and inconvenient route of administration [14–16]. Palivizumab, which specifically targets RSV infection, is available in certain countries for prophylactic use in restricted high-risk pediatric populations, such as preterm infants and children aged <2 years with hemodynamically significant congenital heart defects [17].

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Although the primary role of RSV in bronchiolitis-associated hospitalization of infants is well established [18–21], the details of symptoms and diagnosis in children by different age subgroups is yet to be defined. The aim of this retrospective study was to describe the MRU, patient pathway, symptoms, and rehospitalizations in children aged ≤5 years hospitalized with RSV infection at a tertiary care university children's hospital in Germany over the period of 3 consecutive RSV seasons, exploring possible differences by age.

METHODS

Study Design and Patient Population

This retrospective medical record review study described the clinical burden of RSV infection for 3 consecutive seasons (2015–2016, 2016–2017, and 2017–2018) in University Hospital Würzburg, Germany. For study center details, see Supplementary Methods. Infants and children aged ≤5 years who had a reverse-transcription polymerase chain reaction (RT-PCR)–confirmed RSV infection that required hospitalization or were infected by RSV while in hospital during the prespecified seasons were included. The first PCR-confirmed RSV hospitalization in the season was considered the patient's index hospitalization. Nosocomial infections were defined as detection of a viral infection ≥72 hours after hospitalization, or based on the investigator's discretion. For details on data collection, see Supplementary Methods.

The study was conducted in accordance with applicable regional and local regulations and the study protocol was approved by the Independent Ethics Committee/Institutional Review Board, University Hospital of Würzburg.

Assessments

A PCR-based assay (Fast Track Diagnostics™ Respiratory Pathogens 21) was used to confirm a diagnosis of RSV infection from respiratory samples and to determine high, moderate, and low viral load (cycle threshold [Ct] values <25, 25–35, and >35, respectively); for details, see Supplementary Methods. MRU prior to hospitalization, during hospitalization, and at discharge from the hospital were retrieved from the respective patient's medical records. See Supplementary Methods for details of specified predefined comorbidities.

Endpoints

The prespecified primary endpoint was to describe MRU in infants and children aged ≤5 years with confirmed RSV infection, based on the following parameters: overall hospital length of stay (LOS), proportion of patients admitted to the ICU, LOS at ICU, proportion of patients receiving oxygen supplementation and the method of administration used (invasive/noninvasive), and use of antibiotic and antiviral therapy and other acute respiratory tract infection–related medications. Secondary endpoints are described in the Supplementary Methods.

Statistical Analysis

Statistical analysis was conducted on the data of patients with RSV infection as well as age subgroup populations. Patients were stratified based on the following age groups: 0 to <6 months, 6 to <12 months, 1 to <2 years, and 2–5 years. Multivariate logistic regression analysis was used to identify predictors for hospital LOS >5 days and for ICU admissions (for details, see Supplementary Methods).

RESULTS

Study Population

In the 3 consecutive RSV seasons, a total of 312 patients with PCR-confirmed RSV infection were identified. A similar number of RSV infections were reported in each season, with 85 occurring in 2015–2016, 118 in 2016–2017, and 109 in 2017–2018. The median age of patients in the total study group was 11.5 (interquartile range [IQR], 3.0–23.5) months; 108 (35%) patients were aged 0 to <6 months, 48 (15%) were aged 6 to <12 months, 78 (25%) were aged 1 to <2 years, and 78 (25%) were aged 2–5 years. Overall, 178 (57.1%) were male and 26 of 156 infants aged <1 year were born preterm (Table 1). More than 1 type of virus was detected in 29.8% of patients with confirmed RSV infection (Supplementary Results and Supplementary Table 1). The origin of RSV infections was identified as nosocomial in 5 (1.6%) patients. Overall, 51 patients (16.3%) had predefined comorbidities (risk factors). Of these, patients aged 2–5 years had significantly more predefined comorbidities (risk factors; 29.5% [23/78]) than patients aged 0 to <6 months (6.5% [7/108]) ($P < .0001$), particularly congenital heart disease (11.5% [9/78] vs 3.7% [4/108]) and other congenital disease (9.0% [7/78] vs 0.9% [1/108]). Other comorbidities (not predefined) were reported in 112 (35.9%) patients, of which the most commonly reported were chronic lung disease (n = 41), hematologic diseases (n = 13), and cardiovascular diseases (n = 12). Most baseline household characteristics were similar between age groups (Supplementary Results and Supplementary Table 2).

The patient pathway was similar across all age groups, with the exception of those aged 0 to <6 months (Supplementary Figure 1). The majority of patients had been seen by a general practitioner (GP) prior to hospitalization (63%). However, a higher proportion of patients aged 0 to <6 months (44% [48/108]) presented directly to the ED without any previous GP visit compared with those aged 6 to <12 months (26% [13/48]), 1 to <2 years (29% [23/78]), and 2–5 years (32% [25/78]). Furthermore, of the 10 patients aged 0 to <6 months who were admitted to the ICU, 7 (70%) presented at the ED without previously seeing a GP.

Table 1. Baseline Demographics and Disease Characteristics (Selected) in Hospitalized Pediatric Patients With Respiratory Syncytial Virus Infection (N = 312), Germany, 2015–2018

Characteristic	Overall Population (N = 312)	Age 0 to <6 Months (n = 108)	Age 6 to <12 Months (n = 48)	Age 1 to <2 Years (n = 78)	Age 2–5 Years (n = 78)
Age at diagnosis, mo, median (IQR)	11.5 (3.0–23.5)	2.0 (1.0–3.0)	8.0 (7.0–9.0)	18.0 (14.0–20.0)	34.5 (28.0–47.0)
Preterm children, No. (%) [95% CI]	NA	17 (15.7) [9.4–24.0]	9 (18.8) [8.9–32.6]	NA	NA
Preterms stratified by age[a], No. (%) [95% CI]					
<32 weeks' gestation	NA	7 (6.5) [2.6–12.9]	2 (4.2) [.5–14.3]	NA	NA
≥32 to ≤35 weeks' gestation	NA	5 (4.6) [1.5–10.5]	5 (10.4) [3.5–22.7]	NA	NA
>35 to <37 weeks' gestation	NA	5 (4.6) [1.5–10.5]	2 (4.2) [.5–14.3]	NA	NA
Predefined comorbidities (risk factors), No. (%) [95% CI]					
Predefined comorbidities (all)	51 (16.3) [12.4–20.9]	7 (6.5) [2.6–12.9]	8 (16.7) [7.5–30.2]	13 (16.7) [9.2–26.8]	23 (29.5) [19.7–40.9]
Bronchopulmonary dysplasia	8 (2.6) [1.1–5.0]	1 (0.9) [.0–5.1]	1 (2.1) [.1–11.1]	4 (5.1) [1.4–12.6]	2 (2.6) [.3–9.0]
Cystic fibrosis	1 (0.3) [.0–1.8]	0 (0)	0 (0)	0 (0)	1 (1.3) [.0–6.9]
Congenital heart disease	25 (8.0) [5.3–11.6]	4 (3.7) [1.0–9.2]	6 (12.5) [4.7–25.2]	6 (7.7) [2.9–16.0]	9 (11.5) [5.4–20.8]
Other congenital disease	16 (5.1) [3.0–8.2]	1 (0.9) [.0–5.1]	3 (6.3) [1.3–17.2]	5 (6.4) [2.1–14.3]	7 (9.0) [3.7–17.6]
Neuromuscular disease	7 (2.2) [.9–4.6]	1 (0.9) [.0–5.1]	1 (2.1) [.1–11.1]	1 (1.3) [.0–6.9]	4 (5.1) [1.4–12.6]
Immunodeficiency	5 (1.6) [.5–3.7]	0 (0)	0 (0)	2 (2.6) [.3–9.0]	3 (3.8) [.8–10.8]
Down syndrome	2 (0.6) [.1–2.3]	0 (0)	0 (0)	0 (0)	2 (2.6) [.3–9.0]
Other comorbidities[b], not predefined, No. (%) [95% CI]	112 (35.9) [30.6–41.5]	18 (16.7) [12.1–26.5]	15 (31.3) [18.7–46.3]	35 (44.9) [33.6–56.6]	44 (56.4) [44.7–67.6]
All comorbidities, No. (%) [95% CI]	132 (42.3) [36.8–48.0]	24 (22.2) [14.8–31.2]	20 (41.7) [27.6–56.8]	38 (48.7) [37.2–60.3]	50 (64.1) [52.4–74.7]

Sections with NA considered not applicable for older children due to a lack of recorded data.

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable.

[a]Out of the total number of preterm children (n = 26), 34.6% were born at <32 weeks, 38.5% were born between ≥32 weeks and ≤35 weeks, and 26.9% were born between >35 and <37 weeks.

[b]Other comorbidities were not further specified in the database.

Medical Resource Utilization

Overall, the median hospital LOS for patients with RSV infection was 5.0 (IQR, 4.0–7.0) days and was similar across all of the age groups (Figure 1). Sixteen (5.1%) patients were admitted to the ICU; the median age of these patients was 10.5 (IQR, 0.2–69.0) months. Across all age groups, the highest proportion of ICU admissions were observed in those aged 0 to <6 months (10/108 [9.3%]) (Supplementary Figure 2*A*). Overall, 2.2% (7/312) of RSV-infected patients were transferred to the ICU during their hospital stay and 2.9% (9/312) were admitted directly (Supplementary Figure 2*B*). No patients aged 6 to <12 months were admitted to the ICU. Younger patients were admitted directly to the ICU more frequently than older patients (0 to <6 months, 6.5% [7/108]; 1 to <2 years, 1.3% [1/78]; 2–5 years, 1.3% [1/78]) and a similar proportion of patients transferred to the ICU during their hospital stay in each age group (0 to <6 months, 2.8% [3/108]; 1 to <2 years, 2.6% [2/78]; 2–5 years, 2.6% [2/78]). In the overall study population, the median LOS in the ICU was 5.0 (IQR, 2.0–8.0) days. Median LOS in the ICU was highest for those aged 0 to <6 months (5.5 days) compared with those aged 1 to <2 years and ≥2 years (both 2.0 days).

Overall, 57.7% of patients with RSV required supplemental oxygen during hospitalization (median age, 10.5 [IQR, 0.2–69.0] months). Supplemental oxygen was required for 62.0% of patients aged 0 to <6 months (67/108), 56.3% aged 6 to <12 months (27/48), 51.3% aged 1 to <2 years (40/78), and 59.0% aged 2–5 years (46/78). Nasal cannula was the most common method of oxygen supplementation overall (56.4%) and in all age groups (0 to <6 months, 60.2% [65/108]; 6 to <12 months, 56.3% [39/78]; 1 to <2 years, 50.0% [39/78]; 2–5 years, 57.7% [45/78]) (Supplementary Table 3). Median duration of oxygen supplementation via nasal canula in RSV patients (N = 312) was 2.0 (IQR, 1.0–4.0) days. Invasive mechanical ventilation was rare (1.9% [6/312]) across all age groups (0 to <6 months, 2.8% [3/108]; 6 to <12 months, 0% [0/78]; 1 to <2 years, 2.6% [2/78]; 2–5 years, 1.3% [1/78]).

In preterm infants aged <1 year (n = 26), median hospital LOS was 7.5 (IQR, 5.0–11.0) days, 19.2% were admitted to the ICU with a median LOS in the ICU of 7.0 (IQR, 6.0–9.0) days, and 88.5% required supplemental oxygen.

Short-acting β-agonists were the most commonly recorded concomitant medications prior to hospitalization (29.8%) and prior to discharge (65.7%) (Supplementary Results and Supplementary Table 4; for data stratified by patient diagnosis of bronchiolitis/pneumonia: Supplementary Results and Supplementary Table 5). Ribavirin and palivizumab were not provided to any patients before, during, or prior to discharge from hospital.

Symptoms, Clinical Manifestations, and Diagnoses

The median duration of symptoms prior to hospitalization was 3.0 days across ages, except those aged 6–12 months, whereby it was 4.0 days. While symptoms were generally similar across the

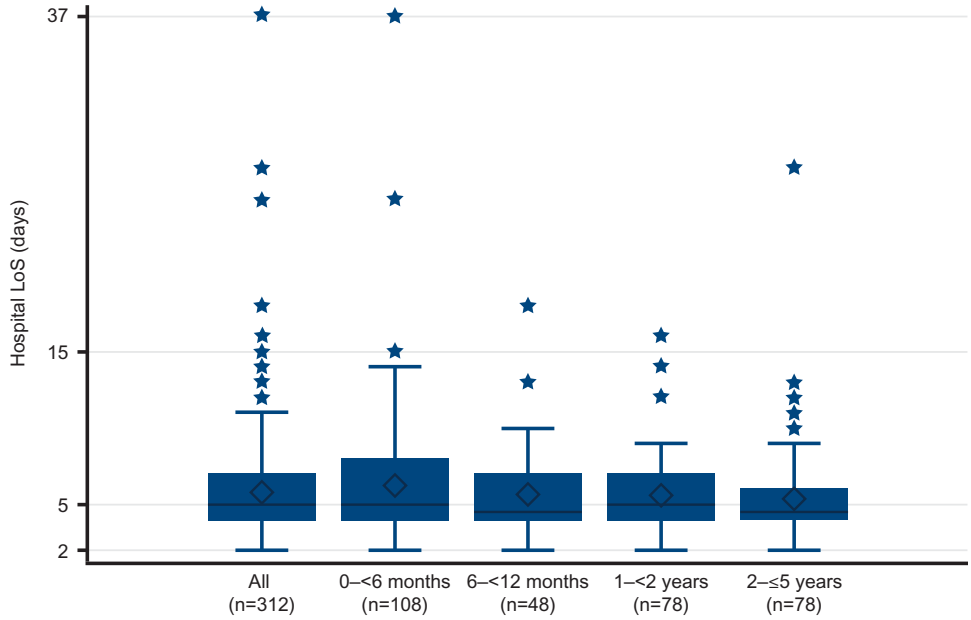

Figure 1. Overall median hospital length of stay (LOS) in hospitalized pediatric patients with respiratory syncytial virus infection (N = 312), stratified by age. The length of the box represents the interquartile range (IQR), the horizontal line within the box represents the median value, the whiskers represent the 1.5 IQR of the 25th quartile or 1.5 IQR of the 75th quartile, and the stars represent outliers.

Table 2. Prespecified Signs and Symptoms in Hospitalized Pediatric Patients With Respiratory Syncytial Virus Infection (N = 312), Stratified by Age

	Age <6 Months (n = 108)		Age 6 to <12 Months (n = 48)		Age 1 to <2 Years (n = 78)		Age 2–5 Years (n = 78)		Overall (N = 312)	
Symptom	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)
Runny nose	77 (71.3)	(61.8–79.6)	31 (64.6)	(49.5–77.8)	45 (57.7)	(46.0–68.8)	39 (50.0)	(38.5–61.5)	192 (61.5)	(55.9–67.0)
Dry cough	87 (80.6)	(71.8–87.5)	28 (58.3)	(43.2–72.4)	44 (56.4)	(44.7–67.6)	54 (69.2)	(57.8–79.2)	213 (68.3)	(62.8–73.4)
Wheezing	61 (56.5)	(46.6–66.0)	27 (56.3)	(41.2–70.5)	29 (37.2)	(26.5–48.9)	22 (28.2)	(18.6–39.5)	139 (44.6)	(39.0–50.3)
Tachypnea	58 (53.7)	(43.8–63.3)	24 (50.0)	(35.2–64.8)	39 (50.0)	(38.5–61.5)	36 (46.2)	(34.8–57.8)	157 (50.3)	(44.6–56.0)
Subcostal and/or intercostal retractions	59 (54.6)	(44.8–64.2)	18 (37.5)	(24.0–52.6)	23 (29.5)	(19.7–40.9)	25 (32.1)	(21.9–43.6)	125 (40.1)	(34.6–45.7)
Hypoxia	33 (30.6)	(22.1–40.2)	14 (29.2)	(17.0–44.1)	29 (37.2)	(26.5–48.9)	32 (41.0)	(30.0–52.7)	108 (34.6)	(29.3–40.2)
Fine end inspiratory crackles	22 (20.4)	(13.2–29.2)	10 (20.8)	(10.5–35.0)	19 (24.4)	(15.3–35.4)	27 (34.6)	(24.2–46.2)	78 (25.0)	(20.3–30.2)
Poor feeding/drinking	52 (48.1)	(38.4–58.0)	23 (47.9)	(33.3–62.8)	35 (44.9)	(33.6–56.6)	27 (34.6)	(24.2–46.2)	137 (43.9)	(38.3–49.6)
General presentation/low activity level	36 (33.3)	(24.6–43.1)	17 (35.4)	(22.2–50.5)	38 (48.7)	(37.2–60.3)	41 (52.6)	(40.9–64.0)	132 (42.3)	(36.8–48.0)
Other symptoms[a]	85 (78.7)	(69.8–86.0)	46 (95.8)	(85.7–99.5)	69 (88.5)	(79.2–94.6)	72 (92.3)	(84.0–97.1)	272 (87.2)	(83.0–90.7)

Only symptoms occurring in >10% of patients are included in the table.

Abbreviation: CI, confidence interval.

[a]Other symptoms included abnormal respiratory sounds (ronchi, crackles, stridor, humming); abnormal breathing (prolonged expiration, aggravated expiration, obstruction, nasal flaring, jugular retraction, dyspnea, respiratory failure); cough/croup; mouth, throat, and tonsil disorders (reddened throat, tonsil disorders, coated tongue, white sputum, small enoral vesicles); thoracic pain; epistaxis; ear disorders; eye disorders/symptoms; gastrointestinal symptoms; fever; skin disorders (exanthema, dry skin, petechiae); lymph node disorders; neurological disorders; agitated/weight loss.

age groups, there was a trend for wheezing with decreasing age (0 to <6 months, 56.5%; 6 to <12 months, 56.3%; 1 to <2 years, 37.2%; 2–5 years, 28.2%; $P = .0002$) (Supplementary Results and Table 2).

Respiratory diagnoses were reported in 271 patients (86.9%), with bronchiolitis occurring in 62.8% (196/312) of patients, pneumonia occurring in 29.5% (92/313), and otitis media occurring in 7.4% (23/312) (Table 3). Bronchiolitis and pneumonia diagnoses by age were as follows: 0 to <6 months, 79.6% and 19.4%, respectively; 6 to <12 months, 81.3% and 18.8%; 1 to <2 years, 51.3% and 29.5%; and 2–5 years, 39.7% and 50.0%. There were no deaths related to RSV hospitalization. For information on time to clinical stability and time to discharge, see Supplementary Figure 3.

Table 3. Clinical Manifestations Reported in Hospitalized Pediatric Patients With Respiratory Syncytial Virus Infection (N = 312), Stratified by Age

	Age <6 Months (n = 108)		Age 6 to <12 Months (n = 48)		Age 1 to <2 Years (n = 78)		Age 2–5 Years (n = 78)		Overall (N = 312)	
Clinical Manifestation	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)	No. (%)	(95% CI)
Respiratory manifestations	103 (95.4)	(89.5–98.5)	41 (85.4)	(72.2–93.9)	61 (78.2)	(67.4–86.8)	66 (84.6)	(74.7–91.8)	271 (86.9)	(82.6–90.4)
Bronchiolitis	86 (79.6)	(70.8–86.8)	39 (81.3)	(67.4–91.1)	40 (51.3)	(39.7–62.8)	31 (39.7)	(28.8–51.5)	196 (62.8)	(57.2–68.2)
Pneumonia	21 (19.4)	(12.5–28.2)	9 (18.8)	(8.9–32.6)	23 (29.5)	(19.7–40.9)	39 (50.0)	(38.5–61.5)	92 (29.5)	(24.5–34.9)
Otitis media	1 (0.9)	(.0–5.1)	3 (6.3)	(1.3–17.2)	7 (9.0)	(3.7–17.6)	12 (15.4)	(8.2–25.3)	23 (7.4)	(4.7–10.9)
Other[a]	86 (79.6)	(70.8–86.8)	32 (66.7)	(51.6–79.6)	54 (69.2)	(57.8–79.2)	53 (67.9)	(56.4–78.1)	225 (72.1)	(66.8–77.0)
Cardiovascular manifestations	3 (2.8)	(.6–7.9)	0	…	0	…	1 (1.3)	(.0–6.9)	4 (1.3)	(.4–3.2)
Other clinical manifestations[b]	67 (62.0)	(52.2–71.2)	32 (66.7)	(51.6–79.6)	51 (65.4)	(53.8–75.8)	56 (71.8)	(60.5–81.4)	206 (66.0)	(60.5–71.3)

More than 1 manifestation could be reported for a single patient. One child (aged 36 months) with respiratory syncytial virus (RSV) infection died 7 and a half months after the RSV hospitalization. A congenital heart disease was reported for this child as an underlying risk factor. There was no association between the death and symptoms or clinical manifestations related to the RSV hospitalization.

Abbreviation: CI, confidence interval.

[a]Other respiratory manifestations included cyanosis, hypoxia, oxygen saturation <90%, oxygen saturation <92%, apnea, apneic episodes, fine end inspiratory crackles, respiratory distress, respiratory failure, atelectasis, pneumothorax, hyperinflation, hyperinflation of chest, need of oxygen, exacerbation of preexisting asthma, bronchitis, sternal recession, stridor, subcostal and/or intercostal retractions, tachypnea, pleural effusion.

[b]Other clinical manifestations included general presentation/low activity level, poor feeding/drinking, low activity level, dehydration, fever >38.5°C.

RSV Viral Load

A greater proportion of patients had a high RSV viral load (Ct value <25; 67.9% [n = 212]) than a moderate (Ct value 25–35; 27.9% [n = 87]) or low viral load (Ct value >35; 1.9% [n = 6]), with the highest proportion (80.6%) observed in the age group 0 to <6 months (Supplementary Results and Supplementary Figure 4). Approximately 24.7% of all patients had a high viral load and symptoms for 3 to <5 days before admission (Supplementary Figure 5). A significantly higher proportion of patients with high RSV viral load required supplemental oxygen than those with moderate or low viral load (67.5% [n = 143] vs 41.4% [n = 36] and 0% [n = 0], respectively; $P < .0001$).

Rate and Reasons of Rehospitalization

In total, 14 patients (4.5% of 312) were rehospitalized within 6 months after their initial RSV hospitalization; of these, respiratory manifestations (not further specified) were reported in 12 of 14 patients requiring rehospitalization, and/or other clinical manifestations were reported in 6 of 14 patients. Of rehospitalized patients, 50% (n = 7) were aged 0 to <6 months and were rehospitalized within 1 month of discharge.

Predictors for Longer Hospital LOS and ICU Admission

In the stepwise multivariate logistic regression analysis, pneumonia (odds ratio [OR], 2.33 [95% confidence interval {CI}, 1.30–4.15]; $P = .0042$), admission through the outpatient ward (OR, 10.69 [95% CI, 2.38–48.09]; $P = .0020$), supplemental oxygen need (OR, 5.09 [95% CI, 2.72–9.54]; $P < .0001$), and preterm birth (OR, 3.37 [95% CI, 1.22–9.27]; $P = .0187$) were significantly associated with longer hospital LOS (>5 days). Bronchiolitis was not significantly associated with longer hospital LOS (Figure 2*A*).

Patients with pneumonia (OR, 6.41 [95% CI, 2.01–20.45]; $P = .001$), those admitted directly through the ED (OR, 7.36 [95% CI, 1.89–28.61]; $P = .004$) or outpatient ward (OR, 11.73 [95% CI, 1.62–84.91]; $P = .0148$), and preterm births (OR, 5.60 [95% CI, 1.43–22.0]; $P = .014$) were significantly more likely to be admitted to the ICU (Figure 2*B*). For data on univariate logistic regression analyses, see the Supplementary Results.

DISCUSSION

This study retrospectively evaluated the clinical burden of RT-PCR–confirmed RSV in children aged ≤5 years in a tertiary university children's hospital in Germany over 3 consecutive seasons (2015–2018), demonstrating that RSV causes substantial MRU within this population. The highest proportion of hospitalizations with RSV infection occurred in patients aged 0 to <6 months, further supporting evidence that hospitalization rates for RSV acute respiratory tract infections increase with decreasing age, peaking in the first few months of life [6, 8, 21–25].

This study observed a longer median hospital LOS in patients with confirmed RSV infection than recent findings exploring national datasets from the United Kingdom and the United States [26, 27]. However, our patient data were collected from a tertiary care hospital, and, hence, are likely to include a higher proportion of patients with a more complicated course of disease requiring specialist treatment than patients treated in basic, regular, or central service hospitals. Furthermore, a recent systematic review found that hospital LOS ranged from 2 to 11 days across Western countries (defined as the United States, Canada, and Europe, including Turkey and the Russian Federation). The variation in hospital LOS may be

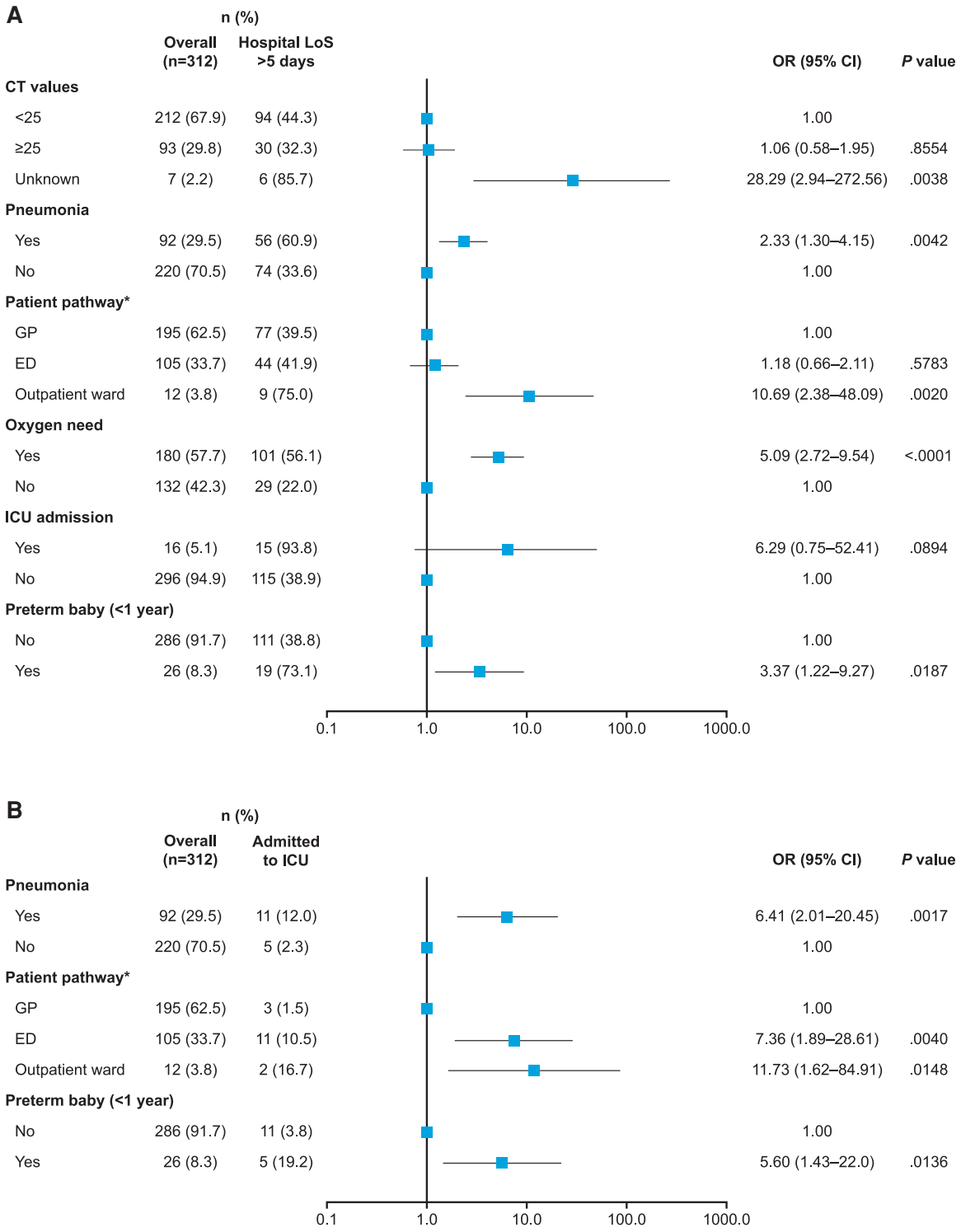

Figure 2. Predictors for prolonged hospital length of stay (LOS) (>5 days) (*A*) and intensive care unit (ICU) admission (*B*) in hospitalized pediatric patients with respiratory syncytial virus infection (N = 312). Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for selected covariates based on multivariate logistic regression with stepwise selection. A threshold of 15% for selecting criteria for stepwise approach in multivariate logistic regression modeling was applied to identify the most impactful predictors on the outcome of interest. The cycle threshold (Ct) value, defined as the number of cycles required for the fluorescent signal to cross the threshold of detection, is inversely proportional to the viral load; values of <25 are indicative of a high viral load, whereas values of ≥25 indicate a moderate or low viral load. The denominator used to calculate proportions shown in the Overall column is the overall population number (N = 312). To calculate each proportion shown in the hospital LOS >5 days and admitted to ICU columns, the total number of patients within each subgroup was used as the denominator. *Patient pathway was classed as general practitioner (GP) if patients were seen by the GP before being admitted, emergency department (ED) if patients presented directly to the ED without any prior GP or outpatient ward visit, and outpatient ward if patients were seen in an outpatient ward before being admitted.

explained, for example, by differences between countries and individual hospitals in terms of discharge criteria and healthcare insurance policies, or heterogeneity among the level of the hospitals included (eg, basic or tertiary care) [6]. In our study, hospital LOS did not appear to be noticeably different between age groups; however, there was more variation in LOS among patients aged 0 to <6 months, with some patients having longer hospital stays, suggesting that this is a more vulnerable population or that preemptive hospitalizations are common in very young children. ICU admission rates observed in our study are consistent with findings from other recent studies [26, 28]. Patients aged 0 to <6 months often present directly to the ED without any previous GP visit, due to acute respiratory worsening. This age group also had the highest ICU admission rate (9%), which is consistent with previous findings [29, 30]. These data, in addition to a trend for these patients to be admitted to the ICU directly from the ED rather than by transfer during the hospital stay, may reflect more severe disease in this population [31].

Supplemental oxygen and concomitant medications, particularly short-acting β-agonists, were common. Antibiotics were frequently used during hospitalization (43.6%), despite the limited number of bacterial coinfections detected (5.8%), presumably due to difficulties in clinically excluding bacterial coinfections of the lower airways. This finding reflects previous evidence of antibiotic overuse in children with RSV bronchiolitis [32, 33]. Frequent usage of supportive care further highlights the significant unmet medical need for efficacious therapies for RSV infection.

Predefined comorbidities, such as prematurity, bronchopulmonary dysplasia, neuromuscular diseases, congenital heart or pulmonary abnormalities, and Down syndrome, are widely reported as risk factors for hospitalization of children with RSV infection [28, 34–37]. A 15-year epidemiologic survey in Spain found that 3.2% of children aged ≤5 years hospitalized due to bronchiolitis (n = 315 872) had at least 1 predefined comorbidity, the most frequent being congenital cardiopathies (2.3%) [34]. Furthermore, a prospective cohort study found that 13.7% of children aged <3 years hospitalized with RSV infection (n = 460) had predefined comorbidities, with pulmonary disease reported as the most frequent [36]. In this study, predefined comorbidities were present in approximately 16% of patients, which is in line with the findings described above and suggests that the majority of RSV hospitalizations occur in otherwise healthy children. However, we did not specifically assess the following comorbidities that are recorded in other studies assessing RSV: low birth weight, cerebral palsy, renal disease, diabetes, and anemia [26, 34–36]. These diagnoses may have been included in the category "other" comorbidities, which was recorded in a high proportion of children (35.9%). Of the children hospitalized with RSV infection, 25% were aged 1 to <2 years and 25% were aged 2–5 years, demonstrating that RSV still causes significant burden in children aged >1 year. Furthermore, the proportion of RSV patients with predefined comorbidities (such as congenital diseases) increased with age. While symptoms were generally similar between age groups, there was a trend for increased incidence of wheezing with younger age. This is likely due to the smaller airway dimensions in younger patients, as only a slight closing of the airways could give rise to wheezing [38].

Respiratory manifestations were most commonly observed and cardiovascular manifestations were rare; patients aged 0 to <6 months had the highest rates of respiratory manifestations. Findings from this study confirm findings from previous studies identifying that, despite the relatively low RSV-associated ICU admission rates, the rate of RSV-related manifestations remains high [18, 23, 39–41]. The trend for bronchiolitis decreasing with age corresponds with previous findings, as bronchiolitis is a leading cause of hospitalization in children aged <2 years [19, 20, 25, 34].

Otitis media was diagnosed in 7.4% of patients with RSV infection in this study. The authors acknowledge that this is lower than rates seen in other studies [18, 39]. As RSV patients treated at our tertiary care hospital were most frequently admitted due to lower respiratory tract infections, data collection methods may not have captured all additional otitis media occurrences in these patients. In some cases, otitis symptoms may have resolved prior to hospitalization, or patients presenting solely with otitis media may have been admitted to a secondary care hospital in the area.

The majority of patients presented with a high RSV viral load at admission. The proportion of patients with a high RSV viral load was highest in the group aged 0 to <6 months. The need for supplemental oxygen was significantly higher in patients with a high viral load compared with those with a moderate or low viral load, in line with findings from previous studies [42–45]. Previously studies have also demonstrated low RSV viral load at admission to be associated with prolonged hospital stay [31]. We cannot draw conclusions on low viral load as a predictor of prolonged hospital LOS or ICU admission from our study due to the limited sample size in this group, as only 6 patients had Ct values of >35. These patients may have had prolonged hospital stay due to worsening disease course by additional clinical manifestations, with all 6 patients experiencing "other clinical manifestations" (not further specified) and respiratory diagnoses reported in 5 (83.3%) patients.

Other factors associated with prolonged hospital LOS were pneumonia, need for supplemental oxygen, admission to the ICU and preterm births. Furthermore, pneumonia, preterm births, and patient pathway through the ED without a GP visit were identified as predictors of ICU admission. Notably, modeling data from this study concur recent findings that preterm birth is a predictor of severe RSV disease, with definitions of severe outcomes including clinical pneumonia or bronchiolitis,

prolonged hospital stay, oxygen supplementation, mechanical ventilation, ICU admission, and mortality [11, 46–48].

To our knowledge, this is the first study to retrospectively collect data on patients who were rehospitalized within 6 months of initial hospitalization with RSV infection (<5%). The majority of rehospitalizations were in patients aged 0–6 months and were due to respiratory conditions (not further specified).

The main strength of this study was that PCR diagnostic testing for RSV infection was conducted systematically in patients with acute respiratory infection and data were collected over 3 consecutive RSV seasons. This study also provides insights on patient or disease characteristics associated with or predictive of prolonged hospital stay and ICU admission, an area that is yet to be widely researched. There are also some limitations to this study; the data were only collected for informative purposes; therefore, it is descriptive and not powered for comparisons between age groups. Due to the monocentric design, the extent to which the results can be applied to other hospitals and or/countries is unclear; inclusion of additional sites would have increased the generalizability of the findings. Additionally, the retrospective design may have underestimated study-specific treatment modalities. Finally, the small sample size does not allow for thorough comparisons to be made for all analyses.

CONCLUSIONS

RSV infection in hospitalized children aged ≤5 years causes substantial burden and significant MRU. Only a limited proportion of hospitalized children have underlying predefined comorbidities. The clinical burden is highest in the youngest infants, with increased ICU admissions and rates of respiratory manifestations, particularly bronchiolitis. However, there is substantial burden observed in children aged >1 year and in those with underlying comorbidities, whose proportions increase with age. Preterm infants aged <1 year have longer hospital LOS, higher rates of ICU admissions, longer ICU LOS, and higher oxygen need compared with those not born preterm or aged >1 year. Pneumonia and preterm births are significant predictors of prolonged hospital LOS (>5 days) and ICU admission. These data can provide insights into which patient population may benefit most from potential future RSV prophylactic and therapeutic measures. Furthermore, insights such as these provide a rationale for RSV diagnostic testing and subsequent cohorting to reduce transmission of RSV in the hospital setting. The factors identified may also be considered when planning policies to reduce LOS in children infected with RSV.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. P. T., J. D., and K. W. were involved in the conception and design of the study and responsible for the statistical analysis. K. H., J. G. L., D. K., and A. S. contributed to the design and/or revised the data analysis. K. H., J. G. L., D. K., C. P., B. W., and A. S. were responsible for the acquisition of data. All authors were involved in the interpretation of the data, and reviewed and approved the final manuscript.

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