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ORIGINAL ARTICLE

Risk factors for severe bronchiolitis in children less than 2 years old: a retrospective cohort study

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ABSTRACT

Background: Bronchiolitis is the most common reason for hospitalization and frequent cause of viral infection. This study aimed to determine the risk factors for severe bronchiolitis in children admitted through the emergency department at Sultan Qaboos University Hospital in Oman.

Methods: A retrospective chart review was conducted among children <2 years of age with acute bronchiolitis between January 2015 and December 2018. Patients' demographics and clinical information were collected from the electronic hospital information system. Severe bronchiolitis is defined as a child requiring non-invasive ventilation (NIV) or mechanical ventilation (MV).

Results: A total of 857 charts were reviewed and 684 met the inclusion criteria, where 86% of the patients were hospitalized. Mean corrected age was 5.08 ± 4.70 months and 59% were male. Out of all admitted children, 111 (19%) required NIV or MV. Two patients died. Children with severe disease had prolonged length of stay in days (10.2 *vs.* 4.4, $p < 0.001$). Using multivariate logistic regression analysis, the study identified severe outcomes to be independently associated with corrected age (<3 months) (OR 1.84, 95% CI 1.12-3.03), chronic disease (OR 3.24, 95% CI 1.79-5.86), O_2 saturation (≤92%) (OR 4.12, 95% CI 2.57-6.60), PCO_2 (≥45) (OR 2.72, 95% CI 1.67-4.45), C-reactive protein (≥20) (OR 1.86, 95% CI 1.13-3.04), and abnormal chest X-ray findings (OR 1.88, 95% CI 1.20-2.94).

Conclusion: This study identified six variables as predictors of severe bronchiolitis. The younger and sicker children associated with comorbidities are more likely to have severe outcomes.

Keywords: Bronchiolitis, emergency medicine, non-invasive ventilation, mechanical ventilation, Oman.

Introduction

Bronchiolitis is the most common reason for hospitalization and frequent cause of viral infection. It is presented as rhinitis and cough, with the risk of further increasing tachypnea, wheezing, crackles, use of accessory muscles, and/ or nasal flaring in young patients as defined by the American Academy of Pediatrics (AAP) [1].

In the United States, lower respiratory tract infection causes more than 100,000 hospitalizations annually in young infants. In addition, respiratory syncytial virus (RSV) is the main virus in this age group [2,3]. It is estimated that 120,000 deaths related to RSV alone occur annually worldwide, with most of these happening in low to middle-income countries, where intensive care facilities are almost absent [4]. A substantial proportion of children experience at least one episode of RSV bronchiolitis at around 2 years of age but 1%-2% younger children may require hospitalization during the first year of life [5]. RSV causes 60%-80% of acute bronchiolitis cases in children <1 year of age. Rhinovirus (RV) comprises the second common virus and causes 14%-30% of acute infections. Co-infections are reported in 30%-41% of bronchiolitis cases but are not associated with a severe course [6-8].

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Acute bronchiolitis infection can occur throughout the year, but epidemics occur during the cold weather. The peak incidence of RSV infection occurs during fall and winter in the temperate climate areas of Europe and Asia [9]. In addition, RSV causes outbreaks in the hot, rainy season from June to November in tropical countries [10,11]. There are several risk factors for severe RSV bronchiolitis identified by the AAP. The most common factors comprise prematurity, chronic lung disease (CLD), and congenital heart disease (CHD) [12]. However, during outbreaks, majority of previously well children are admitted due to acute bronchiolitis without these underlying risk factors [13,14]. Currently, there is no established pharmacological treatment except for supportive care. Between 5% and 6% of infants hospitalized for acute bronchiolitis are shifted to the pediatric intensive care unit (PICU) for escalated care. Children who presented with moderate to severe bronchiolitis and non-invasive ventilation (NIV) had become the first choice of respiratory support [15]. In regional studies, RSV-associated hospitalization was 46%-60% in Qatar [16,17] and 64% in Jordan [18]. In a previous study in Oman, almost 40% of children less than 5 years of age were admitted due to RSV pneumonia and bronchiolitis [19]. The aim of this study was to describe the clinical characteristics, hospital course, and to identify the risk factors for severe bronchiolitis in children admitted through the emergency department at Sultan Qaboos University Hospital Muscat (SQUH), Oman.

Subjects and Methods

A retrospective chart review of infants and young children, who presented to the emergency department at Sultan Qaboos University Hospital, with primary diagnosis of acute bronchiolitis was conducted during the period of January 2015 till December 2018. Children <2 years of age with a first episode of acute bronchiolitis were included and nasopharyngeal aspirate (NPA) for rapid viral antigen test was collected on that visit. The diagnosis of bronchiolitis was clinically determined according to the presence of a history of upper respiratory tract infection, followed by respiratory distress with cough, tachypnea, retractions, wheezing, and bilateral crackles on auscultation. All children whose NPAs for virology test were not collected and those with primary diagnosis other than bronchiolitis were excluded from the study.

Patients' data were retrieved from SQUH's electronic medical record system by using the discharge code of acute bronchiolitis and RSV bronchiolitis. A data collection sheet was developed to document the necessary information. The study personnel screened the data and completed the data collection sheet. The following descriptive variables of each patient were extracted, which met the inclusion criteria: demographic features (age and sex), epidemiologic data (date of presentation and season), underlying conditions (prematurity, CHD, and other chronic diseases), comorbidities (pneumonic consolidation/atelectasis, acute otitis media, and urinary tract infection), laboratory tests and other work-ups [complete blood count (CBC), C- reactive protein (CRP), blood culture, blood gas, nasopharyngeal aspirate, chest X-ray, treatment received (salbutamol, ipratropium bromide, epinephrine, 3% hypertonic saline, antibiotics use, and systemic steroids), and outcome [NIV or mechanical ventilation (MV)]. NIV was used as the preferred first-line modality for respiratory distress. MV was used for children who had severe respiratory failure refractory to NIV or with severe apnea. The term NIV includes high-frequency nasal cannula and nasal continuous positive airway pressure. Eleven respiratory viruses were investigated in nasopharyngeal aspirate: RSV, RV, adenovirus, parainfluenza-2, 3, and 4, enterovirus, influenza A and influenza B, H1N1, and parechovirus.

Data were analyzed using STATA 15 software (Stata Corp LLC, College Station, TX). Categorical and continuous values were presented as frequency (%) and mean ± SD. Frequencies were rounded to the nearest whole number. Categorical variables were analyzed using the χ^2 test or Fischer's exact test and continuous variables by Student's *t*-test. *p*-value of < 0.05 was considered statistically significant. The independent association between risk factors for severe disease and outcomes were analyzed using a stepwise multivariate logistic regression (The following variables were modeled as categorical variables like corrected gestational age <3 months, O2 saturation ≤92%, PCO2 ≥ 45, CRP ≥ 20). Adjusted odds ratios with 95% confidence intervals were reported. Multiple imputation techniques were used to accommodate and account for missing data for the laboratory variables and to have less biased results.

Results

A total of 857 patients were screened for eligibility and 684 met the inclusion criteria. A total of 589 (86%) patients were admitted to the hospital. Out of them, 226 (39%) and 60 (10%) were admitted to the high dependency unit (HDU) and PICU, respectively. The mean corrected age of hospitalized patients were 5.08 ± 4.70 months (range: 1-24 months), 418 (71%) were under 6 months, 287 (49%) were under 3 months, and 59% were male (Figure 1). Out of the total, 347 (59%) children were previously healthy. Among the hospitalized children, 16% were premature, out of which 10% were born between 33 and 36 weeks of gestational age (GA) and 6% were born at or before 32 weeks. Premature children who required admission were younger when compared to discharged patients (5.08 *vs.* 6.61 months; $p < 0.001$). Children who had associated chronic diseases were 25% as compared to 8% of discharged patients ($p < 0.002$). During the hospital stay, other comorbidities were diagnosed: 16 consolidation / atelectasis, two acute otitis media, and two urinary tract infection (Table 1).

There was a peak in hospital admission rates during the fall season (46%), followed by winter (28%), spring (17%), and summer (9%) (Figure 2). RSV bronchiolitis showed annual peaks starting in the month of September, followed by October, November, December, and January. Non-RSV bronchiolitis hospital visits occurred throughout the year with peaks between the months of August till February (Figure 3).

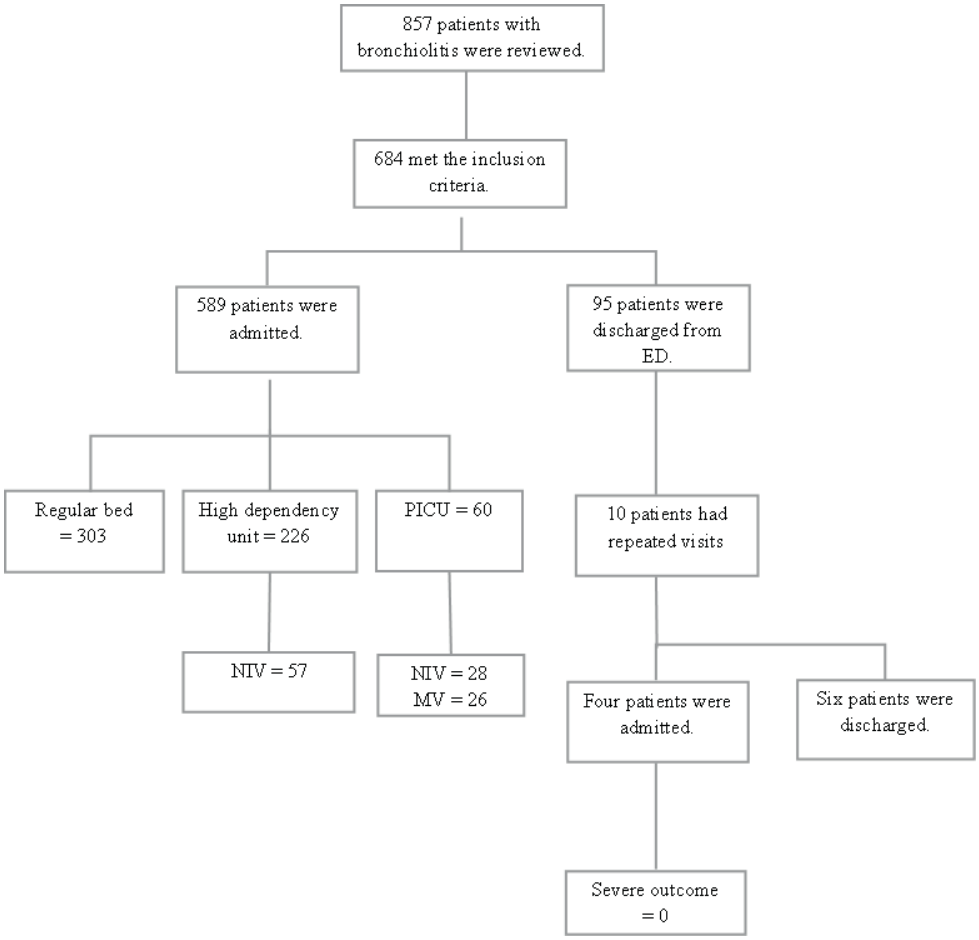

Figure 1. *Flow chart of the study population. ED = Emergency department; PICU = Pediatric intensive care unit; NIV = Non-invasive ventilation; MV = Mechanical ventilation.*

All children had respiratory viral panel screening and 91% were positive for at least one virus. Among the children with positive results, 67% had a single virus, 29% had a dual virus, and 4% had three viruses (Table 1). RSV was the most common pathogen causing (47.7%) total bronchiolitis cases, followed by RV (39.2%), adenovirus (14.5%), parainfluenza-3 (6.3%), enterovirus (3.4%), influenza A (3%), influenza B (2.6%), parainfluenza-4 (1.8%), H1N1 (1.4%), parechovirus (1%), and parainfluenza-2 (0.8%). In children <3 months of age, RSV (61%) and RV (46%) were the most common detected single viruses. In addition, dual virus infection (46%) was prevalent in <3-month-old children; however, triple virus infection (38%) was common in the age category between 7 and 12 months. Co-infection with dual (59%) and triple viruses (54%) had the highest incidence in males.

More than half of the admitted children received oxygen. They tended to have low mean oxygen saturation and high mean PCO_2 when compared to the discharged children, although not statistically significant. Majority of the hospitalized patients (96%) had a chest X-ray, of which 62% showed abnormal findings (bilateral infiltrates, symmetric hyperinflation, and diffuse interstitial markings) which were statistically significant ($p < 0.001$). CBC, CRP, and blood culture were carried out on 99%, 90%, and 87% of hospitalized children, respectively. High White blood count (WBC) (12.02 ± 4.98 *vs.* 6.08 ± 6.88; $p < 0.001$) and high CRP (21.26 ± 32.52 *vs.* 6.50 ± 15.39; $p < 0.001$) were observed in admitted children. Blood culture was positive in 2% of the cases. *Staphylococcus aureus* was the most common pathogen, followed by Gram-positive *Micrococcus*, *Kytococcus sedentarius*, and *Moraxella catarrhalis*, respectively (Table 2). Hospitalized children received a variety of respiratory and other treatments. The most commonly used treatments were intravenous hydration (90%), 3% hypertonic saline nebulization (70%), antibiotics (62%), systemic steroids (16%), and epinephrine nebulization (14%). Frequency of all these treatments remained high in sick children, who were admitted in both HDU and PICU when compared to discharged patients from emergency department (ED) ($p < 0.05$) (Table 1). Among the discharged patients, from both ward and ED, 10 patients revisited the ED. Out of them, four patients required admission and none of them had severe outcome.

Of the 589 children enrolled, 111 (19%) study subjects had clinically significant outcomes. Out of them, 85 (77%) received NIV in HDU and PICU, 15 (13%) were intubated due to severe respiratory distress and directly shifted to PICU for MV. Eleven (10%) infants who were initially admitted in HDU for NIV, later on experienced worsening respiratory distress, were transferred to PICU for escalated care. Average days of NIV and MV for sick hospitalized subjects were 4 and 5.92 days, respectively.

Table 1. *Demographics, underlying conditions, comorbidities, and management of the study population.*

Variables	Admission *n* = 589 (86%)	Discharge from ED *n* = 95 (14%)	*p*-value
Demographics			
Corrected GA (months)	5.08 ± 4.70	6.61 ±5.60	0.001
Mean ± SD			
Sex			
Male – *n* (%)	347 (59)	64 (67)	0.118
Underlying conditions –– no. (%)			
Prematurity	94 (16)	11 (11)	
<28 weeks	18 (03)	01 (01)	0.272
28–32 weeks	20 (03)	05 (05)	
33–36 weeks	56 (10)	05 (05)	
[a]Chronic diseases – no. (%)			
CHD	61 (10)	02 (02)	
CLD	45 (08)	03 (03)	
Immunodeficiency	07 (01)	01 (01)	0.002
Neurological disease	21 (04)	01 (01)	
Metabolic disorder	14 (02)	01 (01)	
Comorbidities –– no. (%)			
Consolidation/Atelectasis	16 (03)	00 (00)	0.104
Acute otitis media	02 (0.3)	01 (01)	0.329
Urinary tract infection	02 (0.3)	00 (00)	0.569
O_2 Saturation			0.133
Mean ± SD	92.17 ± 9.46	96.49 ± 2.81	
Investigations conducted –– *n* (%)			
NPA	589 (100)	95 (100)	
NPA +ve	531 (90)	89 (94)	
1 –– Virus	360 (68)	55 (62)	
2 –– Virus	147 (28)	32 (36)	
3 –– Virus	24 (04)	02 (02)	
X-ray chest	563 (96)	56 (59)	
[b]Abnormal findings	348 (62)	23 (41)	0.001
Blood gas	493 (84)	12 (13)	
PH – Mean ± SD	7.32 ± 0.05	7.33 ± 0.02	0.998
PCO_2 – Mean ± SD	45.16 ± 9.41	39.41 ± 5.23	0.998
CBC	587 (99)	48 (50)	
WBC – (cells/mm^3)	12.02 ± 4.98	6.08 ± 6.88	0.001
CRP	532 (90)	35 (37)	
CRP –– (mg/dl)	21.26 ± 32.52	6.50 ± 15.39	0.001
Blood culture	511 (87)	35 (37)	
Positive –– no. (%)	08 (02)	00	0.988
Treatment received			
0.9% Saline	237 (40)	26 (27)	0.017
Salbutamol	478 (81)	71 (75)	0.145
Atrovent	170 (29)	15 (16)	0.008
Epinephrine	80 (14)	01 (01)	0.001
3% Hypertonic saline	413 (70)	19 (20)	0.001
Antibiotics	364 (62)	06 (06)	0.001
Systemic steroids	93 (16)	00 (00)	0.001
IV Hydration	533 (90)	28 (29)	0.001

ED = Emergency department; GA = Gestational age; NPA = Nasopharyngeal aspirate; CBC = Complete blood count; WBC = White blood count; CRP = C-reactive protein; IV = Intravenous.

[a]Multiple patients had more than one comorbidity.

[b]Abnormal chest X-ray findings (bilateral infiltrates, symmetric hyperinflation, and diffuse interstitial markings). For some variables the sum is not equal to total *n* = 589; 95 due to laboratory work-up and chest X-ray were not conducted on these patients; respective % were computed based on available observations.

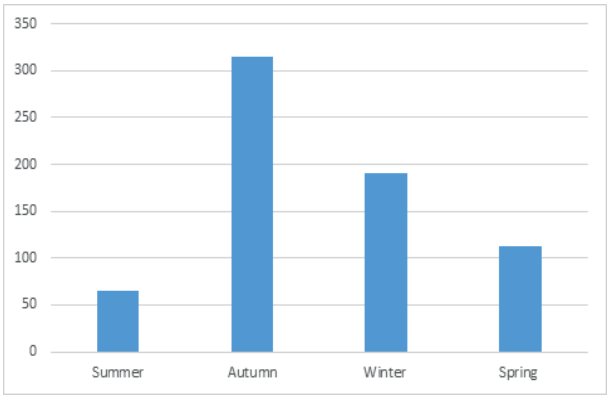

Figure 2. *Seasonal variation of bronchiolitis cases.*

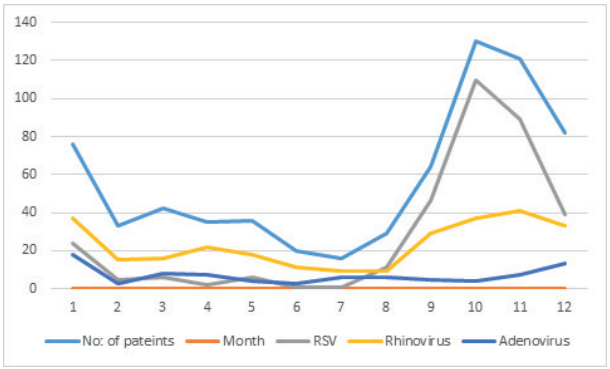

Figure 3. *Monthly trends of respiratory viruses with acute bronchiolitis cases.*

Table 2. *Bacterial co-infection in admitted acute bronchiolitis patients.*

Bacteria	PICU	HD	Ward
Staphylococcus aureus	–	1	3
Kytococcus sedentarius	–	–	1
Moraxella catarrhalis	–	1	–
G^{+ve} *Micrococcus*	1	–	1
	01	02	05

Patients with severe disease were younger than their counterparts (3.87 ± 3.42 *vs.* 5.37 ± 4.91 months), although not statistically significant. In this study population, there was no difference in sex and prematurity status between the two groups. Children with severe bronchiolitis had associated chronic disease (53% *vs.* 19%, $p < 0.050$), low O_2 saturation (84.9 *vs.* 93.8, $p < 0.001$), high PCO_2 (50.9 *vs.* 43.5, $p < 0.053$), high CRP (30.3 *vs.* 19.1, $p < 0.003$), abnormal chest X-ray findings (73% *vs.* 56%, $p < 0.001$), and prolonged length of stay in days (10.2 *vs.* 4.4, $p < 0.001$) when compared to the patients with less severe disease. There was no correlation between consolidation on chest X-ray (7 *vs.* 9, $p < 0.353$), white blood cell count (11.6 ± 4.4 *vs.* 12.1 ± 5.1, $p < 0.849$), and positive blood culture (3 *vs.* 5 $p < 0.546$) with disease severity. RSV was the most commonly detected 61 (55%) in infants with severe disease and more prevalent 47 (77%) in young infants <3 months of age (Table 3). Comparing RSV with non-RSV, RSV bronchiolitis subjects with positive outcome were younger (<3 months) in age ($p < 0.057$) than non-RSV bronchiolitis. The stepwise logistic regression analysis identified as variables independently associated with severe bronchiolitis were corrected GA (<3 months) (OR 1.84, 95% Cl 1.12-3.03 $p < 0.016$), chronic disease (OR 3.24, 95% Cl 1.79-5.86, $p < 0.000$), O_2 saturation (≤92%) (OR 4.12, 95% Cl 2.57-6.60, $p < 0.000$), CRP (≥20) (OR 1.86, 95% Cl 1.13-3.04, $p < 0.014$), PCO_2 (≥45) (OR 2.72, 95% Cl 1.67-4.45, $p < 0.000$), and abnormal chest X-ray findings (OR 1.88, 95% Cl 1.20-2.94, $p < 0.005$) (Table 4).

Discussion

This was a retrospective single-center study of children hospitalized with their first episode of bronchiolitis, and the outcomes intended by NIV and MV as indicators of severe disease. The risk of severe disease was more in infants, especially <3 months of age, and in those with underlying risk factors like prematurity, CHD, and CLD [20]. A high incidence of severe disease was found in young infants (<6 months of age) and premature children with mean corrected GA of 3.87 ± 3.42 months and other associated chronic diseases. These results are in line with the AAP-established risk factors [1]. Gender and previously healthy children were not associated with severe disease in the study population. Damore et al. [21] reported in their study that age <2 months was associated with ICU admission. However, other chronic medical conditions and prematurity were not correlated with ICU admission. In the present study, the children admitted to HDU and PICU were more likely to have age <6 months, more sick (in terms of low oxygen saturation on pulse oximeter and high PCO_2 on blood gas analysis), a history of prematurity, and other associated chronic diseases including CHD, bronchopulmonary dysplasia, and immunodeficiency with severe outcome. These observations were consistent with previously published studies [22,23]. As young kids have reduced lung compliance and higher airway resistance with impaired innate immunity, they may be predisposed to severe disease in the early months of life. Premature or low birth weight infants and children with CLD and CHD usually have abnormal base line oxygenation accompanied by an ability to manage the pulmonary inflammation observed in bronchiolitis.

There is a seasonal pattern of RSV, RV, and adenovirus. All are generally distributed throughout the year but peaks of RSV infection was found in fall and winter seasons in the present study. RSV remained consistent and more aggressive in infants comprising around half of the viruses detected overall and more prevalent in young infants <3 months of age with severe bronchiolitis. The present findings are in line with previous observations by Janahi et al. [24] and Al-Toum et al. [25], who respectively reported percentages of RSV in 51.2% and 27% of children admitted with bronchiolitis. These similarities in results may depend on the same geographical and seasonal patterns in those areas.

The use of diagnostic tests and other treatments in the management of bronchiolitis remains controversial and is not recommended in the revised AAP guidelines. In the present study, blood work-up was carried out for most of the patients. However, a high CRP value

Table 3. *Univariate correlation of variables for clinically significant outcomes for acute bronchiolitis cases.*

Variables	Positive outcomes *n* = 111 (19%)	Negative outcomes *n* = 478 (81%)	*p*-value
Corrected GA			
Mean ± SD	3.87 ± 3.42	5.37 ± 4.91	0.647
Sex			
Male –– no. (%)	68 (61)	279 (58)	0.379
Prematurity	29 (26)	65 (14)	0.626
Chronic diseases — no. (%)			
CHD	24 (22)	37 (08)	0.050
CLD	21 (19)	24 (05)	
Immunodeficiency	01 (01)	06 (01)	
Neurological disorder	08 (07)	13 (03)	
Metabolic disorder	05 (04)	09 (02)	
Consolidation	07 (06)	09 (02)	0.353
O_2 Saturation			
Mean ± SD	84.9 ± 14.9	93.8 ± 6.6	0.001
PH - Mean ± SD	7.30 ± 0.07	7.33 ± 0.04	0.458
PCO_2 - Mean ± SD	50.9 ± 12.1	43.5 ± 7.8	0.053
WBC – (cells/mm^3)	11.6 ± 4.4	12.1 ± 5.1	0.849
CRP –– (mg/dl)	30.33 ± 42.69	19.15 ± 29.32	0.003
Blood culture (+ve)	03	05	0.546
≠Abnormal CXR findings — *n* (%)	81 (73)	267 (56)	0.001
LOS – Mean ± SD	10.2 ± 11.08	4.4 ± 2.3	0.001

NIV = Non-invasive ventilation, MV = Mechanical ventilation, GA = Gestational age, CHD = Congenital heart disease, CLD = Chronic lung disease, CXR = Chest X-ray,
≠ = Abnormal chest X-ray findings (bilateral infiltrates, symmetric hyperinflation and diffuse interstitial markings), LOS = Length of stay in days
p-value < 0.05 is statistically significant.

Table 4. *Stepwise logistic regression analysis to predict clinically significant outcomes from acute bronchiolitis cases.*

Variables	OR (95% CI)	*p*-value
Corrected GA < 3 months	1.84 (1.12–3.03)	0.016
Chronic disease	3.24 (1.79–5.86)	0.000
O_2 Saturation ≤92	4.12 (2.57–6.60)	0.000
CRP ≥20	1.86 (1.13–3.04)	0.014
PCO_2 ≥45	2.72 (1.67–4.45)	0.000
≠Abnormal CXR findings	1.88 (1.20–2.94)	0.005

OR = Odds Ratio; CI = Confidence interval; CXR = Chest X-ray, ≠ = Abnormal chest x-ary findings (bilateral infiltrates, symmetric hyperinflation and diffuse interstitial markings).
p-value < 0.05 is statistically significant.

was found in severely ill children and was statistically significant and associated with severe outcome. This observation may reveal some proof that bacterial co-infection may provoke the clinical course of children with bronchiolitis. Wiegers et al. [26] reported that bacterial co-infection occurred in approximately one-third of mechanically ventilated children and was associated with the prolonged need of MV and PICU stay. The presence of associated bacterial co-infections in sick hospitalized subjects were not associated with a longer length of stay or severe outcome in the present cases. The literature did not support the widespread use of chest X-rays in bronchiolitis but reports demonstrated a significant rate of chest radiographs in children with this viral infection [27]. Consolidation/atelectasis was associated with increase in oxygen need and hospital length of stay in both RSV and non-RSV bronchiolitis cases, and increased the risk of severe disease [28]. Christakis et al.'s [29] study reported that the use of chest X-ray is an independent predictor of antibiotic use. In the present observation, radiographic findings did characterize disease severity and were correlated with severe outcome.

Bronchiolitis-associated deaths occurred in two patients with non-RSV bronchiolitis (0.33%); a similar result was published in Spain earlier [30]. Of the two deaths, one was an adenovirus-positive 11-month-old patient, former 25-weeks GA male with corrected age 8 months, a birth weight of 630 g, and current weight of 5.58 kg. Had underlying CHD and CLD on presentation, had respiratory distress with low oxygen saturation, and required MV; died on day 17 of admission in PICU. Another death occurred on day 5 of admission in a RV and influenza A virus-positive in 2-month-old male infant, ex-preterm 34-weeks GA with birth weight of 2.1 kg, and current weight of 3.4 kg. The patient had a previous history of respiratory distress syndrome and necrotizing enterocolitis during neonatal intensive care unit stay.

Viral and bacterial tests were carried out on almost all children and RSV was the most common virus; concomitant bacterial infection was low when compared with a Gambian study which reported that 3.5% of RSV-positive subjects had bacterial co-infection [31]. This study has limitations. First, it is a retrospective study. Secondly, the study was carried out at a single tertiary care hospital and, therefore, may not be generalizable to other institutions.

Conclusion

This study identified six variables as predictors of severe bronchiolitis in the study population. The younger and sicker children with associated comorbidities are more likely to have severe outcome. Future work is required to replicate the present results and expand other risk factors such as vital signs prospectively.

List of abbreviations

AAP	American Academy of Pediatrics
CHD	Congenital heart disease
CLD	Chronic lung disease
MV	Mechanical ventilation
NIV	Non-invasive ventilation
PICU	Pediatric intensive care unit
RSV	Respiratory syncytial virus
RV	Rhinovirus

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

No consent was taken as this is a retrospective review study.

Ethical approval

Ethical approval was granted by Ethics Committee Sultan Qaboos University Hospital, College of Medicine and Health Science via reference SQU-EC/253/17 dated: 28/12/2017.

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