CHEST

Predictors of Prolonged Hospitalizations in Pediatric Complicated Pneumonia

Oded Breuer, MD; Elie Picard, MD; Naama Benabu, MD; Ira Erlichman, MD; Joel Reiter, MD; Reuven Tsabari, MD; David Shoseyov, MD; Eitan Kerem, MD; and Malena Cohen-Cymberknoh, MD

BACKGROUND: Pediatric community-acquired complicated pneumonia (PCACP) is characterized by a prolonged clinical course, but this may be highly variable.

METHODS: A multicenter observational study was conducted to develop and validate a clinical prediction tool for prolonged hospitalizations in PCACP. The derivation and validation cohorts consisted of 144 and 169 patients with PCACP, respectively, hospitalized between the years 1997 and 2017 in three tertiary care hospitals. Logistic regression analyses were used to identify parameters associated with a prolonged hospitalization and to develop and validate a prediction model for constructing a useful clinical tool.

RESULTS: Higher levels of lactate dehydrogenase (LDH) ($P < .026$) and lower levels of glucose ($P = .018$) in pleural fluid were significantly associated with prolonged hospitalization. A predictive stepwise logistic regression model was developed and applied to the validation cohort. The area under the receiver operating characteristic curve (AUROC) constructed indicated that the model retained good predictive value (AUROC for the derivation vs validation data, [0.77 (95% CI, 0.66-0.87) vs 0.82 (95% CI, 0.72-0.91)], respectively). From these data, a clinical tool was derived; the combination of pleural LDH >1,000 units/L and pleural glucose levels < 1 mmol/L or pleural LDH levels > 2,000 units/L and pleural glucose levels < 2 mmol/L or pleural LDH levels > 3,000 units/L and pleural glucose < 3 mmol/L predict prolonged hospitalization with positive and negative predictive values of 78% (95% CI, 0.71-0.85) and 73% (95% CI, 0.59-0.85), respectively.

CONCLUSIONS: In children, pleural fluid LDH and glucose levels are useful parameters for assessing the severity of PCACP. The model developed in this study accurately predicts patients who will have prolonged hospitalization. CHEST 2018; 153(1):172-180

KEY WORDS: empyema; infectious disease; pediatric infections; pleural effusion; pneumonia

ABBREVIATIONS: AUROC = area under the receiver operating characteristic curve; CAP = community acquired pneumonia; EMP = empyema; Hb = hemoglobin; LDH = lactate dehydrogenase; LOS = length of stay; NP = necrotizing pneumonia; NPV = negative predictive value; PCACP = pediatric community-acquired complicated pneumonia; PLT = platelet; PPV = positive predictive value

AFFILIATIONS: From the Department of Pediatrics and Pediatric Pulmonology (Drs Breuer, Reiter, Tsabari, Shoseyov, Kerem, and Cohen-Cymberknoh), Hadassah-Hebrew University Medical Center; Pediatric Pulmonology Unit (Dr Picard), Shaare Zedek Medical Center; and the Faculty of Medicine (Drs Benabu and Erlichman), Hadassah Medical School, The Hebrew University, Jerusalem, Israel.

FUNDING/SUPPORT: This project was supported by internal departmental funds.

This work was presented at the annual conference of the Israel Society for Clinical Pediatrics, February 8, 2017, Tel-Aviv, Israel.

CORRESPONDENCE TO: Oded Breuer, MD, Pediatric Pulmonology, Hadassah-Hebrew University Medical Center, 91120 Jerusalem, Israel; e-mail: odedbreuer@gmail.com

Copyright © 2017 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: https://doi.org/10.1016/j.chest.2017.09.021

Complications of community-acquired pneumonia (CAP) in children include parapneumonic pleural effusion, empyema, necrotizing pneumonia (NP), and lung abscess, which together are referred to as complicated pneumonia.[1,2] *Streptococcus pneumonia* is the most common bacterial pathogen causing pediatric CAP and its complications.[3-6] Pediatric community-acquired complicated pneumonia (PCACP) is a major cause of morbidity in children worldwide,[7] and its incidence is increasing despite adequate antibiotic treatment and the introduction of early antipneumococcal vaccination.[1,2,8-11]

In adults, complicated pneumonia is associated with high rates of mortality and severe morbidity.[12-14] However, in children who were previously healthy, complete recovery is usually expected without long-term sequelae.[15-17] Despite this favorable prognosis, PCACP may have a protracted clinical course requiring prolonged hospitalization,[2,15,18] but this is highly variable, and some children recover within a few days.[19,20] Currently, objective clinical criteria that allow PCACP outcome prediction are not available. In adults, pleural effusion characteristics such as WBC count, lactic dehydrogenase (LDH) and glucose levels, and fluid acidity have been used to guide clinical decisions regarding invasive treatment.[12,21-24] However, in children, as stated in clinical guidelines, these pleural effusion characteristics have not been adequately studied.[3,6,25] Thus, this variable clinical course and lack of indices that predict outcome may cause difficulty in clinical decision-making regarding invasive and fibrinolytic therapy.

At present there is no consensus on the optimal management of PCACP, and guidelines are based on expert opinion and not evidence-based data.[15,25] Some authors advocate conservative therapy, whereas others recommend the early use of invasive chest drains and surgical procedures despite the risk of complications and the overall favorable prognosis.[26]

Early identification of pediatric patients with complicated pneumonia expected to have a prolonged clinical course will offer physicians the opportunity to discuss the expected clinical course of disease with the parents and make informed decisions on treatment options. Finally, this may assist in standardizing patient groups in clinical trials.

We have previously reported data collected on all children with PCACP hospitalized in Jerusalem between the years 2000 and 2010.[15] The purpose of this study was to develop a clinical tool for the prediction of prolonged hospitalization in PCACP and subsequently validate it on a second cohort of patients.

Methods

Study Population

An observational cohort study in the three major Medical Centers in Jerusalem (Hadassah Ein Kerem, Hadassah Mount Scopus, and Shaare Zedek) was conducted. Included in the study were previously healthy children with complicated pneumonia.

Derivative cohort: We analyzed data from a registry of 144 previously reported patients hospitalized with PCACP between the years 2001 and 2010.[15] Clinical and laboratory parameters were evaluated from this derivative group for the development of a model for prediction of a prolonged length of stay (LOS).

Validation cohort: Due to the relatively low incidence of PCACP and to allow broader assessment of the derived prediction model, data from two different study groups were analyzed for validation. Validation group A consisted of 64 previously healthy children with PCACP hospitalized between 2011 and 2016 in Hadassah Ein Kerem and Mount Scopus medical centers. Data on validation group B was extracted from a previously reported registry of 120 children with PCACP admitted to Shaare Zedek between the years 1997 and 2006.[27]

An overlap existed between validation group B and the derivation cohort in 15 patients from Shaare Zedek; these patients were excluded from validation group B. Both validation groups were combined into one validation cohort for assessment of the derived model.

Data Sources

Clinical data as available in the registry of the derivation group and validation group B were assessed and analyzed. All patients included in these registries were included in the study; no additional data were extracted from medical files or institutional computerized databases. Patients for whom data in the registry were missing were excluded from the final analysis.

For validation group A, clinical records of pediatric patients (< 18 years of age) hospitalized with an International Classification of Diseases, ninth revision diagnosis of NP, empyema (EMP), complicated pneumonia, pleural effusion, need for a chest drain, lung abscess, bacterial pneumonia, and pneumococcal pneumonia between the years 2011 and 2017 were retrieved from the hospitals' records and reviewed for the presence of complicated pneumonia. Patients with a previous history of chronic illness (chronic lung or heart disease, chronic neurologic impairment, immunodeficiency, cancer, or postcancer chemotherapy) were excluded from the study.

Definitions

For the purpose of this study, complicated pneumonia was defined as clinical pneumonia and the presence of a pleural effusion, EMP, or parapneumonic effusion (PPE) and/or NP, as recorded in patient files or registries, or both.

A hospitalization of 10 days or less was considered a standard length of hospitalization, whereas a hospitalization of 11 days or more was considered a prolonged LOS. We decided on the 10-day LOS cutoff

in view of the population size in the derivation cohort and the percentage of children hospitalized > or < 10 days. The median LOS in the derivation group was 13 days (range, 3-59 days; interquartile range, 7); thus, 30% of patients had a LOS < 10 days.

Predictor Variables

Candidate variables were selected from the derivation group registry based on their ability to reflect a prolonged LOS. Specifically, we explored demographic factors, clinical factors (duration of fever and cough prior to admission [days], antibiotic treatment prior to admission [yes/no] and, vital signs), laboratory test results (WBC count, polymorphonuclears, hemoglobin [Hb], platelets [PLTs], and C-reactive protein levels at admission and maximal or minimal values, and blood culture results), pleural fluid parameters (glucose levels [mmol/L], pH, LDH levels [units/L], protein [g/L], amount of fluid drained, and pleural fluid culture results).

Statistical Analysis and Model Development

Demographic, clinical, and laboratory variables were summarized by standard descriptive statistics. Bivariate comparisons in the derivative group between patients with prolonged LOS and those with short LOS used the *t* test in the case of normal distributions and the Mann-Whitney test in the case of nonnormal distributions for continuous variables. For nominal variables, the Wald χ^2 test or the Fisher exact test was used as necessary. Values were expressed as means ± SD for continuous variables or as percentages for nominal variables.

Variables associated with a prolonged LOS in the univariate analysis ($P < .05$) were included in a logistic regression model, and a backward stepwise multivariate approach was used to identify independent predictors of a prolonged LOS (explanatory variables). A prediction model based on the logistic regression equation was calculated. Predicted values of ≥ 0.5 were considered true or false for prediction of a prolonged LOS, respectively, as is customary.

The discriminatory power of the model in the derivation group was assessed by calculating the area under the receiver operating characteristic curve (AUROC). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the prediction rule were calculated using the Fisher exact test. The Cox-Snell R^2 and the Nagelkerke R^2 were used to assess the goodness of fit of the derived model.

The discriminative ability of the model to predict a prolonged LOS in the validation cohort was assessed using ROC curve analysis and by calculating the sensitivity, specificity, PPV and NPV of the prediction rule, as previously described.

All statistical analyses were performed using SPSS, version 22 (IBM Corp) and GraphPad Prism 6 (GraphPad). All tests applied were two-tailed, and a *P* value of 5% or less was considered statistically significant. This research was approved by our institutional review board (HMO-0390-11), and informed consent was waived because of the retrospective observational nature of the study.

Results

Three hundred thirteen patients with PCACP were included in the study. Table 1 describes the distribution of patients and their clinical characteristics.

Construction of the Predictive Model

Patients from the derivation cohort were stratified into one of two groups according to hospital LOS: standard LOS (n = 44) and prolonged LOS (n = 100). Univariate analysis identified that the following variables are associated with a prolonged LOS: low pleural fluid glucose levels, high pleural fluid LDH levels, total amount of pleural fluid drained (mL), relative amount of fluid drained (mL/kg), total IV treatment (days), minimal Hb value, maximal PLT value, and bacterial growth on blood culture results (Table 2).

After multivariate analysis, only high pleural fluid LDH levels (units/L) and low pleural fluid glucose levels (mmol/L) were still significantly associated with a prolonged LOS (Table 2) and regarded as explanatory variables for construction of the predictive model; combined data for pleural glucose and LDH levels were available for 104 patients in the derivative cohort. The logistic regression equation derived coefficients for pleural fluid LDH and pleural fluid glucose levels (0.000034 units/L and –0.524 mmol/L, respectively). The final logistic regression formula for a subject's risk for a prolonged LOS based on pleural fluid LDH and glucose values is given by:

$$P = \frac{e^z}{1 + e^z}$$

where

$z = 1.033 + 0.000034 \times \mathbf{LDH} - 0.524 \times \mathbf{glucose}$

P = predicted risk for a prolonged LOS

Model Assessment and Validation

The AUROC for data from the derivation cohort was 0.77 (95% CI, 0.66-0.87; $P < .0001$), indicating that the model is a good predictor of a prolonged LOS (Fig 1) (n = 104 with available data for analysis). The $P = .5$ cutoff displayed a PPV of 80% (95% CI, 0.7-0.88), NPV of 68% (95% CI, 0.41-0.88), sensitivity of 93% (95% CI, 0.84-0.97), and specificity of 41% (95% CI, 0.22-0.61) ($P = .002$). The Cox-Snell R^2 and the Nagelkerke R^2 were 19% and 28%, respectively.

The prediction model also provided good discrimination in the validation cohort, as demonstrated by AUROC = 0.82 (95% CI, 0.72-0.91; $P < .0001$) (Fig 2); combined data for pleural glucose and LDH levels were available for 87 patients in the validation cohort. The PPV, NPV, sensitivity, and specificity were 80% (95% CI, 0.66-0.89), 70% (95% CI, 0.51-0.84), 81% (95% CI, 0.68-0.91), and 67% (95% CI, 0.49-0.83),

TABLE 1] Patient Characteristics in the Derivation and Validation Cohorts

Variable	Derivation Cohort (2000-2010) n = 144	Validation Group A (2011-2016) n = 64	Validation Group B (1997-2006) n = 120
Age, mo	55.6 (41.96)	70.35 (56.74)	43.44 (28.92)
Sex, male	94 (65)	40 (62)	77 (64)
WBC, 10^9/L	17.8 (9.8)	19.66 (8.5)	19.17 (11.1)
Hb, g %	11.23 (1.6)	11.16 (1.8)	10.95 (1.4)
PLTs (10^9/L)	390 (197)	362.24 (155)	425 (216)
PMN leukocytes, %	75 (14)	75 (13)	NA
CRP, mg %	24.9 (15.1)	23.4 (40.4)	NA
Days of fever prior to admission	4.71 (2.43)	4.68 (2.11)	4.9 (2.75)
Antibiotic treatment prior to admission	70 (48.61)	34 (53.12)	48 (40)
Initial empirical antibiotic treatment			
Penicillin	37 (25)	23 (35)	0 (0)
Cephalosporin	102 (70)	34 (53)	120 (100)
Other	5 (3)	4 (6)	0 (0)
Chest tube insertion	109 (75)	26 (40)	80 (66)
Use of fibrinolysis	30 (20)	5 (7)	30 (37)
Positive bacterial culture result	30 (20)	2 (3)	26 (21)
Positive pleural fluid culture result	50 (34)	9 (14)	33 (27)
LOS, d	14.43 (2.12)	9.66 (5.81)	11.5 (4.9)

Data presented as mean (SD) or No. (%). CRP = C-reactive protein; Hb = hemoglobin; LOS = length of stay; NA = not available, PLTs = platelets; PMN = polymorphonuclear.

respectively ($P < .0001$). The correlation between hospital LOS and the prediction model result is presented in Figure 3. Figure 4 provides a flowchart for inclusion of patients and available data for analysis.

Construction of a Useful Clinical Tool

Analyzing all numerical data associated with a model prediction score ≥ 0.5 and its association with a short or prolonged LOS easily derived a simple clinical tool

TABLE 2] Clinical Variables Associated With a Prolonged LOS as Assessed in the Derivation Cohort

Variable	Short LOS (n = 44)	Prolonged LOS (n = 100)	*P* Value
Pleural effusion glucose level,[a] mmol/L (n = 105)	2.47 (1.88) n = 27	1.33 (0.98) n = 78	.005 **.018**[a]
Pleural effusion LDH level,[a] units/L (n = 104)	15,410 (16,282.56) n = 27	33,228.06 (26,371.41) n = 77	< .001 **.026**[a]
Total amount of pleural fluid drained, mL (n = 71)	115.73 (119.81) n = 19	333.55 (412.25) n = 52	.001
Relative amount of pleural fluid drained, mL/kg (n = 52)	5.97 (9.35) n = 12	17.26 (19.14) n = 40	.055
Hb minimal value,[b] g % (n = 127)	10.39 (1.51) n = 39	9.31 (1.67) n = 88	.001
PLT maximal value,[b] 10^9/L (n = 125)	605 (252) n = 39	846 (320) n = 86	< .001
Total IV treatment, d (n = 144)	7.66 (1.83) n = 44	16.22 (7.24) n = 100	< .01
Identification of bacteria in blood cultures, no/yes (n = 141)	35.1/13.3 n = 43	64.9/86.7 n = 98	.046

Data presented as mean (SD) or %. LDH = lactate dehydrogenase. See Table 1 legend for expansion of abbreviations.
[a]Boldface values remained significant after multivariate analysis.
[b]Maximal or minimal values during hospitalization.

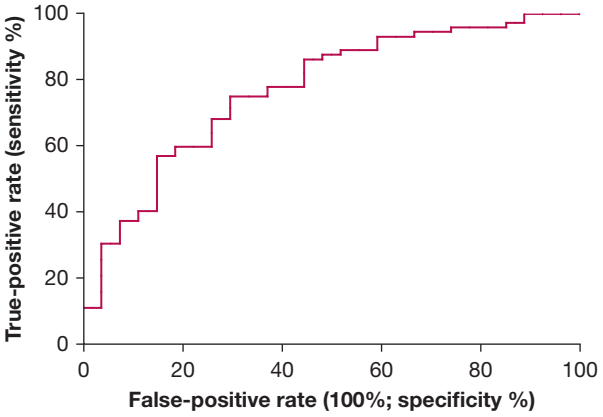

Figure 1 – *Receiver operator characteristic curves (ROCs) of the prediction model for the derivative cohort (n = 104). Area under the ROC curve = 0.77 (95% CI, 0.66-0.87).*

representative of the validated model. The clinical tool uses a combined assessment of pleural fluid LDH and glucose levels for predicting prolonged LOS: pleural LDH level > 1,000 units/L and pleural glucose level < 1 mmol/L or pleural LDH level > 2,000 units/L and pleural glucose level < 2 mmol/L or pleural LDH level > 3,000 units/L and pleural glucose level < 3 mmol/L (Table 3) predicts a prolonged LOS with a PPV, NPV, sensitivity, and specificity of 78% (95% CI, 0.71-0.85), 73% (95% CI, 0.59-0.85), 90% (95% CI, 0.84-0.95), and 52% (95% CI, 0.40-0.64), respectively ($P < .0001$). A 98% agreement exists between the validated model and this clinical tool, that is, the clinical tool underlines the importance of a combined assessment of both pleural fluid LDH and glucose levels for predicting a prolonged LOS. In a patient with very low pleural glucose levels, only moderate increased pleural LDH levels are required, and

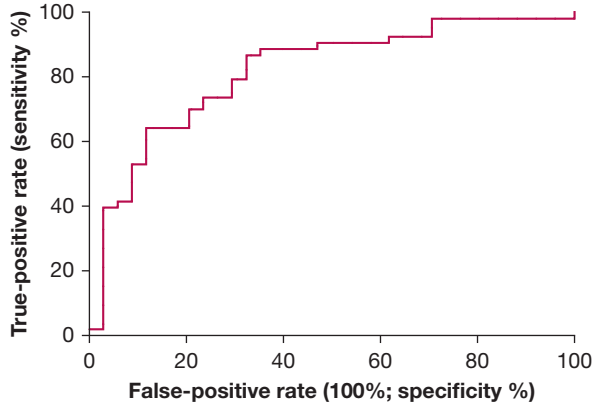

Figure 2 – *Receiver operator characteristic curves (ROCs) of the prediction model in the validation cohort (n = 87). Area under the ROC curve = 0.82 (95% CI, 0.72-0.91).*

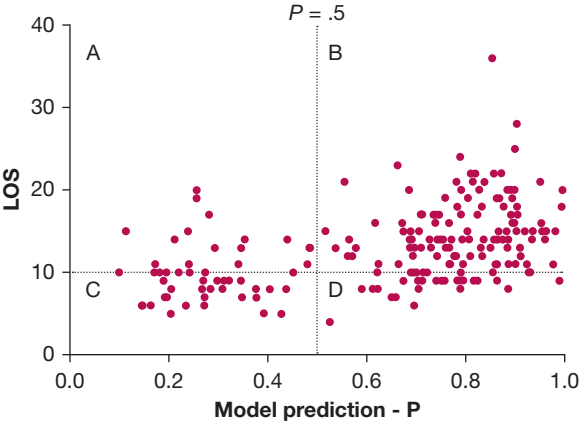

Figure 3 – *Correlation between length of stay (LOS) and the prediction model. A, False negative; B, true positive; C, true negative; D, false positive. A cutoff value of 10 days for a short or prolonged LOS was used. A cutoff model prediction value of 0.5 was used for sensitivity, specificity, and predictive analysis, as accepted in the logistic regression analysis.*

in a patient with markedly elevated pleural fluid LDH levels, only modest decreased pleural glucose levels are required.

In addition, due to the arbitrary cutoff for a prolonged LOS of 10 days used in this study, we also tested the predictive power of the derived clinical tool for predicting a LOS > 7 days. The tool additionally provides a PPV, NPV, sensitivity, and specificity of 97% (95% CI, 0.94-0.99), 27% (95% CI, 0.159-0.41), 80% (95% CI, 0.74-0.86), and 76% (95% CI, 0.50-0.93), respectively ($P < .0001$ for predicting an LOS > 7 days).

Discussion

We have shown that the combination of lower levels of pleural fluid glucose and higher levels of pleural fluid LDH are significantly associated with prolonged hospitalization in patients with PCACP. The combination of these variables in a prediction model creates a useful clinical tool for identifying patients who are expected to have a more prolonged clinical course during hospitalization. Early identification of patients at risk of a prolonged LOS offers physicians the opportunity to discuss the expected clinical course of disease with the parents, make informed decisions about treatment options regarding conservative or early invasive treatment, and may allow better patient selection for clinical trials for assessing the optimal therapeutic approach for PCACP.

Current guidelines from the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America recommend assessing the degree of the

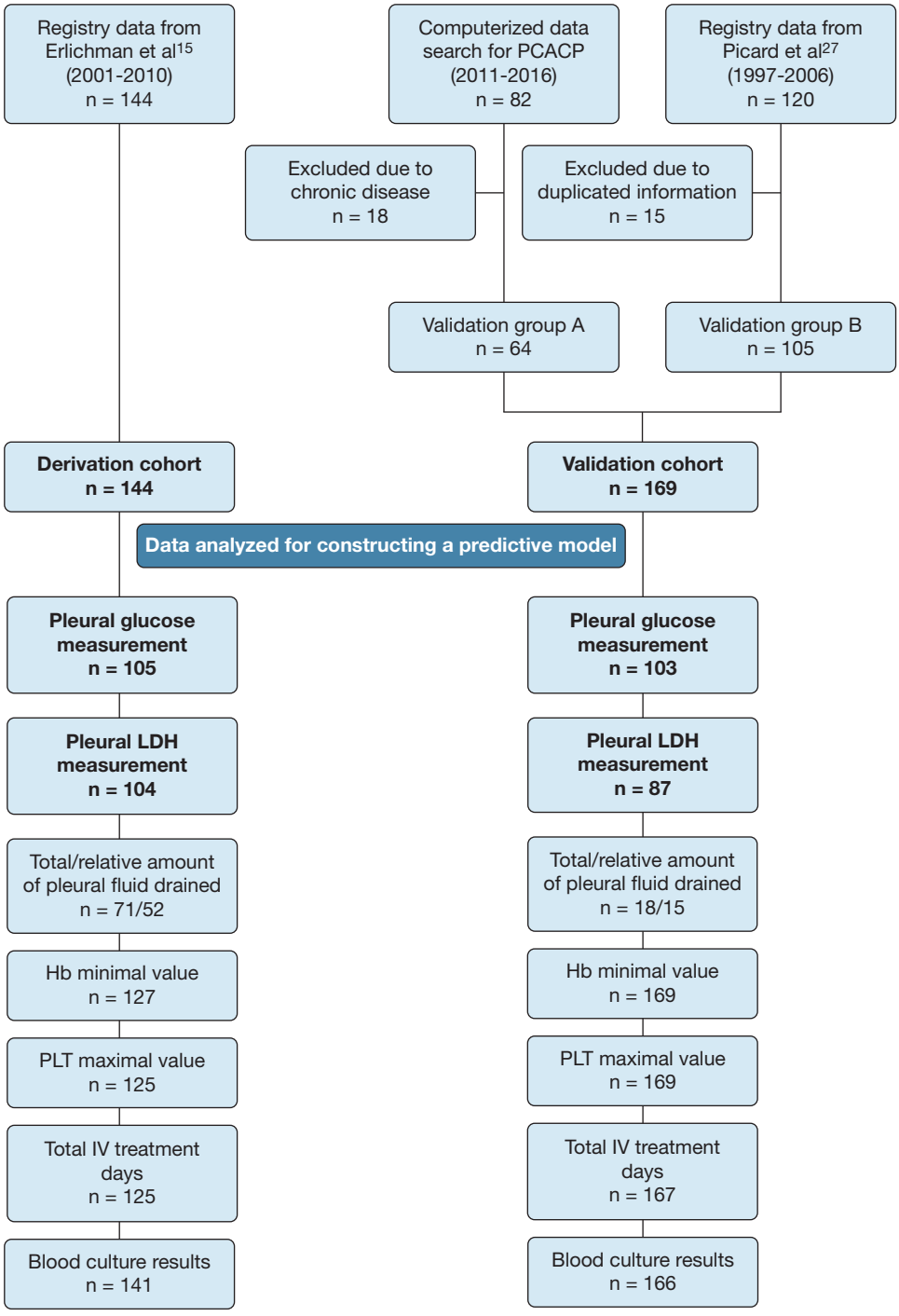

Figure 4 – *Study population. Identification of study population for model construction and validation showing the derivation cohort and validation groups A and B. LDH = lactate dehydrogenase; Hb = hemoglobin; PLT = platelets.*

respiratory compromise and the size of the effusion when considering invasive treatment.[3] Similarly, the British Thoracic Society guidelines for the management of pleural infection in children recommend that effusions that are enlarging or compromising respiratory function, or both, should not be managed conservatively.[6] These recommendations are based on clinical experience, logic, and retrospective observational data.[25,28] In our study, effusion size as based on standard effusion size classification criteria was not available.[12,29] Effusion size was assessed by the total (mL) and the relative (mL/kg) amount of pleural

TABLE 3] Prediction of a Prolonged Hospitalization in Children With Complicated Pneumonia According to High Pleural Fluid LDH Levels and Low Pleural Fluid Glucose Levels Derived From the Validated Prediction Model

Children at Risk of a Prolonged LOS
Pleural LDH level > 1,000 units/L and pleural glucose level < 1 mmol/L
or
Pleural LDH level > 2,000 units/L and pleural glucose level < 2 mmol/L
or
Pleural LDH level > 3,000 units/L and pleural glucose level < 3 mmol/L

Sensitivity, 90%; specificity, 52%; positive predictive value, 78%, negative predictive value, 73%. See Table 1 and 2 legends for expansion of abbreviations.

fluid drained, and neither were found to predict the patients' hospital LOS. Clinical appearance could not be assessed due to the retrospective nature of our study. The current British Thoracic Society and Infectious Diseases Society of America guidelines do not recommend standard measurements of pleural fluid LDH and glucose levels due to a lack of sufficient evidence regarding their usefulness in pediatric patients, but the guidelines state that the recommendations are based on very low quality of evidence.[3,6] Several studies have analyzed pleural fluid indices in PCACP as predictors of a complicated disease course. In a retrospective series in 81 pediatric patients, pleural fluid pH < 7.27 correlated with fibrin septations and the need for interventional therapy.[30] In another retrospective study of 67 children, pH values < 7.2 on pleural tap fluid, especially if combined with low pleural glucose levels, were associated with a higher reintervention rate and the need for pleural fluid drainage.[31] Retrospective data also suggest that pleural fluid pH, glucose levels, and the LDH pleural to serum ratio are associated with prolonged fever, suggesting worse disease.[27] Furthermore, data from studies in adults have also demonstrated that pleural fluid LDH and glucose levels, but especially pH, have good diagnostic accuracy for identifying complicated parapneumonic effusions that require drainage.[32,33] In our analysis, pleural fluid pH was not predictive of a prolonged LOS. This could be due to the complexity of correctly measuring pleural fluid pH.[34] Despite the inconsistency regarding pleural fluid pH, the studies in children mentioned earlier, in accordance with our findings and similar to those in adults, present evidence that pleural fluid biochemical indices predict outcome in PCACP and thus should be assessed in this condition. Furthermore, our study has also evaluated other clinical variables for prediction of a more complicated course not related to pleural fluid analysis. No other clinical variable was found on a multivariate analysis to significantly predict a prolonged LOS. We have found that only pleural fluid indices (specifically, glucose and LDH levels) significantly predict a prolonged LOS, emphasizing the importance of pleural fluid analysis for treatment guidance in PCACP. Therefore, we think that pleural fluid analysis should be considered in most children hospitalized with PCACP. Still, the observational nature of the study precludes us from recommending pleural fluid analysis in patients with mild disease in which overaggressive diagnosis may not contribute to their management.

Uncertainty still exists regarding the right choice of treatment in PCACP, especially in view of the overall favorable outcome expected in previously healthy children regardless of the type of treatment approach.[3,6,25,28] Due to the favorable outcome in PCACP, studies that have assessed different treatment protocols have aimed to show an overall shorter clinical course as the primary end point. Using a prediction model, as presented in this study, may assist in patient selection for clinical trials and thus help resolve inconsistencies in the management of PCACP.

The main strength of our study lies in the relatively large number of patients included, the multicenter design, the multivariate analysis, and the validation of the identified model, which was performed in two different cohorts over a wide time range. However, it has several limitations: The retrospective design may have resulted in patient selection bias and needs to be validated in a prospective study. Many variables that were not assessed in this observation study, such as treatment modalities and departmental guidelines, can influence LOS in patients with PCACP. This is probably the reason that our model provides only a moderate predictor for a prolonged LOS (AUROC = 0.77). Furthermore, not all children with PCACP underwent pleural fluid analysis, and some relevant clinical information was lacking; therefore, it reduced the sample study in the derivation and validation cohorts. We have tried to overcome these limitations by including a large number of patients and assessing objective parameters of the disease course.

Conclusions

The incidence of PCACP has been increasing worldwide despite treatment protocols and early immunization. PCACP continues to be an illness with high morbidity and health expenditures. This study allowed us to establish a useful clinical tool that can identify patients expected to have a prolonged disease course. Our model emphasizes the importance of measuring pleural fluid characteristics in children. Measurements of pleural LDH and glucose levels were strongly correlated with a prolonged period of hospitalization in PCACP and were validated as good predictors of hospital LOS as an indirect indicator of disease severity.

Acknowledgments

Author contributions: O. B. takes responsibility for the content of the manuscript, including the data and analysis. O. B. conceptualized and designed the study, coordinated and supervised the data collection, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. E. P. contributed substantially to the data analysis and interpretation and the writing of the manuscript. N. B. and I. E. carried out the data collection, participated in the initial analyses, and approved the final manuscript as submitted. J. R., R. T., and D. S. contributed to the study design, data analysis and interpretation, and approved the final manuscript as submitted. E. K. provided project oversight, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. M. C. C. conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Tan TQ, Mason EO Jr, Wald ER, et al. Clinical characteristics of children with complicated pneumonia caused by Streptococcus pneumoniae. *Pediatrics*. 2002;110(1 pt 1):1-6.
2. Sawicki GS, Lu FL, Valim C, Cleveland RH, Colin AA. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. *Eur Respir J*. 2008;31(6):1285-1291.
3. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53(7):e25-e76.
4. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835-845.
5. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics*. 2004;113(4):701-707.
6. Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax*. 2011;66(suppl 2):ii1-ii23.
7. Principi N, Esposito S. Management of severe community-acquired pneumonia of children in developing and developed countries. *Thorax*. 2011;66(9):815-822.
8. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. *Pediatrics*. 2010;125(1):26-33.
9. Fletcher M, Leeming J, Cartwright K, Finn A, South West of England Invasive Community Acquired Infection Study Group. Childhood empyema: limited potential impact of 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2006;25(6):559-560.
10. Grijalva CG, Nuorti JP, Zhu Y, Griffin MR. Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. *Clin Infect Dis*. 2010;50(6):805-813.
11. Fletcher MA, Schmitt HJ, Syrochkina M, Sylvester G. Pneumococcal empyema and complicated pneumonias: global trends in incidence, prevalence, and serotype epidemiology. *Eur J Clin Microbiol Infect Dis*. 2014;33(6):879-910.
12. Colice GL, Curtis A, Deslauriers J, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest*. 2000;118(4):1158-1171.
13. Davies CW, Kearney SE, Gleeson FV, Davies RJ. Predictors of outcome and long-term survival in patients with pleural infection. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1682-1687.
14. Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*. 2005;352(9):865-874.
15. Erlichman I, Breuer O, Shoseyov D, et al. Complicated community acquired pneumonia in childhood: different types, clinical course, and outcome. *Pediatr Pulmonol*. 2017;52(2):247-254.
16. McLaughlin FJ, Goldmann DA, Rosenbaum DM, Harris GB, Schuster SR, Strieder DJ. Empyema in children: clinical course and long-term follow-up. *Pediatrics*. 1984;73(5):587-593.
17. Honkinen M, Lahti E, Svedstrom E, et al. Long-term recovery after parapneumonic empyema in children. *Pediatr Pulmonol*. 2014;49(10):1020-1027.
18. Kelly MM, Shadman KA, Edmonson MB. Treatment trends and outcomes in US hospital stays of children with empyema. *Pediatr Infect Dis J*. 2014;33(5):431-436.
19. Sonnappa S, Cohen G, Owens CM, et al. Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. *Am J Respir Crit Care Med*. 2006;174(2):221-227.
20. Mahant S, Cohen E, Weinstein M, Wadhwa A. Video-assisted thorascopic surgery vs chest drain with fibrinolytics for the treatment of pleural empyema in children: a systematic review of randomized controlled trials. *Arch Pediatr Adolescent Med*. 2010;164(2):201-203.
21. Light RW. Parapneumonic effusions and empyema. *Clin Chest Med*. 1985;6(1):55-62.
22. Light RW. A new classification of parapneumonic effusions and empyema. *Chest*. 1995;108(2):299-301.
23. Janda S, Swiston J. Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyemas: a systematic review and meta-analysis. *Chest*. 2012;142(2):401-411.
24. Light RW. Clinical practice. Pleural effusion. *N Engl J Med*. 2002;346(25):1971-1977.
25. Proesmans M, De Boeck K. Clinical practice: treatment of childhood empyema. *Eur J Pediatr*. 2009;168(6):639-645.
26. Islam S, Calkins CM, Goldin AB, et al. The diagnosis and management of empyema in children: a comprehensive review from the APSA Outcomes and Clinical Trials Committee. *J Pediatr Surg*. 2012;47(11):2101-2110.
27. Picard E, Joseph L, Goldberg S, et al. Predictive factors of morbidity in childhood parapneumonic effusion-associated pneumonia: a retrospective study. *Pediatr Infect Dis J*. 2010;29(9):840-843.
28. Carter E, Waldhausen J, Zhang W, Hoffman L, Redding G. Management of children with empyema: pleural drainage is not always necessary. *Pediatr Pulmonol*. 2010;45(5):475-480.

29. Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc*. 2006;3(1):75-80.

30. Chiu CY, Wong KS, Huang YC, Lai SH, Lin TY. Echo-guided management of complicated parapneumonic effusion in children. *Pediatr Pulmonol*. 2006;41(12):1226-1232.

31. Mitri RK, Brown SD, Zurakowski D, et al. Outcomes of primary image-guided drainage of parapneumonic effusions in children. *Pediatrics*. 2002;110(3):e37.

32. Heffner JE, Brown LK, Barbieri C, DeLeo JM. Pleural fluid chemical analysis in parapneumonic effusions. A meta-analysis. *Am J Respir Crit Care Med*. 1995;151(6):1700-1708.

33. Jimenez Castro D, Diaz Nuevo G, Sueiro A, Muriel A, Perez-Rodriguez E, Light RW. Pleural fluid parameters identifying complicated parapneumonic effusions. *Respiration*. 2005;72(4):357-364.

34. Rahman NM, Mishra EK, Davies HE, Davies RJ, Lee YC. Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. *Am J Respir Crit Care Med*. 2008;178(5):483-490.