Article

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A Multivariable Prediction Model and Bedside Score for Death or Bronchiolitis Obliterans in Pediatric Severe Adenovirus Pneumonia

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Background: Severe adenovirus pneumonia (SAP) in children is associated with both in-hospital mortality and long-term respiratory sequelae, particularly bronchiolitis obliterans (BO). However, most previous studies have focused on single biomarkers or single clinical endpoints, limiting integrated prognostic assessment. This study aimed to develop and internally validate a multivariable prediction model for a composite adverse outcome of in-hospital death or BO in pediatric SAP.

Methods: This single-center, retrospective, patient-level integrated analysis included 90 unique children with SAP after cross-study deduplication and eligibility screening of three partially overlapping source cohorts. The primary outcome was a composite of in-hospital death or BO. Candidate predictors were screened using least absolute shrinkage and selection operator regression with 10-fold cross-validation, followed by multivariable logistic regression and backward elimination based on the Akaike information criterion. Model performance was assessed by discrimination, calibration, decision curve analysis, and bootstrap internal validation. A simplified bedside risk score was subsequently derived from the final model.

Results: The composite adverse outcome occurred in 21 of 90 children (23.3%), including 13 in-hospital deaths and 8 cases of BO. Five predictors were retained in the final model: an increase in the neutrophil-to-lymphocyte ratio from baseline to the treatment-intensive phase ($p = 0.001$), systemic immune-inflammation index of 1500 or greater during the treatment-intensive phase ($p = 0.007$), higher treatment-intensive-phase lactate dehydrogenase ($p = 0.011$), longer total fever duration ($p = 0.039$), and bacterial co-infection ($p = 0.038$). The apparent area under the receiver operating characteristic curve was 0.887, and the bootstrap-corrected value was 0.845. The derived bedside score stratified patients into low-, intermediate-, and high-risk groups, with observed event rates of 4.2%, 25.0%, and 85.7%, respectively.

Conclusion: In this single-center retrospective integrated analysis, a multivariable model incorporating dynamic inflammatory change, fever burden, tissue injury, and bacterial co-infection showed promising internally validated discrimination for the composite outcome of in-hospital death or BO in children with SAP. The derived bedside score should be regarded as a hypothesis-generating tool for internal risk stratification, and external validation is required before clinical implementation.

Keywords: human adenovirus infections; viral pneumonia; bronchiolitis obliterans; prognosis; risk assessment; biomarkers

Introduction

Human adenovirus is a major pediatric respiratory pathogen capable of causing a broad spectrum of illness, from self-limited upper respiratory infection to severe pneumonia with respiratory failure, systemic complications, and death [1]. In children, severe adenovirus pneumonia (SAP) is clinically important not only because of acute in-hospital deterioration but also because of its association with long-term respiratory sequelae, particularly post-infectious bronchiolitis obliterans (PIBO) [2,3,4]. Recent reviews have emphasized that SAP continues to pose substantial challenges in early recognition, prognostic assessment, and management — in part because no universally effective antiviral therapy has been established and treatment remains largely supportive and complication-oriented [1]. Cohort data have further documented considerable rates of severe disease and subsequent respiratory morbidity, with bronchiolitis obliterans among the most consequential chronic sequelae [2,4].

Growing attention has been directed toward identifying clinical and laboratory markers that may help stratify risk in children with adenoviral pneumonia [1,5,6]. Published studies have linked poor outcomes to prolonged fever, hypoxemia, mechanical ventilation, low albumin, elevated inflammatory indices, and biochemical evidence of tissue injury, including increased lactate dehydroge-

nase (LDH) [1,5,6,7,8]. A recent meta-analysis found that elevated pre-treatment LDH was associated with severe adenoviral pneumonia, PIBO development, and in-hospital mortality [7]. Predictive tools have also begun to emerge: nomogram-based models have been proposed for SAP severity [9,10], for PIBO after severe adenoviral pneumonia [11], and for BO development in children with SAP [12] — collectively indicating that prognostic modeling in this field is both feasible and clinically relevant.

Several gaps, however, persist in the current literature. First, most existing studies have focused on a single endpoint — such as severe versus non-severe pneumonia, in-hospital mortality, or PIBO/BO alone — rather than a broader adverse outcome spectrum capturing both acute fatal events and major chronic sequelae [5,8,9,10,11,12]. Second, many studies have relied on isolated biomarkers or relatively simple prediction frameworks that may not fully reflect the multifactorial nature of SAP progression [7,13,14,15]. Third, PubMed-indexed reports identified in our review still largely model SAP severity or BO separately rather than integrating these outcomes into a unified prognostic framework [9,10,11,12]. Taken together, these considerations point to a need for a more comprehensive model that moves beyond single-marker or single-outcome analyses and better reflects the real clinical burden of SAP.

Against this background, we conducted a single-center, retrospective, patient-level integrated re-analysis of three partially overlapping exploratory cohorts of children with SAP. After cross-study deduplication and harmonization of predictor definitions and observation windows, we aimed to develop and internally validate a multivariable prediction model for a composite adverse outcome of in-hospital death or bronchiolitis obliterans. This study focused on a composite endpoint that captures both acute fatal events and major chronic respiratory sequelae. It also incorporated dynamic inflammatory change rather than relying solely on baseline markers, thereby addressing the gap left by prior single-outcome exploratory studies.

Methods

Study Design and Reporting Framework

This study was a single-center, retrospective, patient-level integrated secondary cohort analysis for prognostic model development and internal validation. The analysis integrated partially overlapping individual-patient datasets generated by the same clinical team at the Hebei Children's Hospital, Shijiazhuang, Hebei, China, over the period from January 2017 to June 2023. The study aimed to develop and internally validate a multivariable prediction model for a composite adverse outcome of in-hospital death or BO in children with SAP. Reporting was aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.

Source Studies, Data Integration, and Deduplication

The integrated cohort was derived from three prior retrospective source studies conducted at the same center. These studies respectively examined dynamic neutrophil-to-lymphocyte ratio (NLR) and biochemical indices in SAP, blood routine-derived inflammatory indices for BO development, and NLR combined with biochemical indices in critically ill children with adenovirus pneumonia. They addressed related but non-identical questions and had partially overlapping recruitment periods and patient populations.

To construct the integrated analytic cohort, all source records were cross-linked before analysis to identify potential patient overlaps. Deduplication was performed primarily using the medical record number, with confirmation based on patient name, date of birth, and admission date. Where overlap was identified, source charts were reviewed and the most complete unique patient-level record was retained. The pooled source dataset initially contained 105 records; after removal of 5 duplicates, 100 unique patients remained. Application of the final eligibility criteria excluded 10 additional patients, yielding a final analytic cohort of 90 unique children. For transparency, the relationship between the three source studies and the current integrated analysis is summarized in **Supplementary Table 1**, including study period, sample size, primary outcome, key assessment window, overlap context, and the analytic contribution of the present manuscript. The final exclusion breakdown was as follows: hospital stay <72 hours (n = 3); severely incomplete records or missing key baseline data (n = 2); no eligible treatment-intensive reassessment within the prespecified days 4–10 window (n = 3); pre-existing BO at admission (n = 1). One additional patient was excluded because of a concurrent condition requiring urgent surgical intervention unrelated to SAP (n = 1).

Study Population

Eligible patients were children aged 1 month to 18 years who met the institutional diagnostic criteria for SAP. Inclusion required: (1) virologic confirmation of adenovirus infection in respiratory specimens by molecular testing; (2) clinical and radiologic evidence of pneumonia; and (3) fulfillment of at least one severe-disease criterion, such as persistent high fever, respiratory distress, hypoxemia, rapid radiologic progression, or major systemic complications. Patients were excluded if they met any of the exclusion conditions described above. Because this study comprised a retrospective integrated cohort of all eligible unique patients available during the study period, no formal a priori sample size calculation was performed.

Data Collection and Candidate Predictors

Clinical, laboratory, and outcome data were extracted retrospectively from the source datasets and, where necessary, verified against the original medical records.

Baseline variables included demographic characteristics, underlying disease status, pre-admission clinical course, admission symptoms and signs, adenovirus type 7 status when available, infection characteristics, hematologic markers, inflammatory markers, and organ-injury indicators. Derived inflammatory indices included the NLR, platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). NLR was calculated as neutrophil count divided by lymphocyte count; PLR as platelet count divided by lymphocyte count; and SII as platelet count × neutrophil count divided by lymphocyte count.

Three assessment windows were prespecified to capture baseline status and dynamic changes during treatment. Baseline was defined as data obtained within 24 hours of admission. The treatment-intensive phase was defined as days 5–9 after treatment initiation, with day 7 as the anchor time point; if day-7 data were unavailable, the closest available reassessment value within days 4–10 was used. Dynamic-change variables were derived from baseline and intensive-phase values, including ΔNLR, defined as intensive-phase NLR minus baseline NLR.

A total of 26 prespecified candidate predictors were entered into the initial LASSO screening stage, but the complete variable-level candidate list could not be fully reconstructed from the available documentation. Accordingly, **Supplementary Table 2** is provided as a transparency-oriented reconstructed summary of the candidate predictor set recoverable from the current integrated analysis and the three overlapping source studies; it should not be interpreted as a verbatim reproduction of the original analytic input matrix. Any discrepancy between **Supplementary Table 2** and the original analytic input matrix should be resolved in favor of the original analytic code, if available.

Definitions of Key Clinical Variables

Bacterial co-infection was defined using an integrated adjudication framework based on the source records, given the retrospective nature of the study and potential variability in documentation across source datasets. Cases were classified as positive when clinically relevant bacterial pathogens were documented by culture and/or PCR testing during hospitalization, or when the treating team recorded bacterial co-infection on the basis of compatible clinical, laboratory, and radiologic findings together with antibacterial treatment escalation. This combined microbiologic-and-clinical approach was adopted to reflect real-world retrospective pediatric respiratory-infection adjudication across source datasets.

Adenovirus type 7 status was extracted from the source records and, when available, had been determined using real-time PCR-based typing assays performed on documented institutional platforms within the source datasets.

Laboratory and Diagnostic Procedures

Across the source datasets, complete blood count (CBC) testing, serum biochemical assays, molecular respiratory pathogen testing, high-resolution chest CT (HRCT), and pulmonary function testing were performed using diagnostic systems commonly used at the study center across the source-study periods. CBC testing was conducted using hematology analyzer systems, and biochemical measurements, including C-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and albumin, were performed on automated biochemistry analyzer systems. Adenovirus infection was confirmed using molecular testing workflows that included multiplex RT-PCR-based methods. HRCT examinations were obtained using multidetector chest CT systems. Pulmonary function testing, when applicable for BO evaluation, was performed using standard pediatric pulmonary function systems. Because this study was a retrospective integrated reanalysis of partially overlapping source cohorts spanning multiple years, exact instrument models may have varied across study periods; these descriptions therefore refer to commonly used testing systems across the source datasets rather than implying a single fixed platform for all patients.

Standard Treatment Categories

During the treatment-intensive phase, "standard treatment" referred to the routine inpatient management categories used for SAP at the study center, including antiviral therapy, respiratory support and supportive care, immunomodulatory therapy when clinically indicated, and antibacterial therapy for documented or suspected bacterial co-infection. Treatment was reported at the level of broad clinical categories because a fully standardized patient-level regimen map could not be reconstructed retrospectively across the overlapping source datasets. This conservative approach is consistent with current pediatric adenovirus pneumonia reviews, which describe management primarily in terms of major treatment classes rather than a single universally standardized regimen [1].

Outcome Definitions and Ascertainment

The primary outcome was a composite adverse endpoint defined as in-hospital death or bronchiolitis obliterans (BO).

In-hospital mortality was defined as all-cause death during the index hospitalization for SAP.

BO ascertainment was based on post-discharge follow-up records available in the source datasets; a fully standardized follow-up schedule could not be reconstructed retrospectively. BO diagnosis required a prior SAP episode together with persistent or recurrent respiratory symptoms following the acute infection and supportive objective evidence on HRCT and/or pulmonary function testing, consistent with published pediatric post-infectious bronchiolitis obliterans criteria [3]. HRCT evidence was considered

supportive when the records documented findings compatible with small-airway obstruction, such as mosaic attenuation/perfusion, air trapping, bronchial wall thickening, or bronchiectatic changes. Pulmonary function evidence, when available, was considered supportive when persistent obstructive ventilatory impairment or small-airway dysfunction was documented. Formal blinded outcome adjudication was not implemented in this retrospective integrated analysis.

For patients diagnosed with BO, the interval from the index SAP episode to BO diagnosis was extracted from available follow-up records and summarized as median and range.

Model Development and Internal Validation

This study was designed as a prognostic model development analysis. Candidate predictors were prespecified based on cross-study availability, clinical relevance, and consistency with the integrated clinical framework. Initial variable screening was performed using least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation. Variables with non-zero coefficients were subsequently entered into a multivariable logistic regression model, and backward elimination based on the AIC was applied to derive a parsimonious final model. The threshold for intensive-phase SII was determined using maximally selected rank statistics. The final regression model was then translated into a simplified integer-based bedside score by scaling retained regression coefficients relative to the smallest retained coefficient and rounding the resulting values to clinically interpretable integer points, consistent with standard approaches for developing simplified clinical prediction scores from regression-based prognostic models [16,17]. The category boundaries for ΔNLR, intensive-phase LDH, and total fever duration were selected to simplify bedside point assignment and should not be interpreted as independently validated biological cutoffs. Risk strata were subsequently defined according to the distribution of total scores and the observed event rates in this derivation cohort; these strata were considered exploratory derivation-cohort classifications pending external validation, in accordance with transparent prediction-model reporting principles [16,17].

Statistical Analysis

All statistical analyses were performed using R software, version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range) for non-normally distributed data and as mean ± standard deviation when appropriate. Between-group comparisons were performed using the chi-square test or Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables that did not satisfy distributional assumptions. In Table 1, the corresponding test statistic was reported as χ^2 for chi-square tests and U for Mann-Whitney U tests; Fisher exact tests were labeled as such when used because no χ^2 statistic was generated. All tests were two-sided, and p values < 0.05 were considered statistically significant. Effect estimates are reported with 95% confidence intervals where applicable.

Model discrimination was assessed using the area under the receiver operating characteristic curve, in line with standard reporting for prediction-model studies [16]. Calibration was evaluated visually with a calibration plot and statistically with the Hosmer-Lemeshow goodness-of-fit test [18]. Clinical utility was examined using decision curve analysis [19]. Internal validation was performed using 1000 bootstrap resamples to estimate optimism and derive a bootstrap-corrected area under the receiver operating characteristic curve [17]. Records with severely incomplete baseline information were excluded during cohort integration, and the final model was fitted using a complete-case approach; no imputation procedures were applied. Because this was a prognostic model development study and no formal multiplicity adjustment was prespecified for secondary or exploratory analyses, such findings were interpreted cautiously with attention to the potential for type I error.

Results

Study Population and Participant Flow

The integrated dataset initially comprised 105 patient records derived from three partially overlapping source studies. After cross-study deduplication, 100 unique patients remained. Application of the predefined eligibility criteria excluded 10 additional patients, leaving 90 unique children with severe adenovirus pneumonia in the final analytic cohort (Fig. 1). The composite adverse outcome — in-hospital death or bronchiolitis obliterans — occurred in 21 of 90 patients (23.3%), comprising 13 deaths and 8 BO cases. Among the 8 patients diagnosed with BO, the median interval from the index SAP episode to BO diagnosis was 4.0 months (range, 2–9 months). These counts reflect the final deduplicated analytic cohort after application of the integrated eligibility criteria and should not be interpreted as direct carryovers from any single source study, given the overlapping patient populations and differing primary outcomes across source studies.

Baseline Characteristics

Baseline demographic, clinical, and laboratory characteristics are summarized in Table 1, stratified by composite outcome (adverse vs. favorable). The overall cohort had a median age of 144 months (IQR, 96–180), and 55 patients (61.1%) were male. This age distribution reflects the final post-deduplication integrated analytic cohort rather than any individual source cohort. After recalculation of all between-group tests using the prespeci-

Table 1. Demographic and baseline clinical characteristics of the study cohort.

Characteristic	Overall cohort (n = 90)	Composite adverse outcome (n = 21)	Favorable outcome (n = 69)	Test statistic	*p* value
Demographics					
Age, months, median (IQR)	144 (96, 180)	132 (96, 168)	144 (96, 192)	U = 639	0.412
Male sex, n (%)	55 (61.1)	15 (71.4)	40 (58.0)	χ^2 = 1.227	0.268
Comorbidities					
Any underlying disease, n (%)	33 (36.7)	9 (42.9)	24 (34.8)	χ^2 = 0.452	0.501
Clinical presentation at admission					
Fever duration before admission, days, median (IQR)	7.0 (4.0, 10.0)	8.0 (6.0, 10.0)	6.0 (4.0, 10.0)	U = 551	0.097
Peak temperature, °C, median (IQR)	39.6 (39.2, 40.0)	39.7 (39.4, 40.0)	39.5 (39.1, 39.9)	U = 600	0.235
Hypoxia sign, n (%)	89 (98.9)	21 (100.0)	68 (98.6)	Fisher exact	1.000
Wheezing, n (%)	84 (93.3)	20 (95.2)	64 (92.8)	Fisher exact	1.000
Baseline laboratory values, median (IQR)					
White blood cell count, $\times 10^9$/L	11.6 (9.2, 14.8)	10.6 (7.9, 13.4)	11.9 (9.6, 15.5)	U = 586	0.186
Neutrophil count, $\times 10^9$/L	7.0 (4.8, 9.6)	6.5 (4.8, 9.6)	7.0 (4.9, 9.6)	U = 696	0.788
Lymphocyte count, $\times 10^9$/L	3.5 (2.6, 4.7)	3.0 (1.9, 4.1)	3.7 (2.8, 4.9)	U = 506	0.037
Baseline inflammatory indices, median (IQR)					
Neutrophil-to-lymphocyte ratio (NLR)	2.07 (1.38, 3.24)	2.71 (1.65, 4.70)	1.95 (1.35, 2.99)	U = 540	0.078
Platelet-to-lymphocyte ratio (PLR)	143.6 (107.0, 232.5)	163.8 (118.0, 263.3)	138.2 (105.4, 218.6)	U = 614	0.293
Systemic immune-inflammation index (SII)	815.5 (502.8, 1380.8)	1059.8 (589.2, 1806.0)	760.0 (490.0, 1242.0)	U = 574	0.151
C-reactive protein, mg/L	10.3 (2.1, 31.1)	17.5 (4.0, 55.9)	9.1 (1.9, 26.1)	U = 546	0.088
Organ injury markers, median (IQR)					
Lactate dehydrogenase, U/L	434.5 (344.8, 599.0)	548.0 (393.0, 865.0)	422.0 (338.0, 562.0)	U = 515	0.046
Aspartate aminotransferase, U/L	37.0 (25.0, 55.8)	46.0 (31.0, 80.0)	34.0 (24.0, 50.0)	U = 511	0.042
Albumin, g/L	39.9 (35.7, 44.0)	36.6 (32.5, 39.9)	41.0 (37.0, 44.7)	U = 423	0.004
Infection characteristics					
Adenovirus type 7, n (%)	55 (61.1)	14 (66.7)	41 (59.4)	χ^2 = 0.356	0.551
Bacterial co-infection, n (%)	53 (58.9)	14 (66.7)	39 (56.5)	χ^2 = 0.684	0.408

Notes: Continuous variables were compared using the Mann-Whitney U test and are reported with the U statistic. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate; χ^2 values are reported when the chi-square test was used, whereas Fisher exact test is indicated when applicable. The composite adverse outcome was defined as in-hospital death or bronchiolitis obliterans.
Abbreviations: IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

fied methods shown in Table 1, patients with the composite adverse outcome had significantly lower baseline lymphocyte counts (p = 0.037), higher lactate dehydrogenase levels (p = 0.046), higher aspartate aminotransferase levels (p = 0.042), and lower albumin levels (p = 0.004). No statistically significant between-group differences were observed for age (p = 0.412), sex (p = 0.268), underlying disease (p = 0.501), pre-admission fever duration (p = 0.097), peak temperature (p = 0.235), hypoxia sign (p = 1.000), wheezing (p = 1.000), white blood cell count (p = 0.186), neutrophil count (p = 0.788), adenovirus type 7 status (p = 0.551), bacterial co-infection (p = 0.408), baseline NLR (p = 0.078), PLR (p = 0.293), SII (p = 0.151), or CRP (p = 0.088).

Predictor Selection and Final Model Development

Among 26 prespecified candidate predictors, LASSO regression with 10-fold cross-validation retained 8 variables with non-zero coefficients, which were subsequently entered into multivariable logistic regression. Backward elimination based on the AIC yielded a final parsimonious model containing 5 independent predictors (Table 2, Ref. [16,17,18,19]). In the final model, a greater increase in NLR from baseline to the treatment-intensive phase (ΔNLR) was associated with a higher risk of the composite adverse outcome (adjusted odds ratio [aOR], 1.52 per unit increase; 95% CI, 1.18–1.95; p = 0.001). Other independent predictors included intensive-phase SII ≥1500 (aOR, 6.40;

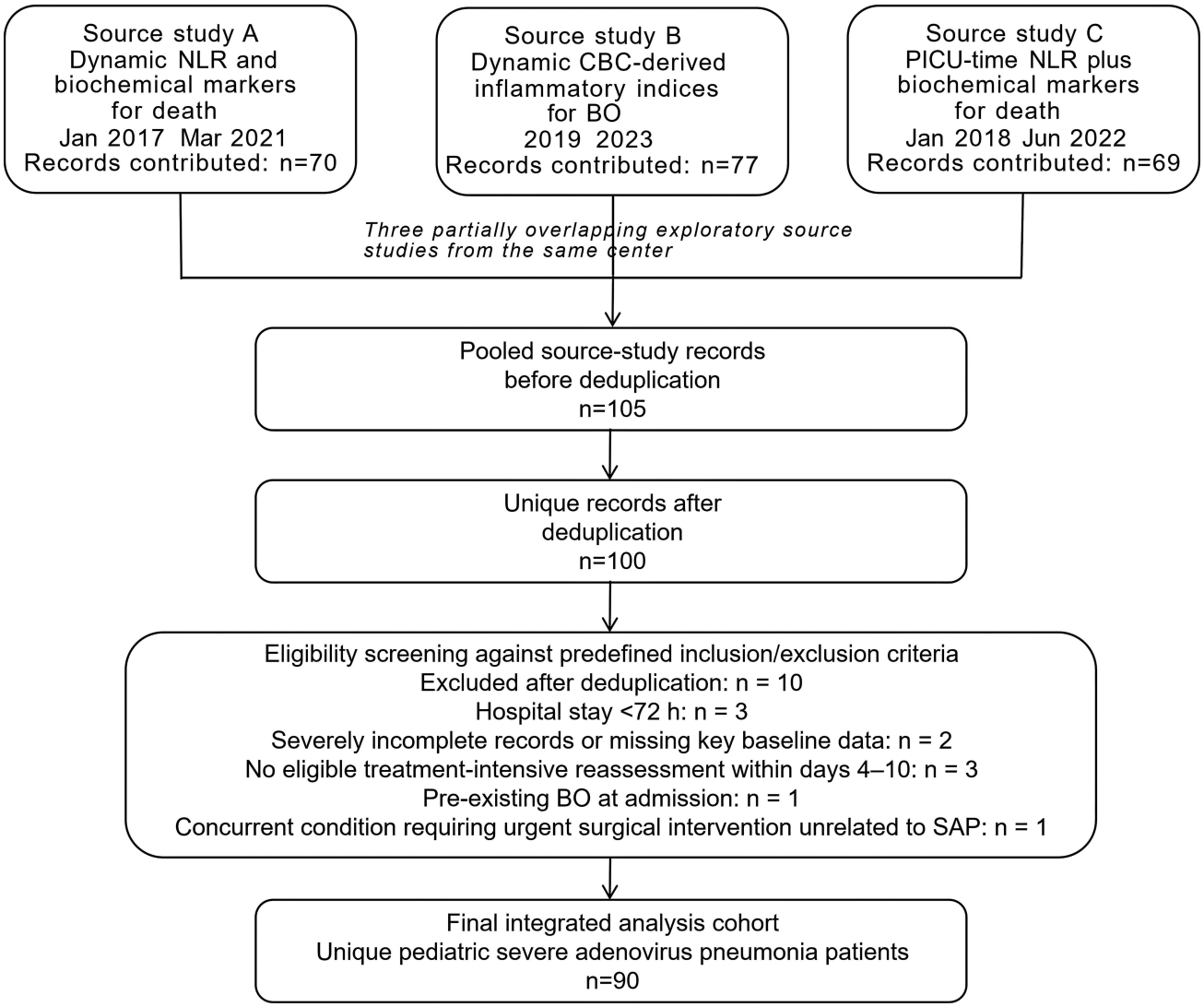

Fig. 1. Flow diagram of source-study integration, cross-study deduplication, eligibility screening, and final cohort assembly. The figure also identifies the three partially overlapping source studies contributing to the pooled dataset before deduplication.

95% CI, 1.65–24.84; p = 0.007), higher intensive-phase LDH per 100 U/L increase (aOR, 1.23; 95% CI, 1.05–1.44; p = 0.011), and longer total fever duration per day (aOR, 1.11; 95% CI, 1.01–1.23; p = 0.039). Bacterial co-infection was also independently associated with the composite adverse outcome (aOR, 4.15; 95% CI, 1.08–15.97; p = 0.038). No meaningful multicollinearity was detected, with all variance inflation factors <2.5.

Model Performance and Internal Validation

Model performance metrics are summarized in Table 3. The apparent discriminative performance of the final model is shown in Fig. 2A, with an AUC of 0.887 (95% CI, 0.815–0.959). Internal validation using 1000 bootstrap resamples yielded a bootstrap-corrected AUC of 0.845 (95% CI, 0.756–0.934), corresponding to an optimism estimate of 0.042. Calibration is shown in Fig. 2B; the Hosmer–Lemeshow test was non-significant (χ^2 = 6.24, df = 8; p = 0.620), indicating acceptable calibration. Decision curve analysis suggested net clinical benefit across threshold probabilities of approximately 10% to 60% (Fig. 2C).

Development and Performance of the Clinical Risk Score

To facilitate exploratory bedside risk stratification, the final regression model was converted into a simplified integer-based scoring system ranging from 0 to 19 points (Table 4, Ref. [16,17]). Point values were derived from the relative magnitude of the retained regression coefficients after scaling and rounding. Higher-risk categories were assigned for larger ΔNLR, intensive-phase SII ≥1500, higher intensive-phase LDH, longer total fever duration, and bacterial co-infection; except for the SII threshold, these category boundaries were used to simplify point assignment rather than to define independently validated biologic cut-

Table 2. Multivariable logistic regression model for predicting the composite adverse outcome.

Predictor	β coefficient	Adjusted OR	95% CI	*p* value
Intercept	–5.892	—	—	<0.001
ΔNLR (intensive phase − baseline)	0.417	1.52	1.18–1.95	0.001
Intensive-phase SII (≥1500 vs <1500)	1.856	6.40	1.65–24.84	0.007
Intensive-phase LDH, per 100 U/L increase	0.205	1.23	1.05–1.44	0.011
Total fever duration, per day increase	0.108	1.11	1.01–1.23	0.039
Bacterial co-infection (yes vs no)	1.424	4.15	1.08–15.97	0.038

Notes: The SII cutoff of 1500 was determined using maximally selected rank statistics. Model performance metrics were reported according to standard prediction-model methodology: discrimination by AUC, calibration by calibration plot and the Hosmer-Lemeshow test, internal validation by bootstrap resampling, and clinical utility by decision curve analysis [16,17,18,19]. All variance inflation factors were <2.5.

Abbreviations: OR, odds ratio; CI, confidence interval; ΔNLR, change in neutrophil-to-lymphocyte ratio from baseline to treatment-intensive phase; SII, systemic immune-inflammation index; LDH, lactate dehydrogenase; AUC, area under the receiver operating characteristic curve.

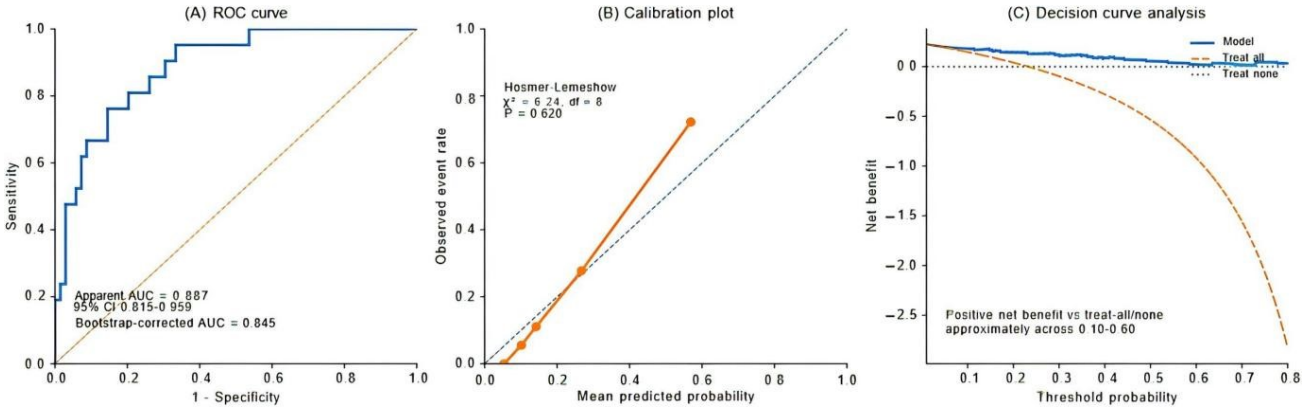

Fig. 2. Performance of the multivariable prediction model. (A) Receiver operating characteristic curve. (B) Calibration plot. (C) Decision curve analysis.

Table 3. Model performance metrics.

Metric	Value
Apparent AUC (95% CI)	0.887 (0.815–0.959)
Bootstrap-corrected AUC (95% CI)	0.845 (0.756–0.934)
Optimism	0.042
Hosmer-Lemeshow test	$\chi^2 = 6.24$, df = 8; $p = 0.620$

Notes: Model discrimination was assessed using AUC, and internal validation was performed using 1000 bootstrap resamples. Calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; df, degrees of freedom.

offs. Based on the score distribution and observed event rates in this derivation cohort, patients were exploratorily stratified into low-risk (0–4 points), intermediate-risk (5–9 points), and high-risk (≥10 points) groups. Observed composite adverse outcome rates increased markedly across these strata: 4.2% (2/48) in the low-risk group, 25.0% (7/28) in the intermediate-risk group, and 85.7% (12/14) in the high-risk group (Table 5). The total score retained strong discriminatory ability, with an AUC of 0.872 (95% CI, 0.792–0.953). Using the Youden index, the optimal cutoff was ≥5 points, yielding a sensitivity of 90.5% and a specificity of 73.9%.

Discussion

This study presents a single-center, patient-level integrated re-analysis of three partially overlapping exploratory cohorts of children with SAP, conducted after cross-study deduplication and harmonization of predictor definitions and observation windows. Among 90 unique patients, the composite adverse outcome of in-hospital death or BO occurred in 21 patients (23.3%). The final multivariable model included five predictors: the change in NLR from baseline to the treatment-intensive phase (ΔNLR), intensive-phase SII ≥1500, intensive-phase LDH per 100 U/L increase, total fever duration per day, and bacterial co-infection. It showed good apparent and internally validated discrimination, with an apparent AUC of 0.887, a bootstrap-corrected AUC of 0.845, and a Hosmer–Lemeshow *p* value

Table 4. Simplified clinical risk scoring system for predicting the composite adverse outcome.

Predictor	Category	Points
ΔNLR	<1.0	0
	1.0–2.9	2
	≥3.0	4
Intensive-phase SII	<1500	0
	≥1500	6
Intensive-phase LDH	<400 U/L	0
	400–799 U/L	1
	≥800 U/L	3
Total fever duration	<7 days	0
	7–13 days	1
	≥14 days	2
Bacterial co-infection	No	0
	Yes	4
Total score range		0–19

Notes: Point values were derived from scaled and rounded β coefficients of the final logistic regression model, consistent with standard regression coefficient-based approaches for simplified clinical prediction score development [16,17]. Except for the intensive-phase SII threshold determined using maximally selected rank statistics, category boundaries were selected for bedside interpretability and require external validation.

Abbreviations: ΔNLR, change in neutrophil-to-lymphocyte ratio from baseline to treatment-intensive phase; SII, systemic immune-inflammation index; LDH, lactate dehydrogenase.

of 0.620. A simplified integer-based bedside score derived from the model yielded an AUC of 0.872 and delineated three risk strata with markedly distinct composite adverse outcome rates: 4.2%, 25.0%, and 85.7% for low-, intermediate-, and high-risk groups, respectively. The present study should therefore be interpreted as an integrated, hypothesis-generating secondary analysis that extends prior single-outcome exploratory reports through patient-level deduplication, outcome harmonization, and multivariable model development with internal validation, rather than as evidence supporting immediate clinical deployment.

The dynamic trajectory of NLR from admission to the treatment-intensive phase was independently associated with the composite adverse outcome. In contrast, baseline NLR alone showed only a non-significant trend. A sustained or rising NLR during this window was associated with a higher probability of the composite adverse outcome in the present cohort. This pattern is consistent with an expanding literature demonstrating that serial or dynamic NLR measurements may provide superior prognostic information relative to single-timepoint assessments [13,14]. Lee et al. [13], in a retrospective study of 175 hospitalized community-acquired pneumonia patients, found that an incrementally rising NLR from admission to day 4 (NLR D4/D1 >1) was a stronger predictor of 30-day mortality than admission NLR alone, and that this incremental change significantly improved the prognostic utility of the Pneumonia Severity Index. A systematic review by Kuikel et al. [14] further confirmed that NLR is a simple, accessible, and consistently predictive marker of adverse outcomes in community-acquired pneumonia across diverse patient populations. In the present pediatric SAP cohort, NLR trajectory across the first week of treatment was independently associated with the composite endpoint encompassing in-hospital mortality and post-infectious BO.

Among the five retained predictors, intensive-phase SII ≥1500 carried the largest adjusted odds ratio, underscoring the potential prognostic relevance of this composite inflammatory index when measured at the treatment-intensive phase [15]. The SII — calculated as platelet count multiplied by neutrophil count, divided by lymphocyte count — integrates thrombocyte activation, innate immune effector burden, and adaptive immune suppression into a single measure that may capture a broader pathophysiological signal than either NLR or PLR alone [15]. Wang et al. [15] reported that SII predicted severe Mycoplasma pneumoniae pneumonia in 304 hospitalized children with an AUC of 0.883, outperforming NLR, PLR, and the systemic inflammation response index. The high odds ratio for SII ≥1500 in the present analysis warrants attention; however, the wide confidence interval (1.65–24.84) and the limited number of composite outcome events (n = 21; approximately 4.2 events per final-model predictor) indicate substantial uncertainty and a risk of overfitting. This estimate therefore requires confirmation in larger external cohorts before any firm conclusions can be drawn.

The independent association between intensive-phase LDH and the composite adverse outcome is consistent with published evidence linking elevated LDH to disease severity, mortality risk, and post-infectious BO in adenoviral pneumonia [1,7]. A meta-analysis by Zou et al. [7], incorporating 23 studies and 4481 children, found that elevated pre-treatment LDH was significantly associated with severe versus non-severe adenoviral pneumonia and was additionally associated with PIBO development and in-hospital mortality. In the present analysis, LDH assessed during the treatment-intensive phase (days 5–9) was independently associated with the composite adverse outcome after multivariable adjustment. Persistently elevated LDH beyond the early admission window may reflect ongoing disease burden in this cohort, though the underlying processes cannot be determined from the available data. Notably, baseline LDH also differed significantly between outcome groups in the unadjusted analysis, reinforcing LDH as a marker that tracks disease burden across multiple time points — a pattern consistent with the observation by Zhang et al. [1] of a positive correlation between LDH and SAP severity.

Table 5. Risk stratification and outcome rates based on the clinical score.

Risk category	Total Score	Patients, n (%)	Composite Adverse Outcome, n	Event Rate, %
Low risk	0–4	48 (53.3)	2	4.2
Intermediate risk	5–9	28 (31.1)	7	25.0
High risk	≥10	14 (15.6)	12	85.7
Total	—	90 (100.0)	21	23.3

Notes: Risk strata were defined in the derivation cohort according to the distribution of total scores and observed event rates and should be interpreted as exploratory pending external validation. Performance of the score: AUC, 0.872 (95% CI, 0.792–0.953). The optimal cutoff determined by the Youden index was ≥5 points, yielding a sensitivity of 90.5% and a specificity of 73.9%.

Bacterial co-infection remained an independent predictor of the composite adverse outcome after multivariable adjustment [5,8]. Notably, the crude comparison of bacterial co-infection rates between outcome groups did not reach statistical significance, a discrepancy that may reflect residual confounding by severity-related covariates in the unadjusted analysis, the small cohort size, and the retrospective composite adjudication approach. Following multivariable adjustment, however, bacterial co-infection was statistically associated with the composite adverse outcome after accounting for inflammatory markers and fever duration. Prior evidence supports this direction: a three-year retrospective pediatric intensive care unit (PICU) series from Shanghai found that co-infection and nosocomial infection were independent predictors of hospital mortality (16.42%) in children with adenovirus pneumonia admitted for acute hypoxemic respiratory failure [8]. A larger single-center study of 189 SAP cases documented bacterial co-infection in approximately one-third of patients, with co-infected individuals demonstrating greater multi-system involvement [5]. These findings may inform how bacterial co-infection is weighted within risk assessment frameworks for children with SAP, though they do not constitute evidence for a specific management strategy.

The association between longer total fever duration and the composite adverse outcome is consistent with prior observations that prolonged fever may mark a more complicated clinical course in adenovirus pneumonia [6]. Wang et al. [6] similarly identified fever duration as a significant risk factor for severe adenovirus pneumonia in a retrospective study of 202 children. In the context of the composite outcome, prolonged fever may reflect greater illness burden rather than a defined causal pathway to either component outcome. Jerkic et al. [3] and Li et al. [4] have outlined the pathological cascade by which severe lower respiratory tract infections in children can lead to BO, with unresolved airway inflammation proposed as a central mechanism,. The inclusion of total fever duration as a clinically measurable, zero-cost variable in the bedside scoring system represents a practical aspect of the model.

Several candidate predictors did not reach statistical significance and were excluded from the final model. Baseline NLR, CRP, and pre-admission fever duration all showed directionally consistent trends without achieving conventional significance, likely reflecting limited statistical power in a cohort of 90 patients with 21 events. Adenovirus type 7 status was not a significant predictor, which may partly reflect its high prevalence in this cohort (61.1%), limiting discriminatory capacity at this distribution. Age and sex did not contribute significantly to risk prediction in this cohort — in contrast to some prior studies reporting younger age as a mortality risk factor in SAP — though the relatively older median age (144 months) and retrospective integrated design of the present analysis constrain direct comparison. The non-significance of these variables does not negate their potential biological relevance in other SAP populations; it indicates only that they did not add independent predictive value within this dataset, beyond the five retained predictors.

The predictors retained in the present score also overlap with several classic clinical indicators previously associated with severe adenoviral pneumonia and adverse outcomes, including prolonged fever, biochemical evidence of tissue injury such as elevated LDH, and bacterial co-infection [1,5,6,7,8]. However, the present model differs from approaches based solely on static baseline indicators by incorporating ΔNLR, which reflects the inflammatory trajectory from admission to the treatment-intensive phase. Thus, the score should not be viewed as replacing established severity indicators; rather, it combines conventional clinical markers with a dynamic inflammatory measure within a unified exploratory prediction framework.

Several prediction models have previously been developed for pediatric adenoviral pneumonia, but most have focused on single clinical targets, such as SAP severity or post-infectious BO, rather than a composite outcome spanning both acute mortality and chronic respiratory sequelae [9,10,11,12]. For example, Shen et al. [9] developed a LASSO-based nomogram for SAP severity in 145 pediatric patients, and Liang et al. [10] constructed a prediction model for SAP using Ridge and multiple logistic regression,. Peng et al. [11] developed a nomogram for post-infectious BO after adenoviral pneumonia following invasive mechanical ventilation, and Xiao et al. [12] reported a model for BO development in children with SAP,. In contrast, the present study used a composite endpoint of in-

hospital death or BO and incorporated ΔNLR as a dynamic inflammatory indicator, together with intensive-phase SII, LDH, total fever duration, and bacterial co-infection. This combination may provide an incremental framework for capturing both acute deterioration and longer-term airway sequelae, although this potential advantage remains exploratory and requires external validation in multicenter cohorts. Decision curve analysis suggested net benefit across threshold probabilities from approximately 10% to 60%; however, this finding should be interpreted as preliminary because the model has undergone internal validation only and has not yet been tested in an independent external cohort.

These findings carry implications for future research on risk stratification in children hospitalized with SAP, though the strength of those implications must be calibrated to the limitations of the present study. The observed event rates across score-defined strata demonstrate substantial risk heterogeneity within this cohort; however, these subgroup estimates should be interpreted cautiously given the modest sample size and require external confirmation. For patients in the intermediate-score range, the present findings may support closer outcome monitoring in future validation studies, but they do not establish a specific post-discharge surveillance protocol. Although the ≥5-point cutoff showed high sensitivity in this cohort, a score below this threshold should not be interpreted as excluding clinically meaningful risk. These observations are framed as hypothesis-generating inferences from the available data and are not intended to constitute prescriptive treatment algorithms; systematic application of the score in clinical practice should await external validation.

This study carries several important limitations. First, the analytic cohort of 90 patients with 21 composite adverse outcome events is modest. With five predictors retained in the final model, the effective events-per-predictor ratio was approximately 4.2. This limited event count constrains the stability of multivariable coefficient estimates and reduces the effective degrees of freedom available for model fitting. It also increases the possibility of residual overfitting, as reflected in the wide confidence interval for intensive-phase SII ≥1500 [20]. Descriptive features reported here, including the age distribution and number of BO events, reflect the final post-deduplication, post-eligibility integrated dataset and should not be interpreted as simple aggregates of the partially overlapping source studies. Although internal validation using 1000 bootstrap resamples was employed to estimate and correct for optimism (observed optimism: 0.042), internal validation cannot substitute for external validation in an independent cohort, and the score should be considered hypothesis-generating until validated in larger multicenter datasets. Second, this was a single-center retrospective integrated re-analysis of three partially overlapping source studies, introducing inherent heterogeneity in data collection practices, treatment protocols, and follow-up procedures. The ascertainment of bacterial co-infection relied on a combined microbiologic-and-clinical framework that could not be standardized across source datasets. BO ascertainment depended on post-discharge follow-up records without a standardized follow-up schedule or formal blinded adjudication. This may have introduced ascertainment bias and variability in the timing and sensitivity of BO detection. Third, missing data were managed using complete-case analysis without imputation, which could introduce selection bias if data were not missing completely at random. Fourth, the cohort is drawn from a single Chinese tertiary pediatric center, and the observed predictor effect sizes and score performance may not generalize to younger children, immunocompromised populations, or settings with materially different adenovirus serotype distributions or healthcare infrastructure. Fifth, the candidate predictor list in **Supplementary Table 2** was reconstructed from available documentation rather than recovered from the original variable-level modeling codebook; it should therefore be interpreted as a transparency aid and may not represent a verbatim reproduction of the original analytic input matrix.

Future research should prioritize multicenter prospective external validation of the five-predictor model and derived bedside score, with pre-specified, standardized BO follow-up protocols to ensure consistent outcome ascertainment. Larger cohorts would also permit investigation of potential effect modification by adenovirus genotype, patient age subgroup, and immunomodulatory treatment category — none of which could be definitively addressed in the current analysis. Whether earlier or later reassessment time points within hospitalization provide comparable or superior predictive utility relative to the days 5–9 treatment-intensive phase deserves prospective evaluation. Incorporation of viral load quantification, imaging severity metrics, or cytokine profiles into future prediction frameworks may further refine risk stratification beyond what hematologic and biochemical variables alone can provide.

Conclusion

In this single-center retrospective integrated analysis, dynamic inflammatory change during the treatment-intensive phase, together with fever burden, tissue-injury markers, and bacterial co-infection, was associated with the risk of in-hospital death or bronchiolitis obliterans in children with severe adenovirus pneumonia. A parsimonious five-predictor model and its derived bedside score demonstrated promising internally validated discrimination and stratified patients into clinically distinct risk groups within this cohort. These findings support the hypothesis that dynamic risk assessment may be useful for future risk-stratification research in pediatric severe adenovirus pneumonia, but the model should not be used for routine clinical decision-making until externally validated in larger multicenter cohorts.

Availability of Data and Materials

The datasets analyzed during the current study are not publicly available due to containing potentially identifiable clinical information but are available from the corresponding author on reasonable request.

Author Contributions

WH and MY contributed to the conception and design of the study and drafted the manuscript. LYT was responsible for study implementation and feasibility assessment, supervised the overall study. XYS and MZ contributed to data collection and data curation. WH performed the statistical analysis. WG contributed to data interpretation. All authors have been involved in revising it critically for important intellectual content. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This integrated secondary analysis was approved by the Ethics Committee of Hebei Children's Hospital (Approval No. 161). Because this study involved the retrospective integration and re-analysis of existing clinical datasets, the requirement for written informed consent was waived. All procedures were conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638210.178.

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