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INPLASY

Risk Factors for Bronchiolitis Obliterans Following Adenovirus Pneumonia in Children: A Systematic Review and Meta-Analysis

INPLASY2026110107
doi: 10.37766/inplasy2026.11.0107
Received: 26 November 2026
Published: 26 November 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026110107

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 November 2026 and was last updated on 26 November 2026.

INTRODUCTION

Review question / Objective To systematically evaluate the risk factors for BO following AVP in children. The study aims to systematically search and integrate primary research on risk factors for BO secondary to AVP in children using a systematic review and meta-analysis approach, and to quantitatively summarize multidimensional clinical data—demographic characteristics, clinical manifestations, laboratory indicators, and treatment-related factors—to reveal their comprehensive impact on the occurrence of BO, resolve existing academic controversies regarding certain predictors, and provide a more robust evidence-based foundation for clinicians to identify high-risk individuals and formulate precision early intervention strategies.

Condition being studied Condition being studied: Bronchiolitis obliterans (BO) following adenovirus pneumonia (AVP) in children.

Human adenovirus (HAdV) is a leading viral pathogen of community-acquired pneumonia (CAP) in children worldwide, accounting for approximately 4%–10% of pediatric viral pneumonia hospitalizations. HAdV is characterized by high tissue invasiveness, particularly serotypes HAdV-3, HAdV-7, and the recently emergent HAdV-55, which frequently cause severe lower respiratory tract infections, leading to severe AVP. Compared with other respiratory viruses such as respiratory syncytial virus (RSV) or influenza, patients with AVP often experience more intense cytokine storms, more persistent febrile courses, and more extensive pulmonary parenchymal damage. Despite advances in acute-phase clinical rescue techniques, children with AVP often face serious long-term chronic pulmonary sequelae after recovery.

BO represents the most catastrophic chronic outcome following severe AVP. As a chronic obstructive lung disease, its pathological essence lies in the abnormal repair of the airway epithelium

following inflammatory injury, resulting in fibrotic narrowing or total obliteration of the small airways. AVP has been recognized as the primary driver of post-infectious bronchiolitis obliterans (PIBO). Statistics suggest that approximately 30% to 60% of children with severe AVP progress to BO within months of discharge, presenting with persistent wheezing, tachypnea, and obstructive ventilatory dysfunction on pulmonary function tests. Once BO develops, children often face irreversible lung development impairment and lifelong disability, imposing a heavy long-term burden on families and social healthcare systems.

In the included studies, the diagnosis of BO must have met recognized clinical criteria (e.g., persistent wheezing, decreased exercise tolerance, and high-resolution CT showing mosaic perfusion, bronchial wall thickening, or bronchiectasis) after excluding other chronic lung diseases. The reported incidence of BO across studies showed significant heterogeneity, ranging from 2.57% to 78%, which may be attributed to differences in inclusion criteria, follow-up duration, and the virulence of adenovirus epidemic strains across centers.

The condition is studied in relation to risk factors during the acute phase of AVP, including demographic characteristics, clinical manifestations, laboratory indicators, and treatment-related factors, because early identification of high-risk individuals is important for implementing preventive interventions and reducing disability rates.

METHODS

Participant or population The review addresses children aged 14 years or younger diagnosed with adenovirus pneumonia (AVP) in the acute phase. Diagnosis of adenovirus infection must have been confirmed by viral isolation and culture, antigen detection, or polymerase chain reaction (PCR). The participants are children with AVP among whom the occurrence of bronchiolitis obliterans (BO) is explicitly reported as the outcome.

Studies were excluded if BO was caused by non-adenoviral factors (e.g., lung transplantation, bone marrow transplantation, inhalational injury, or other pathogens) without a specific subgroup analysis for AVP.

In the included studies, the population comprised 3,844 children with AVP across 13 cohort studies, with individual sample sizes ranging from 66 to 863. The subjects were primarily infants and young children, with ages mostly distributed between 6 months and 3 years. A significant male predominance was observed, with the proportion of males fluctuating between 52.00% and 78.60%. Eleven studies were conducted in China, with one study each from Argentina and South Korea. The reported incidence of BO across studies ranged from 2.57% to 78%.

Intervention This review did not evaluate a specific therapeutic intervention for bronchiolitis obliterans (BO). Instead, it evaluated treatment-related factors as exposures/risk factors for BO following adenovirus pneumonia (AVP) in children. The manuscript states that included studies investigated risk factors including "therapeutic interventions," and the treatment-related factors specifically analyzed were:

Glucocorticoid use — pooled OR = 4.69 (95% CI: 2.57–8.59), with extremely low heterogeneity (I^2 = 0.0%, P = 0.942).

Mechanical ventilation — pooled OR = 4.33 (95% CI: 2.08–9.03), with high heterogeneity (I^2 = 91.0%).

The manuscript also notes that the introduction addressed "acute-phase interventions (such as the timing of glucocorticoid administration and the necessity of mechanical ventilation)" and that glucocorticoid use was positively correlated with BO risk, which the authors interpreted as more likely reflecting "selection bias" in clinical decision-making rather than directly implicating steroids as a causative factor.

Comparator The manuscript does not specify a comparator group or a comparative intervention applied to the target population. This is a systematic review and meta-analysis of risk factors for bronchiolitis obliterans (BO) following adenovirus pneumonia (AVP) in children, based on observational studies (prospective or retrospective cohort studies, case-control studies, and cross-sectional studies). The included studies investigated risk factors associated with BO secondary to AVP and provided effect size measures such as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI), or sufficient raw data to reconstruct these statistics. No intervention-versus-control comparison is defined in the manuscript; therefore, a comparator is not applicable.

Study designs to be included Peer-reviewed, published observational studies, including prospective or retrospective cohort studies, case-

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control studies, and cross-sectional studies, without language restrictions. In the review, the 13 included observational studies were all cohort studies.

Eligibility criteria Inclusion criteria (developed based on the PICOS framework):

1. Population: Children aged 14 years or younger diagnosed with AVP in the acute phase. Diagnosis of adenovirus infection must have been confirmed by viral isolation and culture, antigen detection, or polymerase chain reaction (PCR).

2. Exposures: Studies investigating risk factors associated with BO secondary to AVP, including demographic characteristics, clinical manifestations (e.g., duration of high fever, wheezing), laboratory markers (e.g., lactate dehydrogenase, cytokines), radiographic features, or therapeutic interventions.

3. Outcomes: Studies that explicitly reported the occurrence of BO. The diagnosis of BO must have met recognized clinical criteria (e.g., persistent wheezing, decreased exercise tolerance, and high-resolution CT showing mosaic perfusion, bronchial wall thickening, or bronchiectasis) after excluding other chronic lung diseases.

4. Data Requirements: Studies providing effect size measures for risk factors, such as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI), or providing sufficient raw data to reconstruct these statistics.

5. Study Design: Peer-reviewed, published observational studies, including prospective or retrospective cohort studies, case-control studies, and cross-sectional studies, without language restrictions.

Exclusion criteria:

1. Non-adenoviral Factors: Studies where BO was caused by non-adenoviral factors (e.g., lung transplantation, bone marrow transplantation, inhalational injury, or other pathogens) without a specific subgroup analysis for AVP.

2. Data Quality: Studies with missing raw data, logical inconsistencies, or where complete data could not be obtained after contacting the authors.

3. Duplicate Publications: For studies based on the same study population and observation period, only the most comprehensive report or the one with the largest sample size was included.

Information sources Electronic databases searched: PubMed, Web of Science, the Cochrane Library, and Embase.

Search period: from the inception of each database to April 15, 2026.

Search approach: a combination of Medical Subject Headings (MeSH) and free-text terms; core search terms were developed around the concepts of “Adenovirus” and “Bronchiolitis Obliterans,” with synonyms and related terms linked using “OR” within each core concept and the concepts combined using “AND”.

Language restrictions: none were applied during the search process.

Additional sources: the reference lists of included studies and relevant systematic reviews were manually screened to identify potentially eligible studies that may have been missed.

Contact with authors: for studies with missing or poorly reported data, attempts were made to contact the authors for supplementary information; studies were excluded if the required data remained unavailable.

Other: detailed search strategies for each database are provided in the Supplementary File.

Main outcome(s) The main outcome of the review was the occurrence of bronchiolitis obliterans (BO) following adenovirus pneumonia (AVP) in children. Included studies had to explicitly report the occurrence of BO, and the diagnosis of BO must have met recognized clinical criteria (e.g., persistent wheezing, decreased exercise tolerance, and high-resolution CT showing mosaic perfusion, bronchial wall thickening, or bronchiectasis) after excluding other chronic lung diseases.

The review quantitatively summarized the association between risk factors and BO using odds ratios (OR) with 95% confidence intervals (CI). The main pooled outcomes reported were:

1. Significant risk factors: dyspnea (OR = 7.36, 95% CI: 4.05–13.35), glucocorticoid use (OR = 4.69, 95% CI: 2.57–8.59), mechanical ventilation (OR = 4.33, 95% CI: 2.08–9.03), complications (OR = 2.83, 95% CI: 1.71–4.67), co-infection (OR = 2.65, 95% CI: 1.43–4.91), duration of fever (OR = 1.16, 95% CI: 1.10–1.23), and length of hospital stay (OR = 1.32, 95% CI: 1.15–1.50).

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2. Protective factor: elevated serum albumin level (OR = 0.88, 95% CI: 0.83–0.94).

3. No significant statistical association: age (OR = 0.99), lactate dehydrogenase (OR = 1.00), creatine kinase-MB (OR = 1.01), and hemoglobin levels (OR = 0.98).

Timing: The manuscript does not specify a uniform outcome timing; follow-up duration for BO ranged from weeks to years post-discharge across studies.

Quality assessment / Risk of bias analysis The methodological quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies across eight items in three categories: representativeness of the study population, comparability of the groups, and adequacy of outcome assessment or follow-up. The maximum score is 9 points. Studies with a total score of ≥7 were categorized as high-quality, while those with a score <4 were considered low-quality.

In the review, NOS scores of the 13 included studies ranged from 6 to 9; high-quality studies (score ≥7) accounted for 92.3% (12/13), with only one study receiving a score of 6. In the selection dimension, all studies exhibited a low risk of bias regarding representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure. In the comparability dimension, 38.5% (5/13) of studies successfully adjusted for key confounders—such as age, sex, and disease severity—through multivariate regression analysis, achieving a full score; the remaining studies ensured basic demographic consistency but had room for improvement in adjusting for deeper potential confounders. In the outcome dimension, the majority of studies (84.6%) established rigorous imaging diagnostic criteria and ensured adequate follow-up duration to accurately capture outcome events; only a few studies provided limited descriptions regarding the definition of the outcome-free state at the start of the study or blinding of the assessment.

Strategy of data synthesis Statistical analyses were performed using Stata software. For categorical data, effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (CI).

Heterogeneity among studies was assessed using the I^2 statistic and the Q test:

If I^2 0.1, studies were considered homogeneous, and a fixed-effects model was applied.

If $I^2 \geq 50\%$ or $P \leq 0.1$, significant heterogeneity was assumed, and a random-effects model was employed.

A leave-one-out sensitivity analysis was performed for outcomes involving five or more studies to evaluate the influence of individual studies on the pooled results and to verify the robustness of the findings.

Publication bias was assessed using Egger's and Begg's tests, supplemented by visual inspection of funnel plots.

Unless otherwise specified, the significance level was set at $\alpha = 0.05$.

Subgroup analysis The manuscript does not report any subgroup analysis. No subgroup analyses by region, adenovirus serotype, age, diagnostic modality, follow-up duration, or other factors were described. The only related analyses reported were leave-one-out sensitivity analyses for indicators included in five or more studies (duration of fever, length of hospital stay, co-infection, mechanical ventilation, LDH, and age), along with publication bias assessment using Begg's and Egger's tests and funnel plots.

Sensitivity analysis Given the statistical heterogeneity observed in some evaluation indicators, sensitivity analyses were performed for indicators included in five or more studies to evaluate the robustness of the meta-analysis results and explore the influence of individual studies on the pooled effect sizes. These included:

duration of fever

length of hospital stay

co-infection

mechanical ventilation

LDH

age

Results using the leave-one-out method showed that after sequentially excluding individual studies, the point estimates of the re-pooled effect sizes for all aforementioned indicators did not shift substantially, and their 95% CIs consistently covered the original comprehensive effect size

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estimates. More importantly, the exclusion of any single study did not alter the statistical significance of the results. These observations strongly demonstrate that the meta-analysis conclusions for the primary indicators are not highly sensitive to individual studies, indicating stable and reliable results even in the presence of some heterogeneity.

Country(ies) involved China.

Keywords Adenovirus pneumonia; Bronchiolitis obliterans; Children; Risk factors.

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