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Factors Associated with Open Thoracic Surgery in Children with Pleural Effusion: A Retrospective Observational Study

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Abstract

Background: Pleural effusion may complicate pediatric respiratory disease and occasionally necessitate open thoracic surgery despite medical or minimally invasive management. Evidence regarding clinical and biochemical characteristics specifically associated with open thoracic surgery in children remains limited.

Objectives: To identify demographic, clinical, imaging, laboratory, and preadmission medication factors associated with open thoracic surgery in hospitalized children with pleural effusion.

Methods: This retrospective observational study included children older than 1 month and younger than 18 years who were treated for pleural effusion at Zahra Mardani Azari Children's Hospital, Tabriz, Iran, between March 2023 and March 2024. The primary outcome was open thoracic surgery, defined as thoracotomy with decortication, segmentectomy, or lobectomy. The comparison group included children managed without open thoracic surgery. Between-group comparisons and logistic regression were used to examine associations, which are reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Of the 83 children, 34 (41.0%) underwent open thoracic surgery and 49 (59.0%) did not. Severe imaging-assessed pleural effusion was more common in the open thoracic surgery group (55.9% vs. 28.6%; P = 0.024), and hospitalization was longer (19.1 ± 11.0 vs. 12.9 ± 5.3 days; P < 0.001). Pleural-fluid total protein and lactate dehydrogenase levels were higher, whereas glucose levels were lower, in the open thoracic surgery group (all P < 0.001). In the reported adjusted analyses, pleural-fluid total protein (adjusted OR 4.30 per 1 g/dL increase; 95% CI 1.90 - 9.60), glucose (aOR 0.32 per 10 mg/dL increase; 95% CI 0.19 - 0.54), ibuprofen exposure (aOR 3.39; 95% CI 1.09 - 10.52), and diclofenac exposure (aOR 4.41; 95% CI 1.12 - 17.33) were associated with open thoracic surgery.

Conclusions: Pleural-fluid biochemical characteristics and preadmission nonsteroidal anti-inflammatory drug exposure were associated with open thoracic surgery in this retrospective cohort. These findings are exploratory, do not establish causation or clinical surgical thresholds, and should not be used as a stand-alone prediction rule.

Keywords: Pleural Effusion, Child, Thoracotomy, Risk Factors, Biomarkers, Anti-Inflammatory Agents, Non-Steroidal

1. Background

Pleural effusion (PE) is an important complication of pediatric respiratory disease, particularly pneumonia, and may progress to complicated parapneumonic effusion or empyema, resulting in prolonged hospitalization and invasive treatment (1-3). Contemporary pediatric management follows a stepwise approach based on clinical severity, respiratory compromise, and the complexity of pleural disease. Small, uncomplicated effusions can often be managed without invasive drainage, whereas larger or complicated collections may require chest-tube drainage, intrapleural fibrinolytic therapy, or video-assisted

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thoracoscopic surgery (VATS). Open thoracic surgery is generally considered in selected patients with extensive or refractory pleural disease (4-7). Recent research has also examined the effectiveness and complications of small-bore chest drains for managing pleural disorders, supporting the broader role of minimally invasive drainage techniques; however, evidence from adult populations should not be directly extrapolated to children (8).

Clinical presentation, imaging findings, treatment response, and pleural-fluid characteristics contribute to the assessment of disease severity (9, 10). Thoracic ultrasonography and computed tomography provide complementary information about pleural-fluid characteristics and associated thoracic abnormalities. Recent research has examined their diagnostic utility in differentiating exudative from transudative effusions, although these findings are not specific to pediatric surgical decision-making (11). In children, ultrasonography is particularly useful for evaluating the extent and complexity of parapneumonic effusions, whereas computed tomography is generally reserved for selected clinical situations (4). Pleural-fluid glucose, lactate dehydrogenase (LDH), protein, and inflammatory markers may provide additional information about pleural inflammation and disease severity (12-14). Nevertheless, evidence specifically addressing factors associated with escalation to open thoracic surgery in children remains limited (15-17).

Therefore, this study aimed to identify demographic, clinical, imaging, laboratory, and preadmission medication factors associated with open thoracic surgery among children hospitalized with PE.

2. Objectives

The primary objective was to identify demographic, clinical, imaging, laboratory, and preadmission medication factors associated with open thoracic surgery in children with PE.

3. Methods

3.1. Study Design and Reporting

This retrospective observational study was based on the medical records of children with PE treated at Zahra Mardani Azari Children's Hospital in Tabriz, Iran, from March 2023 to March 2024. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (18).

3.2. Sample Size and Sampling

The study used total-enumeration sampling and included all eligible patients treated during the predefined study period. The minimum sample size was initially estimated to be 80 patients using Power and Sample Size software. The final sample comprised 83 eligible patients: 34 who underwent open thoracic surgery and 49 who did not.

3.3. Study Population

Children were eligible if they were older than 1 month and younger than 18 years, had a confirmed diagnosis of PE documented in the medical record, and had sufficiently complete clinical information for inclusion. Patients were excluded if their clinical records were incomplete, if they had lung or chest-wall malignancy, if they were receiving immunosuppressive therapy, or if they had a congenital immunodeficiency disorder.

These exclusion criteria were applied to reduce clinical heterogeneity because pleural effusions occurring in the setting of malignancy or significant immunosuppression may differ from those in the study population in their underlying mechanisms, clinical courses, and treatment requirements.

Pleural effusion was defined as the presence of fluid within the pleural space, as documented in the patients' medical records and supported by chest imaging. The diagnosis was established during routine clinical care using chest radiography, thoracic ultrasonography, and/or computed tomography, according to the available diagnostic information. Clinical and laboratory findings, including microbiological results and pleural-fluid biochemical characteristics when available, were considered when evaluating the underlying pleural disease.

During the study period, 127 patient records were assessed for eligibility. Of these, 44 were excluded because of incomplete clinical records (n = 26), lung or chest-wall malignancy (n = 6), immunosuppressive treatment (n = 8), or congenital immunodeficiency (n = 4). After the eligibility criteria were applied, 83 children were included in the final analysis, of whom 34 underwent open thoracic surgery and 49 were managed without open thoracic surgery.

3.4. Outcome Definition

The primary outcome was undergoing open thoracic surgery during the index hospitalization. Open thoracic surgery was defined as decortication, segmentectomy, or lobectomy performed through an open thoracotomy.

Patients were classified according to whether they underwent open thoracic surgery at any point during hospitalization, irrespective of preceding nonoperative or minimally invasive interventions. The comparison group comprised children who did not undergo open thoracic surgery, including those managed with medical treatment, chest-tube drainage, and/or VATS.

Management options included medical treatment, chest-tube drainage, VATS, and open thoracic surgery. In accordance with established pediatric management principles, treatment selection generally depends on the patient's clinical condition, respiratory compromise, the extent and complexity of pleural involvement, and response to initial treatment. Small, uncomplicated effusions can often be managed medically, whereas larger or complicated collections may require pleural drainage. Surgical intervention may be considered in selected patients with persistent pleural collections and ongoing clinical compromise despite less invasive management, as well as in those with extensive organized pleural disease or associated pulmonary complications (2, 7). In the present study, treatment escalation was determined during routine clinical care rather than according to predefined study-specific thresholds.

3.5. Data Collection and Variables

Data were retrospectively extracted from medical records using a predesigned collection form. Variables included demographic characteristics, underlying diseases, presenting symptoms, PE severity, duration of hospitalization, preadmission medication exposure, laboratory and pleural-fluid findings, microbiological results, and treatments received.

Preadmission medication exposure was assessed retrospectively using information documented in the patients' medical records. Exposure was defined as documented use of acetaminophen, ibuprofen, or diclofenac during the 7 days preceding hospital admission. In the statistical analyses, each medication was evaluated as a separate categorical variable according to documented exposure status. The analyses focused on the association between preadmission medication use and subsequent open thoracic surgery rather than on dose-dependent or treatment-duration effects.

Pleural-fluid biochemical findings, including total protein, glucose, and LDH, were extracted from available laboratory records. Pleural-fluid testing was considered part of the routine clinical evaluation of children with pleural effusion. The treating clinical team decided whether to obtain pleural-fluid samples according to the patient's clinical presentation and diagnostic or therapeutic requirements. Laboratory measurements were evaluated in relation to the primary outcome of open thoracic surgery.

Pleural effusion severity was recorded as mild, moderate, or severe according to the classifications documented in the clinical records and available imaging reports. Chest radiography, thoracic ultrasonography, and computed tomography were among the imaging modalities considered during routine clinical assessment. Because the study was retrospective, severity categories were extracted from existing documentation rather than assigned using a prospectively standardized research scoring system.

Pleural disease was evaluated in the context of the underlying clinical diagnosis. Parapneumonic effusion was considered pleural-fluid accumulation associated with pneumonia. Uncomplicated parapneumonic effusion refers to a typically sterile, free-flowing collection without substantial pleural infection, whereas complicated parapneumonic effusion is associated with pleural infection or marked inflammatory changes. Empyema refers to the accumulation of purulent fluid in the pleural space. Where documented, microbiological findings, pleural-fluid biochemical characteristics, and imaging features were extracted to characterize pleural disease.

3.6. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23. Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed variables are presented as mean ± standard deviation, and non-normally distributed variables are presented as median (interquartile range). Categorical variables are presented as number (percentage). Between-group comparisons were performed using the independent-samples t-test, Mann-Whitney U test, or chi-square test, as appropriate.

Logistic regression was used to estimate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for factors associated with open thoracic surgery. Adjusted estimates controlled for demographic factors, weight, and underlying diseases. $P < 0.05$ was considered statistically significant. For clinical interpretability, odds ratios for continuous predictors were expressed using the measurement units specified in the regression tables. Pleural-fluid total protein was evaluated per 1 g/dL increase, whereas glucose odds ratios were re-expressed per 10 mg/dL increase by mathematically rescaling the original per-unit estimates and their CIs. This transformation did not alter the fitted regression models or their statistical significance.

Multivariable logistic regression was used to examine associations between candidate explanatory variables and open thoracic surgery. Because only 34 patients

experienced the primary outcome, the number of candidate parameters relative to the available events was considered a potential source of overfitting. Adjusted associations were interpreted cautiously, particularly when estimates had wide confidence intervals. The analyses were considered exploratory and were not intended to develop or validate a clinical prediction model.

3.7. Ethical Considerations

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1402.325). This retrospective observational study used existing hospital medical records and involved no additional patient interventions. Written informed consent for the research use of clinical information was obtained from the parents or legal guardians of the included patients. All patient information was handled confidentially, and identifying information was excluded from the analytical dataset.

4. Results

4.1. Study Population

A total of 83 children were included in the study, of whom 34 (41.0%) underwent open thoracic surgery and 49 (59.0%) were managed without open thoracic surgery. No statistically significant differences were observed between the groups in age, sex, weight, or place of residence. Several coexisting medical conditions were documented, including asthma, recurrent infections, previous pneumonia, seizure disorders, diabetes mellitus, congenital heart disease, and malignancies outside the lung and chest wall. None of these conditions showed a statistically significant between-group difference in the reported analyses (Table 1).

Preadmission ibuprofen use was significantly more frequent among children who underwent open thoracic surgery than among those managed without open thoracic surgery (41.2% vs. 18.4%, P = 0.022). Similarly, diclofenac use was more frequent in the open thoracic surgery group (29.4% vs. 8.2%, P = 0.011). In contrast, acetaminophen exposure did not differ significantly between the groups (20.6% vs. 20.4%, P = 0.984). In the reported adjusted logistic regression analyses, both ibuprofen (adjusted OR 3.39, 95% CI 1.09 - 10.52; P = 0.034) and diclofenac (aOR 4.41, 95% CI 1.12 - 17.33; P = 0.034) remained associated with open thoracic surgery (Tables 1 and 2).

4.2. Clinical Characteristics and Treatment Course

Presenting clinical symptoms did not differ significantly between the study groups. However, imaging-assessed pleural effusion severity differed significantly (P = 0.024): severe effusion was documented in 55.9% of children undergoing open thoracic surgery, compared with 28.6% of those managed without open thoracic surgery. The mean duration of hospitalization was significantly longer in the open thoracic surgery group (19.1 ± 11.0 vs. 12.9 ± 5.3 days; P < 0.001). Chest tube drainage was more frequent among children undergoing open thoracic surgery (97.1% vs. 65.3%; P < 0.001). Video-assisted thoracoscopic surgery was performed in 5.9% and 16.3% of patients in the respective groups, with no statistically significant difference (P = 0.187). These treatment frequencies represent interventions received during hospitalization rather than mutually exclusive management pathways. No in-hospital deaths were reported (Table 3).

4.3. Laboratory Findings

Children who underwent open thoracic surgery had significantly different biochemical profiles compared with those managed without open thoracic surgery. Serum LDH levels were higher in the open thoracic surgery group (median, 1228.5 vs. 656 U/L; P < 0.001). Pleural-fluid total protein concentrations were also higher (3.4 ± 0.9 vs. 2.7 ± 0.7 g/dL; P < 0.001), as were pleural-fluid LDH concentrations (median, 5612 vs. 1728 U/L; P < 0.001). Conversely, pleural-fluid glucose concentrations were significantly lower among patients undergoing open thoracic surgery (median, 27.5 vs. 61 mg/dL; P < 0.001). The remaining evaluated laboratory parameters did not show statistically significant between-group differences (Table 4).

4.4. Factors Associated with Open Thoracic Surgery

Pleural fluid total protein, glucose, and LDH levels, as well as preadmission ibuprofen and diclofenac use, remained associated with open thoracic surgery after adjustment for demographic factors, weight, and underlying diseases (Table 2).

5. Discussion

In this retrospective observational study, open thoracic surgery was associated with greater imaging-assessed severity of PE, higher serum LDH, higher pleural-fluid total protein and LDH, lower pleural-fluid glucose, and documented preadmission use of ibuprofen or diclofenac. Pleural-fluid biochemical characteristics and both medication exposures remained associated with open surgery after adjustment for demographic factors, weight, and underlying diseases.

Table 1. Demographic, Clinical, and Preadmission Medication Characteristics According to Open Thoracic Surgery Status [a]

Variables	No Open Thoracic Surgery (n = 49)	Open Thoracic Surgery (n = 34)	P value
Age, mo; median (IQR)	72 (IQR 43)	50.5 (IQR 36)	0.057
Sex			0.110
Male	23 (46.9)	22 (64.7)	
Female	26 (53.1)	12 (35.3)	
Weight, kg; median (IQR)	23 (IQR 13.5)	17.3 (IQR 8.8)	0.073
Residence			0.202
Urban	31 (63.3)	26 (76.5)	
Rural	18 (36.7)	8 (23.5)	
Documented coexisting medical conditions			
Recurrent infection	5 (10.2)	0 (0)	0.075
Asthma	7 (14.3)	2 (5.9)	0.226
Previous pneumonia	0 (0)	2 (5.9)	0.165
Seizure disorder	0 (0)	1 (2.9)	0.410
Diabetes mellitus	1 (2.0)	0 (0)	1.000
Congenital heart disease	1 (2.0)	1 (2.9)	1.000
Other malignancy [b]	1 (2.0)	0 (0)	1.000
Preadmission medication use			
Acetaminophen	10 (20.4)	7 (20.6)	0.984
Ibuprofen	9 (18.4)	14 (41.2)	0.022
Diclofenac	4 (8.2)	10 (29.4)	0.011

[a] Values are expressed as No. (%) unless otherwise indicated. Preadmission medication use refers to documented use during the 7 days before hospitalization. Coexisting medical conditions represent documented diagnoses identified in the patients' medical histories and were not necessarily considered etiological causes of pleural effusion. The listed conditions should not be interpreted as mutually exclusive categories or as an exhaustive classification of pleural-effusion etiology. Abbreviation: IQR, interquartile range.

[b] Lung and chest-wall malignancies were exclusion criteria; therefore, this category represents other documented malignancy.

Table 2. Logistic Regression Analysis of Factors Associated with Open Thoracic Surgery [a]

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Pleural-fluid total protein, per 1 g/dL increase	3.10 (1.70 - 5.90)	< 0.001	4.30 (1.90 - 9.60)	< 0.001
Pleural-fluid glucose, per 10 mg/dL increase	0.43 (0.29 - 0.61)	< 0.001	0.32 (0.19 - 0.54)	< 0.001
Pleural-fluid LDH, per 1 U/L increase	1.001 (1.001 - 1.002)	< 0.001	1.001 (1.001 - 1.002)	< 0.001
Preadmission ibuprofen use, yes vs no	3.11 (1.15 - 8.41)	0.025	3.39 (1.09 - 10.52)	0.034
Preadmission diclofenac use, yes vs no	4.69 (1.33 - 16.54)	0.016	4.41 (1.12 - 17.33)	0.034

[a] The dependent variable was receipt of open thoracic surgery. Adjusted estimates controlled for demographic factors, weight, and underlying diseases. Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio.

The observed associations with pleural-fluid biochemical characteristics are biologically plausible. The progression of pleural infection is accompanied by increasing inflammatory and cellular activity, which may contribute to reduced pleural-fluid glucose concentrations and increased LDH activity. Previous pediatric investigations have reported associations between pleural-fluid biochemical abnormalities and the complexity or clinical course of parapneumonic effusions (13, 14). More recent evidence from Santotoribio et al. further highlights the potential clinical relevance of pleural-fluid glucose, LDH, total protein, pH, and inflammatory-cell characteristics in evaluating pediatric parapneumonic effusions (12). These findings support the relevance of pleural-fluid biochemical assessment, although individual biomarkers should be interpreted alongside the clinical presentation, imaging findings, and treatment response. In the present study, the association between increased pleural-fluid total protein and open thoracic surgery should be regarded as an exploratory finding rather than as

Table 3. Clinical Characteristics and Treatment Course According to Open Thoracic Surgery Status [a]

Variables	No Open Thoracic Surgery (n = 49)	Open Thoracic Surgery (n = 34)	P value
Presenting symptoms			
Cough	30 (61.2)	27 (79.4)	0.096
Fever	42 (85.7)	30 (88.2)	1.000
Chest pain	19 (38.8)	12 (35.3)	0.747
Tachypnea	41 (83.7)	27 (79.4)	0.620
Dyspnea	23 (46.9)	10 (29.4)	0.109
Sputum production	14 (28.6)	6 (17.6)	0.252
Myalgia	10 (20.4)	10 (29.4)	0.346
Nausea and/or vomiting	7 (14.3)	7 (20.6)	0.451
Abdominal pain	10 (20.4)	13 (38.2)	0.074
Pleural effusion severity on imaging			0.024
Mild	13 (26.5)	3 (8.8)	
Moderate	22 (44.9)	12 (35.3)	
Severe	14 (28.6)	19 (55.9)	
Positive SARS-CoV-2 PCR test	6 (12.2)	3 (8.8)	0.731
Positive influenza PCR test	8 (16.3)	2 (5.9)	0.187
Clinical symptoms reported in family members	23 (46.9)	12 (35.3)	0.291
Length of hospital stay, days	12.9 ± 5.3	19.1 ± 11.0	< 0.001
Treatments received during hospitalization [b]			
Chest-tube drainage	32 (65.3)	33 (97.1)	< 0.001
VATS	8 (16.3)	2 (5.9)	0.187

[a] Values are expressed as No. (%) or mean ± SD. Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VATS, video-assisted thoracoscopic surgery.

[b] Treatments were recorded throughout the index hospitalization, and individual patients could receive more than one intervention. Chest-tube drainage and VATS were not mutually exclusive with open thoracic surgery. The reported frequencies describe treatment utilization and do not establish the chronological sequence of interventions.

evidence supporting a specific biochemical threshold for surgical intervention.

Pleural-fluid LDH remained significantly associated with open thoracic surgery after adjustment for the reported covariates. Although the OR of 1.001 per 1 U/L increase appears numerically small, the magnitude of this association is more clinically interpretable when considered over larger increments. Based on the rounded reported estimate, a 100-U/L increase corresponds to an approximate OR of 1.11. Nevertheless, this interpretation assumes a linear relationship between LDH concentration and the log odds of open thoracic surgery. The findings should therefore be interpreted as continuous associations rather than as evidence supporting a specific biochemical threshold for surgical intervention.

Severe PE was substantially more frequent among children undergoing open surgery. Contemporary guidelines emphasize ultrasonographic characterization and a stepwise treatment strategy, with drainage and fibrinolytic therapy favored initially for many complicated effusions and operative management reserved for selected patients with refractory or extensive disease (4-7). Accordingly, imaging severity should be considered alongside the clinical condition and response to initial treatment rather than as an isolated indication for surgery.

Preadmission exposure to ibuprofen and diclofenac was significantly associated with open thoracic surgery in the present study. These findings are consistent with previous observations suggesting a relationship between nonsteroidal anti-inflammatory drug (NSAID) exposure and complicated respiratory infections. Krenke et al. reported that prehospital ibuprofen use was more frequent among children with complicated community-acquired pneumonia (19). A systematic review by Sodhi et al. identified similar associations between NSAID exposure and pneumonia-related complications, although the available observational evidence was affected by confounding, exposure misclassification, and other potential biases (20). Experimental investigations have also suggested that ibuprofen may impair pleural-fluid absorption, although the clinical applicability of these findings remains uncertain (21). The associations observed in our study should not be interpreted as evidence of causality. Children experiencing more severe symptoms,

Table 4. Laboratory Findings According to Open Thoracic Surgery Status [a]

Variables	No Open Thoracic Surgery (n = 49)	Open thoracic Surgery (n = 34)	P value
WBC, $\times 10^3/\mu L$	13.9 ± 7.3	17.2 ± 9.9	0.098
Hemoglobin, g/dL	10.8 (IQR 2.2)	11.2 (IQR 1.8)	0.870
MCV, fL	79.3 ± 6.6	78.9 ± 5.6	0.784
Platelet count, $\times 10^3/\mu L$	154.5 (IQR 252.5)	284 (IQR 272.3)	0.459
BUN, mg/dL	20.7 (IQR 9.6)	23.7 (IQR 9.9)	0.113
Creatinine, mg/dL	0.5 (IQR 0.2)	0.6 (IQR 0.4)	0.179
CRP			0.450
Negative	12 (24.5)	8 (23.5)	
1+	12 (24.5)	5 (14.7)	
2+	16 (32.7)	10 (29.4)	
3+	9 (18.4)	11 (32.4)	
ESR, mm/h	93 (IQR 41)	98 (IQR 36)	0.206
Sodium, mEq/L	138.8 ± 2.8	139.5 ± 2.4	0.247
Potassium, mEq/L	4.2 (IQR 0.5)	4.1 (IQR 0.4)	0.126
PT, s	12.1 (IQR 1.5)	12.0 (IQR 1.7)	0.419
PTT, s	31.2 ± 6.0	31.0 ± 5.7	0.879
INR	1.0 (IQR 0.1)	1.0 (IQR 0.1)	0.227
Serum total protein, g/dL	5.9 (IQR 0.8)	6.0 (IQR 1.0)	0.179
Serum albumin, g/dL	2.9 (IQR 0.4)	2.8 (IQR 0.5)	0.506
Serum glucose, mg/dL	82.5 ± 28.8	92.3 ± 35.1	0.167
Serum LDH, U/L	656 (IQR 619)	1228.5 (IQR 478)	< 0.001
Positive blood culture for S. pneumoniae	6 (12.2)	2 (5.9)	0.462
Pleural-fluid total protein, g/dL	2.7 ± 0.7	3.4 ± 0.9	< 0.001
Pleural-fluid glucose, mg/dL	61 (IQR 32)	27.5 (IQR 17)	< 0.001
Pleural-fluid LDH, U/L	1728 (IQR 1501)	5612 (IQR 3990)	< 0.001

[a] Values are expressed as mean ± SD, median (interquartile range) or No. (%). Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell count; IQR, interquartile range.

prolonged fever, or greater pain may have been more likely to receive NSAIDs before hospitalization and may also have been more likely to require surgical intervention. Therefore, confounding by indication must be considered when interpreting these findings. Furthermore, evidence specifically linking diclofenac exposure to pediatric pleural complications remains limited. The observed medication associations should consequently be regarded as exploratory findings requiring confirmation in future prospective studies.

Clinically, the identified characteristics may help identify children who warrant closer monitoring, early reassessment, and timely multidisciplinary consultation. They should not be used as independent operative indications or as a prediction rule. Decisions regarding drainage, VATS, or open surgery should continue to incorporate the child's clinical status, pleural complexity, microbiological findings, and response to therapy.

5.1. Strengths and Limitations

Strengths of this study include total-enumeration sampling, assessment of multiple clinical and biochemical characteristics, and reporting of crude and adjusted associations with a clinically meaningful outcome. Nevertheless, the retrospective, single-center design limits generalizability and precludes causal inference. The relatively small number of open thoracic surgery events may affect the precision and stability of multivariable estimates. Treatment decisions were made during routine clinical care rather than according to a standardized protocol; therefore, treatment-selection bias and residual confounding cannot be excluded. Imaging severity was determined from routinely documented assessments without a prospectively standardized scoring system or formal inter-rater reliability evaluation. Furthermore, pleural-fluid pH was unavailable, and preadmission medication exposure depended on medical-record

documentation. The regression findings were not internally or externally validated and should not be interpreted as a clinical prediction model.

5.2. Conclusions

In this retrospective study of 83 children with pleural effusion, open thoracic surgery was associated with greater imaging-assessed disease severity, increased pleural-fluid total protein and LDH concentrations, reduced pleural-fluid glucose concentrations, and preadmission exposure to ibuprofen or diclofenac. The observed biochemical associations may reflect differences in pleural inflammation and disease complexity, whereas the associations involving NSAID exposure should be interpreted cautiously because of potential confounding by indication. These findings highlight the importance of integrating clinical assessment, imaging characteristics, and pleural-fluid biochemical findings when evaluating children with pleural effusion. However, the observed associations do not establish causality or define independent indications for surgery. Further prospective multicenter studies are warranted to confirm their clinical relevance.

Footnotes

AI Use Disclosure: ChatGPT was used to design the figure in the Graphical Abstract section to a substantial extent.

Authors' Contribution: Study concept and design: F. A., N. B., and S. A.; data acquisition: A. E.; data analysis and interpretation: A. E., F. A., and N. B.; manuscript drafting: F. A. and N. B.; critical revision for important intellectual content: F. A., N. B., S. A., and S. P.; statistical analysis: A. E. and S. P.; administrative, technical, and material support: N. B. and S. A.; study supervision: F. A. and N. B.

Conflict of Interests Statement: The authors declare no conflicts of interest related to this study.

Data Availability: The study was based on retrospective clinical records from Tabriz University of Medical Sciences. The patient-level analytical dataset is not publicly available. Access to the original institutional clinical records is subject to applicable confidentiality requirements and authorization from the relevant institutional and ethical authorities.

Ethical Approval: The study protocol was reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences (Approval Code: IR.TBZMED.REC.1402.325). This retrospective observational study used existing hospital medical records and involved no additional patient interventions.

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Informed Consent: Written informed consent for the use of clinical information in research was obtained from the parents or legal guardians of the included patients. All patient information was handled confidentially, and identifying information was excluded from the analytical dataset.

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