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Risk Factors and Outcomes of Respiratory Syncytial Virus in Children Under Three Years; A Systematic Review

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Abstract

Background: Respiratory syncytial virus (RSV) is an RNA virus that affects respiratory epithelial cells. It is one of the major causes of acute lower respiratory tract infection (ALRI), especially in children under one year of age. This virus is one of the main pathogens of early childhood, affecting almost all children before two years of age. This illness is associated with global morbidity and mortality, and its severity ranges from mild and moderate to life-threatening respiratory failure.

Aim: To assess the risk factors and outcomes of respiratory syncytial virus in children under three years old by reviewing previous studies investigating this subject.

Methods: Scientific websites, including PubMed, Science Direct, Google Scholar, Scopus, and Springer, were used to search for related articles using several keywords and terms. The search process was limited to 2014 to 2024, including original English articles reporting RSV risk factors and/or outcomes among children under three years of age.

Results: Eight articles met the eligibility criteria and were included in this review with a total number of 8100 children less than three years old with RSV with an age range of ≤ 28 days of life and within two years of age. The findings included RSV risk factors, outcomes, and risk factors of specific outcomes.

Conclusion: There are several risk factors for RSV infection among children less than three years old, these include birth and discharge during RSV season, lower parity, and older mothers. Furthermore, there were various reported outcomes, including the requirement for intensive care, oxygen supplementation, mechanical ventilation, hospitalization, developing pneumonia, full recovery, and mortality.

Keywords: *RSV; Risk Factors; Outcomes; Neonates; Infants; Toddle*

Introduction

Respiratory syncytial virus (RSV) is an RNA virus of enveloped non-segmented single-strand that belongs to the Pneumoviridae family and affects the respiratory epithelial cells with two subtypes, RSV-A and RSV-B [1,2]. The subtype A is more virulent and usually more prevalent [2]. RSV is seasonal, and its infection rate peaks in temperate climates during the cold season [3]. The incubation period of the

infection is 3 - 5 days, and the clinical presentation of the viral infection varies based on age, with the most common symptoms being nasal congestion, rhinorrhea, fever, cough and respiratory distress [4].

A substantial cause of Acute lower respiratory tract infection (ALRI) in children is RSV, especially in children under one year of age [5]. The global estimation of ALRI causes related to RSV in children under five years of age is 33 million cases [6]. Infection of children aged six months to two years is usually asymptomatic, with almost 40% of cases presenting with pneumonia and bronchiolitis [4]. Up to 40% of infants develop ALRI with wheezing and coughing, which range in severity from mild and moderate illness to life-threatening respiratory failure [7], and it is associated with fundamental global morbidity and mortality [2].

RSV is one of the major pathogens of early childhood, and it is thought to affect almost all children before two years of age [8]. Additionally, the most significant risk factor for RSV disease in childhood is young age, where those aged below three months have the highest risk, and this risk gradually reduces as they grow older [9]. Therefore, this systematic review was performed to identify the risk factors and outcomes of RSV among children less than three years old.

Method and Search Strategy

This review was written following the PRISMA guidelines for systematic reviews [10]. Scientific websites, including PubMed, Science Direct, Google Scholar, Scopus, and Springer, were used to search for eligible articles. The search process was limited to the period from 2014 to 2024. Various terms were used as keywords for the search procedure, such as "RSV, Outcomes, Risk Factors, Association, Infants, Neonates, and Children". All obtained titles were revised thoroughly to ensure that potential studies were included.

Eligibility criteria

The findings were examined to exclude duplicate articles and limit the number of articles. The articles published before 2014 were excluded, and those that reported other infections and appeared coincidently in the search procedure were also excluded. The second step involved precisely checking the articles' titles and aimed to include articles reporting the risk factors and/or outcomes of RSV among children under three years. Then, the type of each article was explored, only original articles were included, and other types of articles were excluded. The original articles were then examined for language to include articles written in English language and then including those providing the full-text articles.

On the other hand, articles written in non-English or provided only abstracts were excluded. Furthermore, studies involving overlapped or incomplete data were excluded. Figure 1 illustrates the inclusion method.

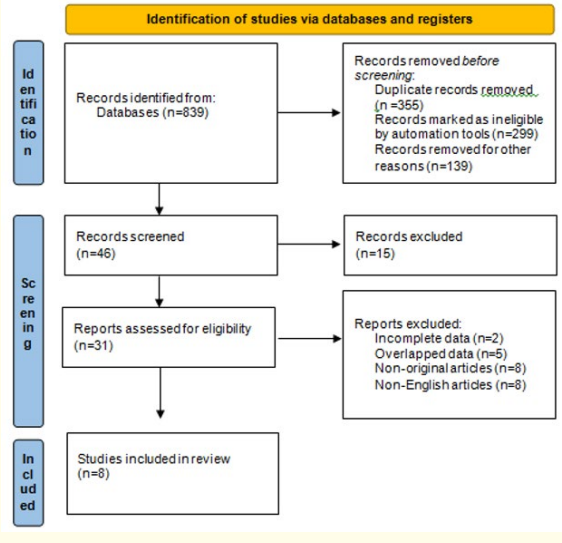

Figure 1: *Scheme for inclusion criteria.*

Reviewing of data and analysis

The abstracts of the eligible studies were examined to determine the data of interest for data extraction. Data was extracted by reviewing the full-text articles and using a specially designed Excel sheet. Then, such extracted data was transferred to a pre-designed table under major titles for summarization.

Results

Only eight of the articles that were obtained met the eligibility criteria and were included in this review [11-18] (Table 1). One study did not state the study design [14], whereas the remaining study designs included retrospective [11,18], prospective [12,16,17], randomized trials [13], and nationwide birth cohort [15]. The study population included RSV-positive neonates required NICU [11], premature infants [12], RSV-positive infants [13], infants with pneumonia [14], RSV-positive hospitalized infants [15], newborns hospitalized with community-acquired or nosocomial RSV [16], infants with respiratory symptoms and/or fever [17], and infants with RSV-associated acute lower respiratory tract infection [18]. The total number of RSV-positive cases was 8100 cases, with an age range of ≤ 28 days of life [11] to within two years of age [15].

Two studies reported the duration of hospital stay [11,16], ranging between 5 [11] and 180 days [16]. Five studies reported risk factors and outcomes of RSV [11-13,16,17], whereas three studies reported outcomes only [14,15,18].

The risk factors of RSV infection included preterm birth (gestational age ≤ 35 weeks) (85.71%) [11], (31.6%) [16], low birth weight (< 2 Kg) (92.85%), history of viral illness in the family individuals (100%) [11], BPD (4.4%), congenital heart (3.6%) and respiratory (1.2%) diseases [16], higher proportions of RSV-positive patients tended to born during or three months prior to RSV season (P = 0.004), discharge during the RSV season (P = 0.01) [12], lower parity mothers (P = 0.03) and older mothers (P = 0.02) [13], breastfeeding (P = 0.01), previously healthy without medical conditions (P < 0.01) and less prone to born prematurely (P = 0.04) [17].

Non-significant risk factors for RSV included very low birth weight (P = 0.4), male gender (P = 0.3), lack of breastfeeding (P = 0.4), maternal smoking and passive smoking after birth (P = 0.6), attendance to daycare (P = 0.2), history of family or maternal atopy or allergy (P = 0.7), low socioeconomic status (P = 0.06), cesarean section (P = 0.1), any respiratory support (P = 0.08) or NICU stay (P = 0.9) [12].

The reported outcomes included requirement for respiratory support [11], supplemented oxygen (69%) [14], (3.6%) [16], (P < 0.01) and longer days for supplemented oxygen support (P = 0.04) [17], CPAP (11%), mechanical ventilation (3%) [14], severe cases (31.5%) [18], severe hospitalized infants (4.2%) [18], full recovery of all patients [11], hospitalization (8.5%) [13], (P = 0.0001), intensive care or mechanical ventilation (P = 0.01), longer duration of hospitalization (P = 0.02) [12], pneumonia (29.4%), febrile acute respiratory infection (70.6%) [13], mortality (0.7%) [13], (1.2%) [16], (1%) [18], lower mortality rate (P = 0.01) [17], and clinical non-response (43.1%) [14].

Some risk factors for some outcomes were reported; the risk factors of RSV severity were NICU graduates, very preterm, and male gender with a slight predominance [11]. Independent risk factors for severe infection included low birth weight (AOR 1.69), age < 3 months (AOR 3.38), congenital heart disease (AOR 1.66), BPD (AOR 8.5), and airway abnormalities (AOR 2.24) [18]. The risk factors for hospitalization included age ≤ 3 Months at admission (OR 2, P = 0.04) [12], age < 6 months [17], male gender (P = 0.04) [13], preterm infants (P < 0.0001), especially those with BPD (P < 0.0001) [15]. Additionally, longer hospitalization duration was significantly associated with age ≤ 3 Months (P = 0.0001) [12]. Preterm with BPD was a risk factor for higher ICU admission rate (p < 0.0001), mechanical ventilation (p < 0.0001), and length of hospital stay (p < 0.001) [15]. The predictors of clinical non-response at 48 hours included age < 6 months (RR 1.97, P = 0.01), use of wood as a cooking fuel (RR 1.66, P = 0.02), moderate or severe malnutrition (RR 1.71, P0.02), and oxygen saturation < 90% on room air (RR 1.56, P = 0.04) [14].

Author and Publication year	Study design	Population and Characteristics	Risk factors and outcomes
Kalane., *et al*. 2022 [11]	Retrospective	-RSV positive Neonates required NICU for ARI -N = 14 neonates -Age: ≤ 28 days of life	*Total duration of hospital stay was 8 (5-14) days. *The reported risk factors included gestational age at birth ≤35 weeks (85.71%), birth weight <2Kg (92.85%), and history of viral illness in family members (100%). * *The severity was higher in NICU graduates who were born very preterm. *NICU graduates were susceptible to RSV illness with a slight male preponderance; male-to-female ratio was 3.67:1. *The majority of infected neonates presented with ARI requiring respiratory support. *All the RSV-infected patients displayed full recovery.
Ozkan., *et al*. 2021 [12]	Prospective	-Premature children -N = 307 *RSV positive = 103 *RSV negative = 204 -Age: <2 years *RSV positive: 4.9 ± 4.6 months *RSV negative: 6.3 ± 5.2 months	*RSV (+) groups were significantly younger at admission (P = 0.02) *The investigated risk factors included very low birth weight (P = 0.4), male gender (P = 0.3), lack of breastfeeding (P = 0.4), maternal smoking and passive smoking after birth (P = 0.6), attendance to daycare (P = 0.2), history of family or maternal atopy or allergy (P = 0.7), low socioeconomic status (P = 0.06), cesarean section (P = 0.1), any respiratory support (P = 0.08) or NICU stay (P = 0.9). On the other hand, significantly higher proportions of the RSV (+) group tended to be born during or three months prior to RSV season (P = 0.004) and discharged during the RSV season (P = 0.01) compared to the RSV (-) group. *Multivariate analysis revealed that age of ≤3 months at admission was a significant risk factor for hospitalization for RSV (OR 2, P = 0.04). *Regarding outcomes, RSV (+) significantly tended to need hospitalization (P = 0.0001), require intensive care or mechanical ventilation (P = 0.01) and spend mean longer duration of hospitalization (P = 0.02). *Additionally, significant higher proportions of RSV (+) with chronological age of ≤3 months significantly tended to need hospitalization (P = 0.001) and stayed for a mean longer duration in hospital (P = 0.0001).
Buchwald., *et al*. 2020 [13]	Randomized trial	-RSV Infants -N = 157 -Age: 12-131 days of life	*RSV cases significantly had mothers with lower parity (P = 0.03) and older mothers (P = 0.02). *There 29.4% presented with pneumonia and 70.6% presented with febrile acute respiratory infection. *Hospitalization among those with pneumonia was 8.5% and the mortality rate was 0.7%. *Hospitalization of RSV was significantly associated with male gender (P = 0.04).

Patel., *et al*. 2019 [14]	-------	-398 Patients with pneumonia -N = 123 RSV positive patient -Age: 1-23 months	*There 69% of infants required supplemental oxygen, 11% required CPAP, and 3% required mechanical ventilation. *Of the 123 RSV infants, 43.1% reported clinical non-response, whereas 56.9% reported clinical response at 48 hours. *The predictors of clinical non-response, included young age (<6 months) (RR 1.97, P = 0.01), household use of wood as a cooking fuel (RR 1.66, P = 0.02), moderate or severe malnutrition (RR 1.71, P = 0.02), and oxygen saturation <90% on room air (RR 1.56, P = 0.04) were independent predictors of clinical non-response at 48 hours.
Chi., *et al*. 2018 [15]	Nationwide birth cohort	- RSV hospitalized Children -N = 5143 *Preterm = 560 -<90 weeks gestation = 90 -29-32 weeks gestation = 156 -33-35 weeks gestation = 314 *Term = 4583 -Age = within 2 years of age	*The preterm group had a significantly higher RSV hospitalization rate than term infants (P < 0.0001). *Preterm infants born at 29 to 35 weeks of gestational age with BPD had significantly higher RSV hospitalization rates than those without BPD (p < 0.0001). *Preterm infants without BPD born at < 32 weeks of gestation had a higher RSV hospitalization rate than those born at 33 ± 35 weeks of gestation (p < 0.0001). *Preterm infants with BPD had a higher ICU admission rate within 18 months of chronological age (p < 0.0001), mechanical ventilation usage within 12 months of chronologic age (p < 0.0001) and length of hospital stay within 18 months of chronologic age (p < 0.001) than those without BPD.
Alan., *et al*. 2015 [16]	Prospective	-Newborn hospitalized with community-acquired or nosocomial RSV -N = 250 RSV cases -Age: 4-153 days	*Rates of risk factors were prematurity (31.6%), chronic lung disease (bronco-pulmonary dysplasia) (4.4%), congenital heart disease (3.6%), and congenital respiratory tract (1.2%). *The duration of hospital stay ranged between 2 and 180 days. *Outcomes included medical treatment or oxygen supply at discharge (3.6%), and mortality (1.2%).
Halasa., *et al*. 2015 [17]	Prospective, year-round viral surveillance	-3168 patients with respiratory symptoms and/or fever. -N = 1397 patient with RSV-positive result. -Age: <2 years (0.06-23.64 months).	*The RSV-associated hospitalization rate was highest in children <6 months. *RSV-positive children compared with RSV-negative were more likely to be breastfed (P = 0.01), previously healthy without underlying medical conditions (P < 0.01), and less likely to be born prematurely (P = 0.04). *Regarding outcomes, RSV-positive infants had a significantly higher frequency of supplemental oxygen requirement (P < 0.01), longer days for oxygen (P = 0.04), lower death rate (P = 0.01), and lower median vitamin D levels (P < 0.01). *On the other hand, there were no significant differences in outcomes between RSV-positive and negative neonates regarding mechanical ventilation (P = 0.5), ICU stay (P = 0.8), and length of stay (P = 0.2).

Zhang., *et al*. 2014 [18]	Retrospective review	-Infants with RSV-associated acute lower respiratory tract infections -N = 913 RSV infants -Age: <3-12 months	*There are 288 (31.5%) severe cases and 625 (68.5%) non-severe cases. *Multivariate analysis revealed that low birth weight (AOR1.698), age less than 3 months old (AOR 3.385), congenital heart disease (AOR1.667). bronchopulmonary dysplasia (AOR 8.505), and airway abnormalities (AOR 2.246) were independent risk factors for severe infection. *The hospital RSV mortality rate was 1%. *Infants with severe RSV accounted for 4.2% of hospitalized children.

Table 1: *Summary of the extracted data.*

RSV: Respiratory Syncytial Virus; NICU: Neonatal Intensive Care Unit; ARI: Acute Respiratory Illness; CPAP: Continuous Positive Airway Pressure; BPD: Bronchopulmonary Dysplasia; ICU; Intensive Care Unit.

Discussion

RSV is the most frequent pathogen identified in young children and causes ALRI [19]; therefore, this systematic review focused on the risk factors and outcomes of RSV among children less than three years old. This review reported several risk factors for RSV infection. The most significant risk factor was preterm birth, but another study reported that being less prone to prematurity was significantly associated with RSV infection [17].

However, several risk factors were reported, including low birth weight, congenital heart disease, BPD, respiratory distress, and a family history of viral illness. However, these risk factors were reported based on their prevalence among the infected children. Therefore, such factors lack strong evidence, as the nature of the association between such factors and RSV infection was not reported.

On the other hand, other factors were reported to have a significant association with RSV infection, including birth during or prior to RSV season, discharge during RSV season, lower parity and advanced maternal age, having no previous medical condition, and lack of prematurity. Such factors displayed a significant association with RSV infection among neonates and infants.

The risk factors of severe RSV illness in childhood include male gender, prematurity, congenital heart disease, and lung disease [20]. In the current analysis, male gender was not a significant risk factor for RSV infection (P = 0.3). In contrast, congenital heart disease and lung disease (BPD) were prevalent among 3.6% and 4.4% of the children with RSV.

A previous analysis concerned with children less than five years old included 20 articles with a total number of 16115 children. It was found that the significant risk factors for RSV among those children were male gender, age, winter season, and environmental factors such as higher relative humidity, cold temperature, exposure to tobacco, living in urban regions, and high concentration of benzene [21]. In this analysis, RSV season was a significant risk factor in case of discharge or birth during the season. However, male gender was not a significant risk factor, and age was not reported in the included studies.

Adverse outcomes can be detected among children with underlying diseases and conditions such as prematurity, congenital heart disease, lung diseases, and acquired or congenital immunodeficiency [22-24]. The present review reported various outcomes, including the requirement for supplemented oxygen, mechanical ventilation, hospitalization, pneumonia, mortality, and complete recovery. Severe RSV disease may require admission to the ICU with ventilator support [25]. In this analysis, children with RSV infection significantly required intensive care (P = 0.01), oxygen supplementation, mechanical ventilation, CPAP, and hospitalization. Risk factors were reported to be associated with the severity of cases, including cases of very preterm and NICU graduates.

RSV is the most common reason for hospitalization for infants [2]. Hospitalization related to RSV is a potential burden for patients and families [26]. We found that RSV-affected children significantly required a longer duration of hospitalization. This can be attributed to many reported risk factors, including a younger age of three months or less, male gender, and preterm birth. Furthermore, longer hospitalization was associated mostly with a younger age of three months or less.

Several risk factors increase RSV hospitalization, including younger age than one year and chronic conditions as well as living in remote communities [26]. A previous review deduced that prematurity was associated with a higher risk of RSV hospitalization and more extended hospital stays [26]. In this review, hospitalization was significantly associated with preterm infants, and being a preterm infant with BPD was a risk factor for ICU admission.

Chronological age is the significant risk factor for RSV hospitalization among term infants, and most hospitalization episodes occur in those under one year of age [27]. Such findings were in agreement with ours. Additionally, the presence of older siblings in the home can increase the risk of RSV hospitalization [28]. However, the presence of a family member with a history of viral illness was found to be a risk factor for RSV infection among infants, as all infants in one study had a family member with a history of viral illness [11].

The majority of children with severe infection of RSV will recover; however, RSV is associated with a significant burden of early childhood mortality [2]. The mortality rate of RSV varies considerably based on the presence of risk factors [25]. Complete recovery of all patients was found in one study [11]. Of the included studies in this review, mortality was reported in four studies with a mortality rate ranging between 0.7% and 1%. However, one study reported a significantly lower mortality rate of children with positive RSV compared to those with respiratory symptoms and fever but with negative RSV [17].

The risk of mortality is increased in the presence of some factors such as prematurity, nosocomial infection, congenital heart diseases, low birth weight, and Down syndrome [19,25,29]. However, in our analysis, no risk factor for mortality was reported by any of the included studies.

In a systematic review and meta-analysis, the risk factors associated with poor outcomes and mortality among young children with RSV were investigated. A total of 27 studies were included, and the outcomes and risk factors were reported for children under three years old. The risk factors significantly associated with RSV-ALRT included the presence of any comorbid condition (OR, 2.69), congenital heart disease (OR, 3.40), prematurity with gestational age < 37 weeks) (OR, 1.75) and gestational age ≤ 32 weeks (OR, 2.68), age < 3 Months (OR, 4.91) and < 6 months (OR, 2.02). Regarding mortality, only prematurity at gestational age < 37 weeks revealed an OR of 3.81 based on univariable analysis [19].

It was found that among those younger than 12 months in the emergency department, RSV is not often identified in discharge diagnoses. Furthermore, RSV testing was negative among 13% of infants with RSV-specific ICD-9 discharge codes referring to a false positive RSV rapid antigen test, or some infants were not tested for RSV despite being assigned an RSV-specific ICD-9 code on discharge. Therefore, there is a need to improve the accuracy of tests in the emergency department as this may result in more precise estimates of the actual burden of RSV disease. Identifying risk factors may improve the accuracy of tests in the emergency department and help patients be appropriately selected for testing [30].

Conclusion

There are several risk factors for RSV infection among children less than three years, including preterm birth, history of viral illness in the family, birth and discharge during RSV season, lower parity, and advanced maternal age. This variation in risk factors can be attributed to the factors assessed in each study. Moreover, there were various reported outcomes, including the requirement for intensive care, oxygen supplementation, mechanical ventilation, hospitalization, developing pneumonia, full recovery, and mortality. Also, there were several risk factors associated with RSV severity and hospitalization that require further investigation for adequate evidence.

Limitations, Strengths, and Recommendations

This review's limitations involve including a few articles; however, only some articles met the eligibility criteria. Also, the heterogeneity of the included studies led to the reporting of various risk factors and outcomes, which needed more solid evidence. Another limitation is that some studies did not report the association between risk factors and RSV infection and outcomes, instead they reported such factors based on proportions of risk factors. Additionally, more risk factors and predictors must be estimated based on univariate and multivariate analysis. However, the strengths of this review are the focus on the most recent studies published in the last ten years, the focus on neonates up to toddlers of three years, the presentation of the review in a simple manner, and the reporting of the gaps in the previous research to avoid them in further studies in order to obtain robust evidenced findings. Hence, further studies are recommended to report risk factors and outcomes based on solid evidence and with deep analysis.

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